European Academy of Neurology guideline on the diagnosis of coma and other disorders of consciousness

D. Kondziella[a,b,c], A. Bender[d,e], K. Diserens[f], W. van Erp[g,h], A. Estraneo[i,j], R. Formisano[k], S. Laureys[g], L. Naccache[l,m], S. Ozturk[n], B. Rohaut[l,m,o], J. D. Sitt[m], J. Stender[p], M. Tiainen[q], A. O. Rossetti[f,*], O. Gosseries[g,*], and C. Chatelle[g,r,*] on behalf of the EAN Panel on Coma, Disorders of Consciousness[†]

[a]*Department of Neurology, Rigshospitalet, Copenhagen University Hospital, Copenhagen;* [b]*Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark;* [c]*Department of Neurosciences, Norwegian University of Science and Technology, Trondheim, Norway;* [d]*Department of Neurology, Ludwig-Maximilians-Universität München, Munich;* [e]*Therapiezentrum Burgau, Burgau, Germany;* [f]*Department of Clinical Neurosciences, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland;* [g]*Coma Science Group, GIGA Consciousness, University and University Hospital of Liège, Liège, Belgium;* [h]*Department of Primary Care, Radboud University Medical Center, Nijmegen, The Netherlands;* [i]*Neurology Unit, Santa Maria della Pietà General Hospital, Nola;* [j]*IRCCS Fondazione don Carlo Gnocchi ONLUS, Florence;* [k]*Post-Coma Unit, Neurorehabilitation Hospital and Research Institution, Santa Lucia Foundation, Rome, Italy;* [l]*Department of Neurology, AP-HP, Groupe hospitalier Pitié-Salpêtrière, Paris;* [m]*Sorbonne Université, UPMC Univ Paris 06, Faculté de Médecine Pitié-Salpêtrière, Paris, France;* [n]*Department of Neurology, Faculty of Medicine, Selcuk University, Konya, Turkey;* [o]*Neuro-ICU, Department of Neurology, Columbia University, New York, NY, USA;* [p]*Department of Neurosurgery, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark;* [q]*Department of Neurology, Helsinki University Hospital, Helsinki, Finland; and* [r]*Laboratory for NeuroImaging of Coma and Consciousness – Department of Neurology, Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA*

See editorial by V. De Herdt on page 739

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Background and purpose: Patients with acquired brain injury and acute or prolonged disorders of consciousness (DoC) are challenging. Evidence to support diagnostic decisions on coma and other DoC is limited but accumulating. This guideline provides the state-of-the-art evidence regarding the diagnosis of DoC, summarizing data from bedside examination techniques, functional neuroimaging and electroencephalography (EEG).
Methods: Sixteen members of the European Academy of Neurology (EAN) Scientific Panel on Coma and Chronic Disorders of Consciousness, representing 10 European countries, reviewed the scientific evidence for the evaluation of coma and other DoC using standard bibliographic measures. Recommendations followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system. The guideline was endorsed by the EAN.
Results: Besides a comprehensive neurological examination, the following suggestions are made: probe for voluntary eye movements using a mirror; repeat clinical assessments in the subacute and chronic setting, using the Coma Recovery Scale – Revised; use the Full Outline of Unresponsiveness score instead of the Glasgow Coma Scale in the acute setting; obtain clinical standard EEG; search for sleep patterns on EEG, particularly rapid eye movement sleep and slow-wave sleep; and, whenever feasible, consider positron emission tomography, resting state functional magnetic resonance imaging (fMRI), active fMRI or EEG paradigms and quantitative analysis of high-density EEG to complement behavioral assessment in patients without command following at the bedside.
Conclusions: Standardized clinical evaluation, EEG-based techniques and functional neuroimaging should be integrated for multimodal evaluation of

Correspondence: Daniel Kondziella, Department of Neurology, Rigshospitalet, Copenhagen University Hospital, DK-2100 Copenhagen, Denmark (tel.: +45-3545-6368; fax: +45-3545-2098; e-mail: daniel_kondziella@yahoo.com).

*Contributed equally as senior authors.
[†]Additional members listed in Supporting information.

patients with DoC. The state of consciousness should be classified according to the highest level revealed by any of these three approaches.

Introduction

Detecting consciousness in unresponsive patients by means of clinical examination is challenging because patients must be awake, they must possess the voluntary drive to mobilize motor function, and the latter must be preserved to a degree that is readily measurable. Moreover, all these requirements need to be fulfilled at the time of examination [1–4].

Further complicating matters, the origin of many clinical signs and behaviors in patients with disorders of consciousness (DoC) is not entirely clear and their significance as to whether the patient is conscious is even less certain [2,5,6]. Moreover, consciousness may wax and wane, both in the short term (seconds to hours) and longer term (days). For instance, although visual pursuit suggests a minimally conscious state (MCS) [7], its presence may fluctuate spontaneously during the day [3], and it may only be elicited by certain salient stimuli (e.g. the patient's own face reflected in a mirror) or in specific situations (e.g. when the presence of relatives may boost arousal) [4,8–14]. Notwithstanding daily fluctuations, consciousness often improves over months and sometimes even years after the brain injury [3,15–18]. It is thus unsurprising that as many as 40% of non-communicating patients with DoC may be wrongly classified as being in the vegetative state/unresponsive wakefulness syndrome (VS/UWS) [5,6,19,20]. This has major ethical and practical implications for patients and their caregivers, including prognosis, treatment, resource allocation and end-of-life decisions [21–30].

Limited knowledge of DoC contributes to this dilemma. The classical locked-in syndrome, in which partially preserved eye movements allow for communication in cognitively intact but paralyzed patients, is well known by neurologists [31]. Yet, it is much less recognized that other patients may be unable to interact with the outside world because of complete motor paralysis or language impairment, despite being conscious. This state of covert consciousness was first documented in 2006 in a landmark paper by Owen *et al*. [32]. Herein, the authors showed that a young traffic accident victim, who met the clinical criteria of VS/UWS, was able to follow commands only by modulating her brain's metabolic activity as measured by functional magnetic resonance imaging (fMRI) [32].

Paradigms to detect consciousness by means of positron emission tomography (PET), fMRI and electroencephalography (EEG) have therefore been developed during the past two decades to supplement the clinical evaluation of DoC (for recent reviews see references [1,33,34]). These include active paradigms in which patients are asked to execute various cognitive tasks [20,35–39]; passive paradigms relying on the assessment of functional connectivity in response to external stimuli [40]; and assessment of spontaneous brain activity during rest [20,41–45]. A number of active paradigm studies have shown that, although patients with severe brain injury may not reveal any signs of consciousness at the bedside, some of them are able to wilfully modulate their brain activity on command, even occasionally answering yes/no questions by performing mental imagery tasks [36]. Indeed, roughly 15% of behaviorally VS/UWS patients are able to follow commands by modifying their brain activity during an EEG- and/or fMRI-based active consciousness paradigm, suggesting that they have covert cognitive abilities [1].

Although many challenges remain, in particular regarding diagnostic definitions of DoC and the sensitivity and specificity of consciousness paradigms [1,46], these data have paved the way for a better understanding of DoC. Accordingly, new concepts have emerged that challenge established neurological practice, including cognitive motor dissociation (i.e. command following during fMRI and EEG despite being unresponsive at the bedside [47]) and higher-order cortex motor dissociation (i.e. fMRI and EEG evidence of association cortex activity to passive stimuli in clinically low-responsive or unresponsive patients [48]).

In summary, multimodal assessment using PET, fMRI and EEG together with standardized clinical behavioral scales provides more robust evaluation of consciousness and higher-order cortical function than routine bedside examination alone, but this knowledge is not yet widely implemented in clinical practice. A comprehensive European guideline for the diagnosis of coma and other DoC based on the best available scientific and clinical data is therefore needed.

Methods

Objectives

The aim is to provide the European neurological community with recommendations based on the best available evidence regarding diagnosis and classification of coma and other DoC, including clinical bedside examination techniques and laboratory investigations based on functional neuroimaging (PET, fMRI) and EEG [including transcranial magnetic stimulation (TMS) and evoked potentials].

Definitions

The term DoC includes patients in coma, VS/UWS and MCS. Coma may be defined as a state of profound unawareness from which the patient cannot be aroused. Crucially, eyes are closed, and a normal sleep–wake cycle is absent. This usually lasts only a few days or weeks following acute brain injury [49]. The term VS/UWS denotes a condition of wakefulness without (clinical signs of) awareness [19]. Such patients may open their eyes but exhibit only reflex (i.e. non-intentional) behaviors and are therefore considered unaware of themselves and their surroundings. In contrast, patients in MCS show unequivocal signs of non-reflex cortically mediated behaviors [50], occurring inconsistently, yet reproducibly, in response to environmental stimuli [7]. Although some MCS patients may follow commands to a certain degree, functional communication is not possible. The differentiation between VS/UWS and MCS is most probably gradual (continuous) rather than binary (all-or-none) [51], and some survivors with VS/UWS may recover to MCS or better, even years after the brain injury [3,15–18]. The heterogeneity of the MCS is now recognized, and consequently patients may be classified according to the degree of their behavioral responses into MCS plus (i.e. if they are able to follow commands, produce intelligible words and/or display intentional communication) or minus (e.g. if they only show voluntary signs of consciousness such as localization to pain or visual pursuit but no behaviors suggestive of language processing) [52]. Patients who recover functional communication or functional object use are considered as 'emerged from MCS' [7].

Disorders of consciousness must be differentiated from conditions mimicking unresponsiveness but in which consciousness is intact. As stated earlier, in the locked-in syndrome a patient is fully aware and, despite being anarthric and tetraplegic, is able to communicate by partially preserved eye movements [31]. Importantly, patients who do not follow commands at the bedside but are able to follow commands by modifying their brain activity during fMRI- and EEG-based active consciousness paradigms are thought to be in a state of cognitive motor dissociation [47]. This condition is also known as non-behavioral MCS, MCS*, functional locked-in syndrome or covert consciousness [16,20,53–55].

Methodology

A chronological overview of the guideline production process is given in Table 1. Detailed information about methodological procedures, including initiation and organization of the task force group, definition of relevant topics and research questions, literature research, data extraction and analysis, grading of the scientific evidence, compilation of recommendations and writing of the paper, can be found in the guideline protocol (Supporting information;Supplemental File S5). An outline of the literature search is provided in Fig. 1.

This guideline was accomplished following the 'practical recommendations for the process of proposing, planning and writing a neurological management guideline by European Academy of Neurology (EAN) task forces' [56]. Briefly, 16 members of the EAN Scientific Panel on Coma and Chronic Disorders of Consciousness from 10 European countries (Fig. S1; Supplemental File S4) collaborated to identify relevant clinical and scientific research questions, using the Patient, Intervention, Comparator, Outcome (PICO) approach [57]. Questions were grouped into three topics: clinical examination, functional neuroimaging, and EEG-based techniques (including evoked potentials and TMS). See later for the definition of target conditions. Owing to the lack of a gold standard [1], clinical bedside evaluation for signs of consciousness, using standardized scales (notably, the Coma Recovery Scale – Revised (CRS-R) [58], was considered as the reference standard. PubMed was searched from 1 January 2002 until 31 December 2018 for relevant literature according to standard methods. January 2002 was chosen because this was the year when the term 'minimally conscious state' was introduced in the medical literature [7]. The search was restricted to English language and adult humans with acute or chronic and traumatic or non-traumatic brain injury. Data were extracted, synthesized, analyzed and interpreted using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [59]. See the guideline protocol for details (Supporting information; Supplemental File S5). The quality of evidence was graded as high, moderate, low or very low; recommendations were classified as strong or weak and approved by all task force group members [59]. Contingency tables (Supplemental File S1), grading of evidence tables (Supplemental File S2) and recommendation tables (Supplemental File S3) are provided online (Supporting information). This 2-year project was funded, supervised and endorsed by the EAN.

RESULTS

Clinical examination

PICO questions 1–3 refer to clinical signs, PICO questions 4–8 to clinical rating scales. Thirteen

Table 1 Steps during the production of the EAN Guideline on the Diagnosis of Coma and Other Disorders of Consciousness

1) The chair of the guideline task force (DK) was appointed by the chair of the EAN Panel on Coma and Disorders of Consciousness (AR) at the 3rd EAN Conference in Amsterdam (*June 2017*)
2) The chair of the guideline task force selected task force members according to the following criteria:
- Senior and junior members with expertise in coma and DoC, including a recent publication record in peer-reviewed journals
- Balanced distribution between gender and country of origin
- Including non-neurological specialties
- No major conflicts of interest

3) Relevant topics were selected and grouped into Clinical Examination, Neuroimaging and EEG/Evoked Potentials
4) Members of the panel were appointed to one of these three major topics; three members were appointed as group leaders (CC – Clinical Examination, OG – Neuroimaging, AR – EEG/Evoked Potentials)
5) The members produced and approved a list of outcomes, the importance of which was rated by each member on a 9-point Likert scale
6) Low-ranking outcomes (1–6 points) were excluded
7) PICO questions for each topic were formulated, discussed and approved
8) PubMed search terms and strategies were designed for each topic
9) A detailed protocol was written, circulated amongst all members and approved (see Supporting information)
10) The protocol was submitted and, following one revision, endorsed by the EAN (*February 2018*)
11) The literature search was performed centrally and supervised by a university librarian from the University of Copenhagen, Copenhagen (*March 2018*; Fig. 1; the search was updated in *December 2018*)
12) Searching, selection and extraction of information related to each PICO question was performed by pairs of two members; disagreement was solved by consensus or by the group leaders/the chair
13) Data were plotted into contingency tables (see Supporting information)
14) Evaluation of the quality of scientific evidence followed the GRADE method
15) For each PICO question, quality of evidence was classified as very low, low, moderate or high, and plotted into Grading of Evidence tables (see Supporting information)
16) Based on the quality of evidence, recommendations for each PICO question were written
17) The strength of the recommendations was rated according to the quality of evidence as weak or strong, following the GRADE methodology
18) The grading of evidence, statement of the recommendations and strength of recommendations were discussed amongst panel members by email, online conferences and a 2-day meeting at the University Hospital Pitié-Salpetrière in Paris (*February 2019*; Fig. S1); results were plotted into Recommendation Tables (see Supporting information)
19) The chair wrote a draft of the guidelines, which was circulated amongst all members for editing, and the final text was approved by all panel members (*May 2019*)
20) The guideline was presented at the 5th EAN Conference in Oslo (*June 2019*)

DoC, disorders of consciousness; EAN, European Academy of Neurology; EEG, electroencephalography; GRADE, *Grading of Recommendations Assessment, Development and Evaluation;* PICO, Patients, Intervention, Comparator, Outcome.

publications were included for final analysis [4–6,9,11,20,58,60–65].

PICO 1 Should the patient's eyelids be opened by the examiner to diagnose voluntary eye movements in patients with DoC without spontaneous eye opening?

No eligible studies were found.

Good practice recommendation: Despite the lack of eligible studies, to assess for signs of voluntary eye movements it is crucial to passively open the eyes of patients without spontaneous or stimulation-triggered eye opening (*very low evidence, strong recommendation*). It is the experience of the task force group members that forgetting this simple advice is one of the reasons why a locked-in syndrome may be missed. Prior to assessing for signs of consciousness, the patient needs to be properly aroused. The examiner must remember to probe for both vertical and horizontal eye movements, as patients with the classical locked-in syndrome have preserved vertical eye movements only [31,66]. If the patient does not show eye movements on command, the examiner should probe for visual tracking (i.e. using a mirror; see PICO 2). Opening eyelids allows locked-in syndrome, MCS and conscious patients with impaired eyelid movements (e.g. ptosis) to be diagnosed [67]. Resistance to passive eye opening may be a sign of preserved consciousness [68].

PICO 2 Should a mirror be used to diagnose visual pursuit in patients with DoC?

Three studies were eligible for inclusion [9,11,64]. One study was excluded due to complete patient

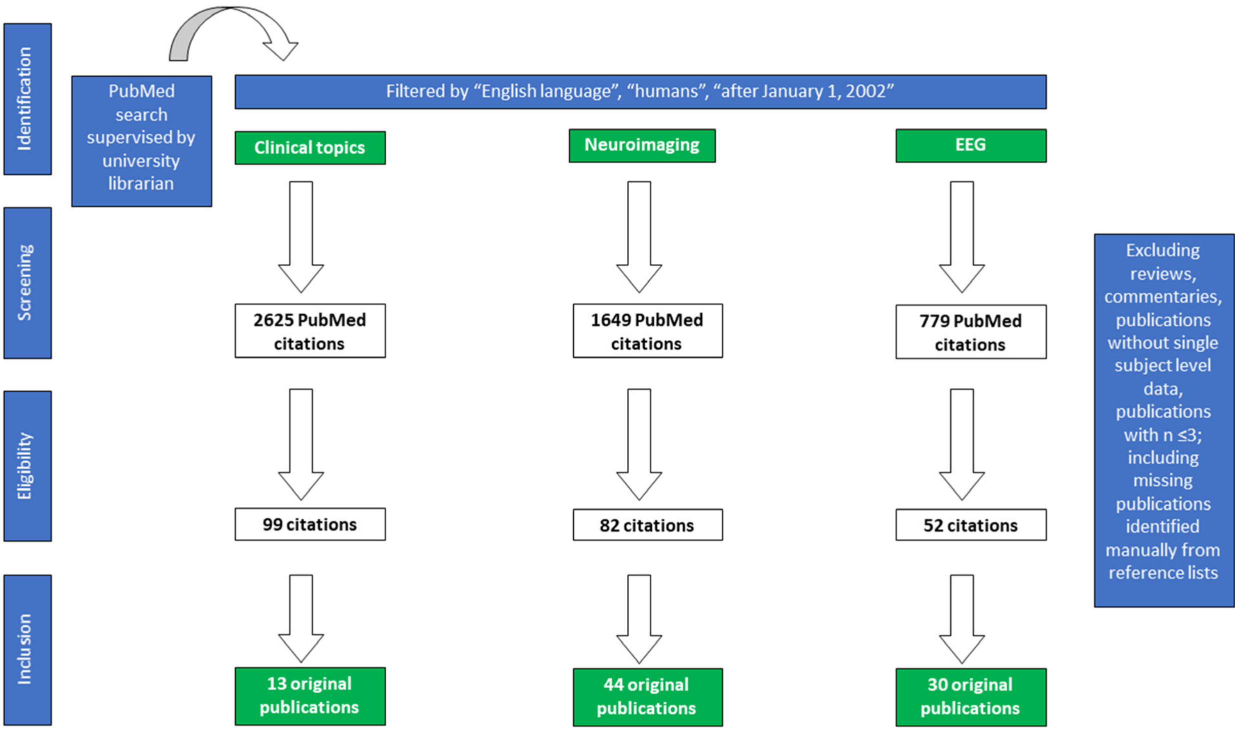

Figure 1 Overview of the literature search (January 2002 to December 2018); see Methods and the guideline protocol (Supporting information) for details. [Colour figure can be viewed at wileyonlinelibrary.com]

overlap [11], resulting in two studies with a total of 272 patients. Relative risk for visual pursuit detected with a mirror compared to other stimuli (e.g. pictures of faces) was 1.47 [95% confidence interval (CI) 1.29–1.66; $P < 0.0001$], suggesting that a mirror is appropriate for the detection of visual pursuit.

Recommendation: Given that a mirror is a convenient bedside tool, it is recommended to always use it in DoC patients to diagnose visual pursuit (*low evidence, strong recommendation*). When testing for visual pursuit, it is necessary to rule out cortical blindness, damage to the optic nervous structures and central or peripheral oculomotor palsies [69]. Regular reassessment is important because levels of consciousness may fluctuate rapidly [3]. If the mirror does not evoke a response, other stimuli such as pictures showing the patient's or relatives' faces or personal objects may be used.

PICO 3 Should spontaneous motor behaviors be observed to diagnose signs of consciousness in patients with DoC?

There were no eligible studies.

Good practice recommendation: Despite the absence of eligible studies, spontaneous motor behavior and automatic motor responses may be observed and documented in the patient charts, including tube pulling, nose scratching, grabbing sheets, leg crossing and localizing behavior, as these may reflect a higher level of residual consciousness [70] (*very low evidence, weak recommendation*). Indeed, some spontaneous behaviors have been suggested as indicating cortically mediated abilities such as automatic motor responses (which is included in the CRS-R [58]) or psychomotor agitation [71]. Observation of spontaneous motor behaviors (that may or may not be intentional) could help diagnose covert consciousness, e.g. using analytical approaches such as the revised Motor Behavior Tool [70,72] or subjective approaches based on caregivers' collective intelligence such as the 'DoC feeling' [28]. The examiner should be mindful of confounding factors such as cranial nerve palsies, central and peripheral causes of quadriplegia, severe spasticity, hypokinesia and bradykinesia, and hypertonus or hypotonus [69].

PICO 4 Should the CRS-R be used to diagnose the level of consciousness in patients with DoC?

Eight studies conducted in different centers and countries including 925 patients were available for inclusion [5,6,20,58,60,61,65,73]. The relative risk for detecting evidence of consciousness with the CRS-R compared to other behavioral assessment methods, including unstructured neurological bedside examination, was 1.45 (95% CI 1.32–1.60; $P < 0.0001$), suggesting that the CRS-R is more sensitive than other scales for detecting signs of consciousness [5,20,58,60,61,63,74,75]. The CRS-R is also the only scale that includes all criteria for MCS (with the notable exception that the CRS-R does not include standardized assessment of appropriate emotional responses as signs of consciousness) [7].

Recommendation: As the CRS-R is freely available, it is recommended that the CRS-R be used to classify the level of consciousness (*moderate evidence, strong recommendation*). This recommendation includes both subacute DoC patients in the intensive care unit (ICU), provided sedation has been stopped (or reduced as much as possible), and chronic patients in rehabilitation and long-term care facilities. The guideline task force group acknowledges that the CRS-R might pose logistical challenges, is time-consuming (15–60 min) and requires experienced personnel. Other assessment methods may be used when time is limited to monitor the patient regularly, keeping in mind their reduced sensitivity for detecting MCS (see PICO 6). The examiner should report the CRS-R subscale scores or use the modified score [76] for diagnosis, as the total score is limited for distinguishing VS/UWS from MCS [76,77]. Confounding factors such as motor, visual, auditory and/or cognitive impairments (e.g. language, memory, flexibility, attention) [78], intubation, sedation and the setting (e.g. presence or absence of relatives) [13,14] should be taken into consideration [69]. One study suggests that the presence of family members might increase chances of detecting visual responses [13].

PICO 5 Should behavioral assessment of the level of consciousness be repeated (and, if so, how often) to diagnose the level of consciousness in patients with DoC?

One study with 123 patients addressed this question [4]. The relative risk for evidence of consciousness with repeated assessments compared to single assessments was 1.36 (95% CI 1.10–1.69; $P = 0.005$). Five assessments over several days (e.g. within 10 days) appear appropriate to evaluate the level of consciousness in patients with prolonged DoC (36% misdiagnosis with a single assessment versus 5% with five assessments) [4]. No data were available for patients in the acute stage. Although daytime variability has rarely been studied systematically [2], inconsistent responsiveness of DoC patients is well known and part of the diagnostic criteria for MCS [2,3,7].

Recommendation: The classification of consciousness levels should never be made based on an isolated assessment (*low evidence, strong recommendation*).

PICO 6 Should the Full Outline of Unresponsiveness (FOUR) score be used to diagnose the level of consciousness in patients with DoC in the ICU?

Three studies compared the FOUR [67] with the Glasgow Coma Scale (GCS) [79] for the classification of DoC patients in the ICU ($n = 313$) [61–63]. Relative risk for evidence of consciousness detected by the FOUR compared to the GCS was 1.46 (95% CI 1.04–2.05; $P = 0.03$).

Recommendation: The task force group recommends that the FOUR score be used to assess the level of consciousness in patients with DoC in the ICU instead of the GCS (*moderate evidence, strong recommendation*). Although less sensitive than the CRS-R, the FOUR score is more convenient for frequent evaluations by clinicians and nursing staff in the ICU, where time is often limited and patients are intubated [61,63]. In contrast to the GCS, the FOUR includes assessment of eye movement, which reduces misdiagnosis of locked-in syndrome and MCS [67] and allows for a more precise distinction between comatose and recovering patients [61–63].

PICO 7 Should the Nociception Coma Scale – Revised (NCS-R) be used to diagnose signs of possible discomfort or nociception in patients with DoC?

No eligible studies were found (i.e. studies comparing the NCS-R with other scales in terms of number of patients detected with pain), although some studies from different centers and countries indicate that the scale may be appropriate for detecting signs of potentially painful condition in DoC [80–87].

Good practice recommendation: It is suggested that the NCS-R is considered for regular monitoring of signs of discomfort (*very low evidence, weak recommendation*). Physicians and nursing staff should screen for signs of discomfort both during manipulation/daily care and at rest [84,88]. It should be kept in mind, however, that the NCS-R is highly dependent on motor abilities, preserved sensory function and whether the patient is intubated [86].

PICO 8 Should the Confusion Assessment Method for the ICU (CAM-ICU) be used to diagnose delirium in DoC patients in the ICU?

No eligible studies on the CAM-ICU in patients with DoC were available. The CAM-ICU appears to be inappropriate to diagnose delirium in comatose, VS/UWS and MCS patients because these patients will automatically be labelled as delirious, which might lead to inappropriate treatment. Delirium scales such as the CAM-ICU [89], the Intensive Care Delirium Screening Checklist [90] or the Confusion Assessment Protocol [91] may be useful to diagnose and monitor delirium in conscious and communicative patients (emerged from MCS; possibly MCS+ with intentional communication). However, in severely brain-injured patients, data on delirium screening tools are sparse [92] and likely to be confounded by sedation, consciousness and cognitive impairments.

Good practice recommendation: It is advised against using the CAM-ICU in DoC patients in the ICU (*very low evidence, weak recommendation*). Rather, it is recommended that patients with severe brain injury who are classified as being delirious benefit from a more detailed neurological examination including the CRS-R. Importantly, one should be aware of possible oversimplification (e.g. categorizing all patients as conscious, delirious or comatose).

Functional neuroimaging

PICO questions 1–3 refer to resting state PET and fMRI, PICO questions 4–6 to passive and active fMRI paradigms. Forty-four publications were included for final analysis [20,36,40–42,48,54,93–128].

> **PICO 1** Should resting state PET be used to diagnose signs of covert consciousness in patients with DoC?

Five publications with a total number of 341 patients were included [20,41,54,93,94]. The relative risk for detection of intrinsic cortical activity in MCS compared to coma or VS/UWS was 3.14 (95% CI 2.40–4.12; $P < 0.0001$). The absolute effect was large (Grading of Evidence tables, Supporting information).

Recommendation: Resting state fluorodeoxyglucose (FDG) PET may be considered as part of multimodal assessment in unresponsive patients (*low evidence, weak recommendation*). Current evidence suggests that resting state PET has a high sensitivity and specificity for the differentiation between VS/UWS and MCS [20,41,54,93,94]. It is necessary to ensure high technical standards, to rule out confounding factors (e.g. diabetes, epilepsy) and to ensure sufficient arousal of the patient during injection of the tracer.

> **PICO 2** Should resting state fMRI be used to diagnose signs of covert consciousness in patients with DoC?

Six publications were identified with 218 patients for final analysis [42,95–99]. The relative risk for detection of intrinsic cortical activity with resting state fMRI in MCS compared to coma or VS/UWS was 2.45 (95% CI 1.81–3.33; $P < 0.0001$).

Recommendation: If a standard clinical (structural) MRI is indicated, it is suggested that a resting state fMRI sequence is added as part of multimodal assessment (*low evidence, weak recommendation*). Resting state fMRI can also provide valuable information in sedated patients but sedation and movement artefacts might confound results [129].

> **PICO 3** Should the default mode network be used to diagnose signs of covert consciousness in DoC patients?

Six articles including 236 patients evaluated the default mode network [42,95–97,99,100]. Relative risk for detection of intrinsic activity in MCS compared to coma or VS/UWS was 2.28 (95% CI 1.70–3.07; $P < 0.0001$).

Recommendation: As stated in PICO 2, it is suggested to add a resting state fMRI sequence as part of multimodal assessment whenever a standard (structural) MRI is indicated; however, the default mode network is just one of several resting state fMRI networks that may be used to complement the behavioral assessment in patients with DoC (*low evidence, weak recommendation*). Other networks to consider include the auditory, salience, executive and fronto-parietal.

> **PICO 4** Should passive fMRI paradigms be used to diagnose signs of covert consciousness in patients with DoC?

Sixteen studies were identified with 313 patients examined using passive fMRI paradigms [40,48,100–113]. Relative risk for detection of preserved connectivity in MCS compared to coma or VS/UWS was 1.69 (95% CI 1.38–2.07; $P = 0.0001$).

Research recommendation: Given the small effect and the heterogeneity of the employed paradigms, it is only suggested that passive fMRI paradigms be used within research protocols (*low evidence, weak recommendation*).

> **PICO 5** Should active fMRI paradigms be used to diagnose signs of covert consciousness in patients with DoC?

Twenty publications including 343 patients were available for analysis [20,35,36,48,101,112,114–127]. Relative risk for command following in MCS compared to coma or VS/UWS was 1.60 (95% CI 1.16–2.20; $P = 0.0037$).

Recommendation: It is suggested that active fMRI paradigms should be considered as part of multimodal assessment in patients without command following at the bedside (*moderate evidence, weak recommendation*). Active fMRI paradigms allow identification of a specific and important group of patients who can follow commands despite appearing completely unresponsive at the bedside (i.e. cognitive motor dissociation). Beware that sedation and cognitive impairment such as language disorders might confound results, and – importantly – absence of command following is not proof of absence of consciousness. It follows that active fMRI paradigms have a high specificity but very low sensitivity for the detection of covert consciousness.

> **PICO 6** Should salient stimuli and/or familiar activities be used to diagnose signs of covert consciousness in patients with DoC examined by fMRI?

Nine studies with 167 patients were included [40,48,103,109–113,116]. Relative risk for preserved intrinsic activity or command following in MCS following salient stimuli compared to coma or VS/UWS was 1.69 (95% CI 1.23–2.32; $P < 0.0011$). Moreover, although data were deemed insufficient for meta-analysis, behavioral and neurophysiological studies suggest that salient stimuli and/or familiar activities may increase sensitivity in active and passive fMRI paradigms compared to non-salient stimuli [111,112].

Recommendation: It is therefore suggested that salient stimuli should be used for examination of DoC patients by fMRI (*very low evidence, weak recommendation*).

EEG-based techniques, including TMS-EEG and evoked potentials

PICO questions 1–3 refer to clinical standard (resting state) EEG, PICO questions 4–6 to consciousness paradigms, including high-density EEG, TMS-EEG and evoked potentials. Thirty publications were included for final analysis [37–39,41,43,54,119,127,130–151].

> **PICO 1** Can visual analysis of clinical standard EEG differentiate coma and VS/UWS from MCS?

Two studies with 117 patients were suitable for analysis [119,130]. Visual EEG analysis includes, amongst other things, background organization, reactivity to stimuli and presence of elements of sleep architecture. Relative risk for signs of covert consciousness suggesting MCS or better with standard EEG compared to clinical examination was 11.25 (95% CI 2.85–44.46; $P = 0.0006$). Of note, this risk ratio was the highest of all our PICO questions.

Recommendation: Visual analysis of clinical standard EEG seems to detect patients with preserved consciousness with high specificity but low sensitivity [119,130] (*low evidence, strong recommendation*). Standard EEG complements behavioral and neuroimaging assessment of DoC. It is critical to rule out non-convulsive status epilepticus. Emphasis should be put on the analysis of EEG background activity and EEG reactivity to external stimuli. A reactive posterior alpha rhythm during wakefulness most probably rules out VS/UWS and is associated with favorable outcome [152]. A flatline EEG of sufficient technical standard in an unsedated patient is incompatible with preserved consciousness.

> **PICO 2** Can non-visual (i.e. numerical) analysis of clinical standard EEG (<32 electrodes) differentiate coma and VS/UWS from MCS?

There were no eligible studies. Quantitative analysis of standard EEG has been insufficiently studied so far.

Research recommendation: Non-visual (i.e. numerical) analysis of standard EEG cannot yet be recommended for the differentiation between VS/UWS and MCS (*very low evidence, weak recommendation*). However, a recent study using machine learning techniques has shown that similar diagnostic performance can be obtained when reducing the number of EEG sensors from high density (256 electrodes) to low density (16 electrodes) [45].

> **PICO 3** Does sleep EEG, as opposed to clinical examination, help to distinguish coma and VS/UWS from MCS?

Six studies with 153 patients were included [119,131–134,153]. Relative risk for signs of covert consciousness suggesting MCS or better with sleep EEG compared to clinical examination was 1.55 (95% CI 1.24 to 1.94; $P = 0.0001$).

Recommendation: It is suggested that sleep EEG be used for the differentiation between VS/UWS and MCS as a part of multimodal assessment (*low evidence, weak recommendation*). The presence of slow-wave sleep [non-rapid-eye-movement (REM) sleep stage 3; relative risk 5.90 (95% CI 2.32–15.01)] or REM sleep [relative risk 4.34 (95% CI 2.11–8.90)] are possibly more accurate for the differentiation between VS/UWS and MCS than sleep spindles [relative risk

(a) COMA RECOVERY SCALE - REVISED						
AUDITORY FUNCTION SCALE						
4 - Consistent Movement to Command						
3 - Reproducible Movement to Command						
2 - Localization to Sound						
1 - Auditory Startle	X	X	X	X	X	X
0 - None						
VISUAL FUNCTION SCALE						
5 - Object Recognition						
4 - Object Localization: Reaching						
3 - Pursuit Eye Movements						
2 - Fixation						
1 - Visual Startle			X			
0 - None	X	X		X	X	X
MOTOR FUNCTION SCALE						
6 - Functional Object Use						
5 - Automatic Motor Response						
4 - Object Manipulation						
3 - Localization to Noxious Stimulation						
2 - Flexion Withdrawal						
1 - Abnormal Posturing	X	X	X	X	X	X
0 - None/Flaccid						
OROMOTOR/VERBAL FUNCTION SCALE						
3 - Intelligible Verbalization						
2 - Vocalization/Oral Movement						
1 - Oral Reflexive Movement	X	X	X	X	X	X
0 - None						
COMMUNICATION SCALE						
2 - Functional: Accurate						
1 - Non-Functional: Intentional						
0 - None	X	X	X	X	X	X
AROUSAL SCALE						
2 - Eye Opening w/o Stimulation						
1 - Eye Opening with Stimulation	X	X	X	X	X	X
0 - Unarousable						
TOTAL SCORE	4	4	5	4	4	4
DIAGNOSIS	UWS	UWS	UWS	UWS	UWS	UWS

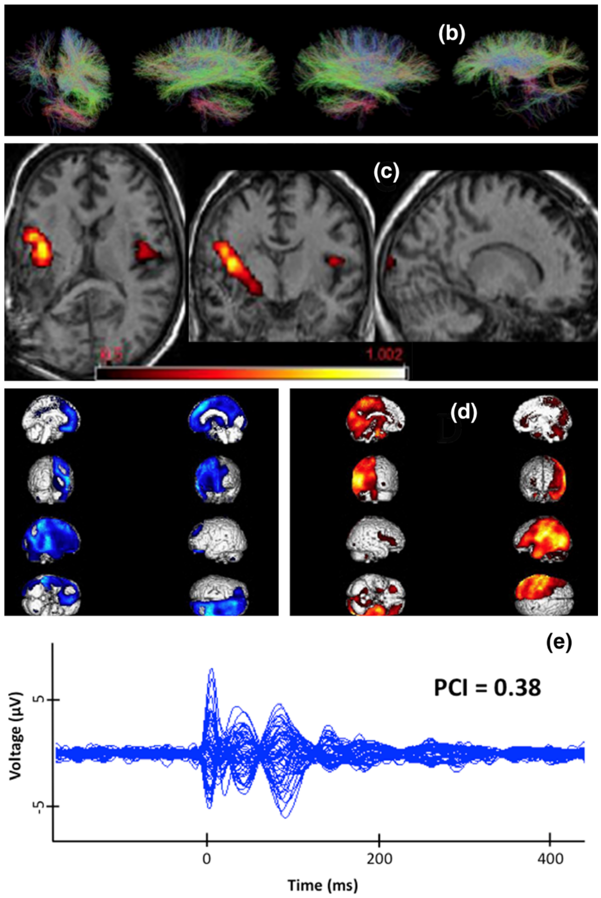

Figure 2 Case example: a 27-year-old woman with a history of focal epilepsy was admitted with headache, confusion and rapid loss of consciousness due to an intracranial hemorrhage from a right parietal arteriovenous malformation. After hematoma evacuation, decompressive hemicraniectomy and prolonged intensive care management, including tracheostomy, intrathecal baclofen pump placement, percutaneous endoscopic gastrostomy and placement of a ventriculo-peritonal shunt, she remained unresponsive and was referred for multimodal consciousness evaluation 13 weeks later. Repeated neurological examinations ($n = 6$) were notable for spontaneous eye opening with preserved blink reflex to visual threat but no fixation or visual pursuit, absence of spontaneous movements other than myoclonic tremor in the right lower limb, auditory startle, stereotyped extensor posturing and grimacing following nociceptive stimuli, and preserved oral reflexes. Her CRS-R scores were consistent with VS/UWS (a). Structural MRI revealed right temporo-parietal cortical atrophy and ischaemic damage to the left cerebral peduncle and mesencephalon (presumably from right-sided mass effect with herniation of the left cerebral peduncle against the tentorium, i.e. Kernohan's notch). Diffusion tensor imaging revealed decreased fractional anisotropy, consistent with axonal damage and decreased fiber intensity in the right cerebral hemisphere (b). On resting state fMRI, the auditory network was relatively preserved (c). PET showed hypometabolism (blue) involving the right hemisphere, including the thalamus, as well as the left prefrontal region, whereas metabolism appeared preserved (red) in the brainstem, the cerebellum and large parts of the left cerebral hemisphere, including the left thalamus (d). Clinical standard EEG revealed right hemispheric background slowing in the theta range and lack of epileptiform activity. Of note, TMS-EEG revealed a perturbational complexity index (PCI) of 0.38 (e), consistent with some degree of preserved consciousness. At the 12-month follow-up the patient remained with severe disability (Glasgow Outcome Scale – Extended score 3) but was clinically in MCS. (Next-of-kin consent obtained. Figures courtesy of Aurore Thibaut, Olivier Bodart, Lizette Heine and Olivia Gosseries from the Coma Science Group, Liège, Belgium.) [Colour figure can be viewed at wileyonlinelibrary.com]

1.78 (95% CI 1.33–2.39)]. Analysis of sleep EEG data by means of machine learning techniques may yield additional diagnostic accuracy [154].

PICO 4 Can high-density EEG (e.g. ≥32 electrodes) with computational techniques, compared to clinical examination, differentiate coma and VS/UWS from MCS?

Six suitable studies were found with a total number of 337 patients [38,41,43,127,134,135]. Relative risk for signs of covert consciousness suggesting MCS or better with high-density EEG compared to clinical examination was 2.21 (95% CI 1.72–2.82; $P < 0.0001$).

Recommendation: It is suggested that quantitative analysis of high-density EEG be considered for the differentiation between VS/UWS and MCS as part of multimodal assessment (*moderate evidence, weak recommendation*). High-density EEG is likely to play a more important role in the future for differentiation between VS/UWS and MCS. Machine learning and similar algorithms for analysis seem promising [155,156]. Active paradigms with high-density EEG (and low-density EEG [38,48]) allow a specific and important group of patients to be identified who can follow commands despite appearing completely unresponsive at the bedside (i.e. cognitive motor dissociation). High-density EEG paradigms appear to have a high specificity but very low sensitivity for the detection of covert consciousness. However, statistical analysis is challenging, and proof of validity is crucial [157,158]. For future research on high-density EEG it is recommended that consciousness paradigms and analysis techniques be refined, including optimizing statistical analysis, rather than maximizing the number of EEG electrodes.

PICO 5 Can cognitive evoked potentials, compared to clinical examination, differentiate coma and VS/UWS from MCS?

Fourteen studies with 1298 patients were eligible for inclusion [37,39,136–145,158,159]. The relative risk for detection of signs of covert consciousness with cognitive evoked potentials compared to clinical examination was 1.49 (95% CI 1.27–1.75; $P < 0.0001$).

Recommendation: Cognitive evoked potentials for the differentiation between VS/UWS and MCS might be considered as part of multimodal assessment (*low evidence, weak recommendation*). P300 seems to differentiate better between VS/UWS and MCS than mismatch negativity. The sensitivity for all cognitive evoked potentials is low, even in healthy subjects [37,39,136–145,158,159]. In addition to visual analysis, evaluation of these potentials should involve statistical analysis including, possibly, machine learning and similar algorithms.

PICO 6 Do EEG paradigms using TMS, as opposed to clinical examination, help to distinguish coma and VS/UWS from MCS?

Six studies with 173 patients were deemed suitable for analysis [54,147–151]. Relative risk for detection of signs of covert consciousness with TMS-EEG compared to clinical examination was 5.40 (95% CI 3.29–8.87; $P < 0.0001$). The absolute effect was large (Grading of Evidence tables, Supporting information).

Recommendation: It is suggested that TMS-EEG should be considered for the differentiation between VS/UWS and MCS as part of multimodal assessment (*low evidence, weak recommendation*). Current evidence suggests that TMS-EEG has a high sensitivity and specificity for the differentiation between VS/UWS and MCS [54,147–151] and is likely to play a more important part in the future.

Discussion

Evidence to support classification of coma and prolonged DoC is still limited but increasing. Importantly, low-cost and easy-to-implement bedside measures can have immediate clinical impact. A few of these have been highlighted, including the importance of probing for voluntary eye movements using a mirror (if necessary after passive eye opening by the examiner); relying on repeated rather than isolated clinical assessments (preferentially using the CRS-R); favoring the FOUR score over the GCS in the acute setting; and visual analysis of standard EEG, including searching for REM and slow-wave sleep patterns. There is a wealth of other clinical bedside markers that were excluded here due to lack of sufficient data but that nevertheless appear promising. These include searching for resistance to eye opening [68], command following using automated pupillometry [160,161], quantitative assessment of visual tracking [12,162], standardized rating of spontaneous motor behavior [70], possibility of oral feeding [163], evidence of circadian rhythms [164], exploitation of vegetative responses such as increased salivation with salient stimuli [165] or modulations of the cardiac cycle [166,167], and sampling of observations made by nursing staff [28].

In contrast to clinical bedside methods, consciousness paradigms involving high-density EEG, PET and fMRI are logistically challenging and require significant technological and computational expertise. However, they enable refined evaluation of consciousness and higher-order cortical function (Fig. 2). Multimodal assessment based on EEG techniques (including TMS-EEG) and neuroimaging is therefore useful to detect covert consciousness, if present, and to avoid misdiagnosis in patients without command following or other signs of consciousness at the bedside. Yet almost all data come from observational single-center studies with well-known biases, including weak power, convenience sampling and patient overlap between studies. Multicenter collaborations are therefore needed, a key issue being external validation of single-center-derived fMRI-, PET- and EEG-based consciousness paradigms [42,44,45]. In the absence of a gold standard for consciousness classification, precise estimates of the sensitivity and specificity of active, passive and resting state EEG- and neuroimaging-based paradigms are impossible. This is an inherent problem of consciousness research. For instance, a patient who is clinically unresponsive but able to follow commands during a fMRI paradigm should be considered conscious, and not a 'false positive'. Serial assessments may increase the diagnostic yield and reveal signs of consciousness in fMRI/PET and EEG paradigms in patients who initially lack such signs [138,146,149].

Recently, the 2018 American Academy of Neurology guideline on DoC has focused on the diagnosis, natural history, prognosis and treatment of prolonged DoC (i.e. at least 28 days after brain injury) [168]. Like its American counterpart, this guideline highlights the necessity of thorough and repeated multimodal evaluations for evidence of preserved consciousness in patients with DoC. In addition, recommendations have been included on coma and acute DoC (i.e. <28 days after brain injury), and a multinational task force group (representing 10 European countries) was brought together to reflect the fact that diagnostic procedures and scientific standards significantly differ across countries [169]. However, it should be kept in mind that the literature on DoC tends to stem from a very limited number of clinical groups, so overlapping patient data are often unavoidable. Although relevant authors were contacted, in most instances it was not possible to retrieve original data and therefore possible patient overlap in our contingency tables cannot be excluded, which is an important limitation. Additional, independent and methodologically robust multicenter studies are certainly needed. Hence, it is hoped that the present guideline might serve as a starting point to improve and share diagnostic methodologies and practice amongst European countries. Of note, network collaboration should be encouraged to support and spread the application of labor-intensive technologies (e.g. centralized data analysis for EEG, fMRI and PET), both for clinical and research purposes.

In conclusion, standardized clinical rating scales such as the CRS-R and the FOUR, including careful inspection of voluntary eye movements, EEG-based techniques and functional neuroimaging (fMRI, PET) should be integrated into a composite reference standard. This means that a given patient should be diagnosed with the highest level of consciousness as revealed by any of the three approaches (clinical, EEG, neuroimaging).

Conflict of interests

The group members declare no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

File S1. Contingency tables.
File S2. Grading of Evidence tables.
File S3. Recommendation tables.
File S4. Figure S1.
File S5. Protocol and appendix.
File S6. List of EAN coma and DoC panel members.

References

1. Kondziella D, Friberg CK, Frokjaer VG, *et al.* Preserved consciousness in vegetative and minimal conscious states: systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 2016; **87:** 485–92.
2. Cortese MD, Riganello F, Arcuri F, *et al.* Coma Recovery Scale – R: variability in the disorder of consciousness. *BMC Neurol* 2015; **15:** 186.
3. Candelieri A, Cortese MD, Dolce G, *et al.* Visual pursuit: within-day variability in the severe disorder of consciousness. *J Neurotrauma* 2011; **28:** 2013–2017.
4. Wannez S, Heine L, Thonnard M, *et al.* The repetition of behavioral assessments in diagnosis of disorders of consciousness. *Ann Neurol* 2017; **81:** 883–889.
5. Schnakers C, Vanhaudenhuyse A, Giacino J, *et al.* Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. *BMC Neurol* 2009; **9:** 35. https://doi.org/10.1186/1471-2377-9-35.
6. van Erp WS, Lavrijsen JCM, Vos PE, *et al.* The vegetative state: prevalence, misdiagnosis, and treatment limitations. *J Am Med Dir Assoc* 2015; **16:** 85.e9–85.e14.
7. Giacino JT, Ashwal S, Childs N, *et al.* The minimally conscious state: definition and diagnostic criteria. *Neurology* 2002; **58:** 349–53.
8. Schnakers C, Perrin F, Schabus M, *et al.* Detecting consciousness in a total locked-in syndrome: an active event-related paradigm. *Neurocase* 2009; **15:** 271–7.
9. Thonnard M, Wannez S, Keen S, *et al.* (2014) Detection of visual pursuit in patients in minimally conscious state: a matter of stimuli and visual plane? *Brain Inj* **28:**1164–1170.
10. Wannez S, Hoyoux T, Langohr T, *et al.* Objective assessment of visual pursuit in patients with disorders of consciousness: an exploratory study. *J Neurol* 2017; **264:** 928–937.
11. Vanhaudenhuyse A, Schnakers C, Bredart S, Laureys S. Assessment of visual pursuit in post-comatose states: use a mirror. *J Neurol Neurosurg Psychiatry* 2008; **79:** 223–223.
12. Trojano L, Moretta P, Loreto V, *et al.* Affective saliency modifies visual tracking behavior in disorders of consciousness: a quantitative analysis. *J Neurol* 2013; **260:** 306–8.

13. Sattin D, Giovannetti AM, Ciaraffa F, *et al*. Assessment of patients with disorder of consciousness: do different Coma Recovery Scale scoring correlate with different settings? *J Neurol* 2014; **261:** 2378–2386.
14. Formisano R, D'Ippolito M, Risetti M, *et al*. Vegetative state, minimally conscious state, akinetic mutism and Parkinsonism as a continuum of recovery from disorders of consciousness: an exploratory and preliminary study. *Funct Neurol* 2011; **26:** 15–24.
15. Estraneo A, Moretta P, Loreto V, *et al*. Late recovery after traumatic, anoxic, or hemorrhagic long-lasting vegetative state. *Neurology* 2010; **75:** 239–245. https://doi.org/10.1212/WNL.0b013e3181e8e8cc.
16. Formisano R, D'Ippolito M, Catani S. Functional locked-in syndrome as recovery phase of vegetative state. *Brain Inj* 2013; **27:** 1332–1332. https://doi.org/10.3109/02699052.2013.809555.
17. Luaute J, Maucort-Boulch D, Tell L, *et al*. Long-term outcomes of chronic minimally conscious and vegetative states. *Neurology* 2010; **75:** 246–252.
18. Hammond FM, Giacino JT, Nakase Richardson R, *et al*. Disorders of consciousness due to traumatic brain injury: functional status ten years post-injury. *J Neurotrauma* 2019; **36:** 1136–1146.
19. Laureys S, Celesia GG, Cohadon F, *et al*. Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. *BMC Med* 2010; **8:** 68.
20. Stender J, Gosseries O, Bruno MA, *et al*. Diagnostic precision of PET imaging and functional MRI in disorders of consciousness: a clinical validation study. *Lancet* 2014; **384:** 514–522.
21. Demertzi A, Jox RJ, Racine E, Laureys S. A European survey on attitudes towards pain and end-of-life issues in locked-in syndrome. *Brain Inj* 2014; **28:** 1209–1215.
22. Kondziella D, Cheung MC, Dutta A. Public perception of the vegetative state/unresponsive wakefulness syndrome: a crowdsourced study. *PeerJ* 2019; **7:** e6575.
23. Gipson J, Kahane G, Savulescu J. Attitudes of lay people to withdrawal of treatment in brain damaged patients. *Neuroethics* 2014; **7:** 1–9.
24. Demertzi A, Ledoux D, Bruno M-A, *et al*. Attitudes towards end-of-life issues in disorders of consciousness: a European survey. *J Neurol* 2011; **258:** 1058–1065.
25. Harvey D, Butler J, Groves J, *et al*. Management of perceived devastating brain injury after hospital admission: a consensus statement from stakeholder professional organizations. *Br J Anaesth* 2018; **120:** 138–145.
26. Turgeon AF, Lauzier F, Simard J-F, *et al*. Mortality associated with withdrawal of life-sustaining therapy for patients with severe traumatic brain injury: a Canadian multicentre cohort study. *CMAJ* 2011; **183:** 1581–8.
27. Ong CJ, Dhand A, Diringer MN. Early withdrawal decision-making in patients with coma after cardiac arrest: a qualitative study of intensive care clinicians. *Neurocrit Care* 2016; **25:** 258–265.
28. Hermann B, Goudard G, Courcoux K, *et al*. Wisdom of the caregivers: pooling individual subjective reports to diagnose states of consciousness in brain-injured patients, a monocentric prospective study. *BMJ Open* 2019; **9:** e026211.
29. van Erp WS, Lavrijsen JCM, van de Laar FA, *et al*. The vegetative state/unresponsive wakefulness syndrome: a systematic review of prevalence studies. *Eur J Neurol* 2014; **21:** 1361–1368.
30. Rohaut B, Eliseyev A, Claassen J. Uncovering consciousness in unresponsive ICU patients: technical, medical and ethical considerations. *Crit Care* 2019; **23:** 78.
31. Laureys S, Pellas F, Van Eeckhout P, *et al*. The locked-in syndrome: what is it like to be conscious but paralyzed and voiceless? *Prog Brain Res* 2005; **150:** 495–511.
32. Owen AM, Coleman MR, Boly M, *et al*. Detecting awareness in the vegetative state. *Science* 2006; **313:** 1402.
33. Marino S, Bonanno L, Giorgio A. Functional connectivity in disorders of consciousness: methodological aspects and clinical relevance. *Brain Imaging Behav* 2016; **10:** 604–608.
34. Gosseries O, Di H, Laureys S, Boly M. Measuring consciousness in severely damaged brains. *Annu Rev Neurosci* 2014; **37:** 457–78.
35. Bekinschtein TA, Dehaene S, Rohaut B, *et al*. Neural signature of the conscious processing of auditory regularities. *Proc Natl Acad Sci USA* 2009; **106:** 1672–7.
36. Monti MM, Vanhaudenhuyse A, Coleman MR, *et al*. Willful modulation of brain activity in disorders of consciousness. *N Engl J Med* 2010; **362:** 579–589.
37. Faugeras F, Rohaut B, Weiss N, *et al*. Probing consciousness with event-related potentials in the vegetative state. *Neurology* 2011; **77:** 264–8.
38. Cruse D, Chennu S, Chatelle C, *et al*. Bedside detection of awareness in the vegetative state: a cohort study. *Lancet* 2011; **378:** 2088–94.
39. Lulé D, Noirhomme Q, Kleih SC, *et al*. Probing command following in patients with disorders of consciousness using a brain–computer interface. *Clin Neurophysiol* 2013; **124:** 101–6.
40. Di HB, Yu SM, Weng XC, *et al*. Cerebral response to patient's own name in the vegetative and minimally conscious states. *Neurology* 2007; **68:** 895–9.
41. Chennu S, Annen J, Wannez S, *et al*. Brain networks predict metabolism, diagnosis and prognosis at the bedside in disorders of consciousness. *Brain* 2017; **140:** 2120–2132.
42. Demertzi A, Antonopoulos G, Heine L, *et al*. Intrinsic functional connectivity differentiates minimally conscious from unresponsive patients. *Brain* 2015; **138:** 2619–31.
43. Sitt JD, King J-RR, El Karoui I, *et al*. Large scale screening of neural signatures of consciousness in patients in a vegetative or minimally conscious state. *Brain* 2014; **137:** 2258–2270.
44. Demertzi A, Tagliazucchi E, Dehaene S, *et al*. Human consciousness is supported by dynamic complex patterns of brain signal coordination. *Sci Adv* 2019; **5:** eaat7603.
45. Engemann DA, Raimondo F, King J-R, *et al*. Robust EEG-based cross-site and cross-protocol classification of states of consciousness. *Brain* 2018; **141:** 3179–3192.
46. Tzovara A, Simonin A, Oddo M, *et al*. Neural detection of complex sound sequences in the absence of consciousness. *Brain* 2015; **138:** 1160–1166.
47. Schiff ND. Cognitive motor dissociation following severe brain injuries. *JAMA Neurol* 2015; **72:** 1413.
48. Edlow BL, Chatelle C, Spencer CA, *et al*. Early detection of consciousness in patients with acute severe traumatic brain injury. *Brain* 2017; **140:** 2399–2414.

49. Posner J, Plum F, Saper C. *Plum and Posner's Diagnosis of Stupor and Coma*. Oxford University Press: New York, NY, 2007.
50. Naccache L. Minimally conscious state or cortically mediated state? *Brain* 2018; **141:** 949–960.
51. Kotchoubey B, Vogel D, Lang S, Müller F. What kind of consciousness is minimal? *Brain Inj* 2014; **28:** 1156–63.
52. Bruno M-A, Vanhaudenhuyse A, Thibaut A, *et al*. From unresponsive wakefulness to minimally conscious PLUS and functional locked-in syndromes: recent advances in our understanding of disorders of consciousness. *J Neurol* 2011; **258:** 1373–84.
53. Gosseries O, Zasler ND, Laureys S. Recent advances in disorders of consciousness: focus on the diagnosis. *Brain Inj* 2014; **28:** 1141–1150.
54. Bodart O, Gosseries O, Wannez S, *et al*. Measures of metabolism and complexity in the brain of patients with disorders of consciousness. *NeuroImage Clin* 2017; **14:** 354–362.
55. Bruno MA, Fernández-Espejo D, Lehembre R, *et al*. Multimodal neuroimaging in patients with disorders of consciousness showing 'functional hemispherectomy'. *Prog Brain Res* 2011; **193:** 323–33.
56. Leone MA, Keindl M, Schapira AH, *et al*. Practical recommendations for the process of proposing, planning and writing a neurological management guideline by EAN task forces. *Eur J Neurol* 2015; **22:** 1505–1510.
57. Methley AM, Campbell S, Chew-Graham C, *et al*. PICO, PICOS and SPIDER: a comparison study of specificity and sensitivity in three search tools for qualitative systematic reviews. *BMC Health Serv Res* 2014; **14:** 579.
58. Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale – Revised: measurement characteristics and diagnostic utility. *Arch Phys Med Rehabil* 2004; **85:** 2020–2029.
59. Balshem H, Helfand M, Schünemann HJ, *et al*. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011; **64:** 401–406.
60. Estraneo A, Moretta P, De Tanti A, *et al*. An Italian multicentre validation study of the Coma Recovery Scale – Revised. *Eur J Phys Rehabil Med* 2015; **51:** 627–34.
61. Iazeva EG, Legostaeva LA, Zimin AA, *et al*. A Russian validation study of the Coma Recovery Scale – Revised (CRS-R). *Brain Inj* 2018; **33:** 1–8.
62. Bruno M-A, Ledoux D, Lambermont B, *et al*. Comparison of the full outline of UnResponsiveness and Glasgow Liege Scale/Glasgow Coma Scale in an intensive care unit population. *Neurocrit Care* 2011; **15:** 447–453. https://doi.org/10.1007/s12028-011-9547-2.
63. Schnakers C, Majerus S, Giacino J, *et al*. A French validation study of the Coma Recovery Scale – Revised (CRS-R). *Brain Inj* 2008; **22:** 786–792.
64. Wannez S, Vanhaudenhuyse A, Laureys S, Brédart S. Mirror efficiency in the assessment of visual pursuit in patients in minimally conscious state. *Brain Inj* 2017; **31:** 1429–1435. https://doi.org/10.1080/02699052.2017.1376755.
65. Tamashiro M, Rivas ME, Ron M, *et al*. A Spanish validation of the Coma Recovery Scale – Revised (CRS-R). *Brain Inj* 2014; **28:** 1744–1747.
66. Smith E, Delargy M. Locked-in syndrome. *BMJ* 2005; **330:** 406–409.
67. Wijdicks EFM, Bamlet WR, Maramattom BV, *et al*. Validation of a new coma scale: the FOUR score. *Ann Neurol* 2005; **58:** 585–593.
68. van Ommen HJ, Thibaut A, Vanhaudenhuyse A, *et al*. Resistance to eye opening in patients with disorders of consciousness. *J Neurol* 2018;**265:** 1376–1380.
69. Chatelle C, Bodien YG, Carlowicz C, *et al*. Detection and interpretation of impossible and improbable Coma Recovery Scale – Revised scores. *Arch Phys Med Rehabil* 2016; **97:** 1295–1300.e4.
70. Pincherle A, Jöhr J, Chatelle C, *et al*. Motor behavior unmasks residual cognition in disorders of consciousness. *Ann Neurol* 2019; **85:** 443–447.
71. Formisano R, Bivona U, Penta F, *et al*. Early clinical predictive factors during coma recovery. *Acta Neurochir Suppl* 2005; **93:** 201–5.
72. Pignat J-M, Mauron E, Johr J, *et al*. Outcome prediction of consciousness disorders in the acute stage based on a complementary motor behavioural tool. *PLoS One* 2016; **11:** e0156882.
73. Schnakers C, Ledoux D, Majerus S, *et al*. Diagnostic and prognostic use of bispectral index in coma, vegetative state and related disorders. *Brain Inj* 2008; **22:** 926–31.
74. Lovstad M, Froslie K, Giacino J, *et al*. Reliability and diagnostic characteristics of the JFK Coma Recovery Scale – Revised: exploring the influence of raters level of experience. *J Head Trauma Rehabil* 2010; **25:** 349–356.
75. Seel RT, Sherer M, Whyte J, *et al*. Assessment scales for disorders of consciousness: evidence-based recommendations for clinical practice and research. *Arch Phys Med Rehabil* 2010; **91:** 1795–1813.
76. Sattin D, Minati L, Rossi D, *et al*. The Coma Recovery Scale Modified Score: a new scoring system for the Coma Recovery Scale – Revised for assessment of patients with disorders of consciousness. *Int J Rehabil Res* 2015; **38:** 350–356.
77. Bodien YG, Carlowicz CA, Chatelle C, Giacino JT. Sensitivity and specificity of the Coma Recovery Scale – Revised total score in detection of conscious awareness. *Arch Phys Med Rehabil* 2016; **97:** 490-492.e1.
78. Schnakers C, Bessou H, Rubi-Fessen I, *et al*. Impact of aphasia on consciousness assessment: a cross-sectional study. *Neurorehabil Neural Repair* 2015; **29:** 41–7.
79. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet* 1974; **2:** 81–84.
80. Chatelle C, De Val M-D, Catano A, *et al*. Is the Nociception Coma Scale – Revised a useful clinical tool for managing pain in patients with disorders of consciousness? *Clin J Pain* 2016; **32:** 321–326.
81. Schnakers C, Chatelle C, Vanhaudenhuyse A, *et al*. The Nociception Coma Scale: a new tool to assess nociception in disorders of consciousness. *Pain* 2010; **148:** 215–219.
82. Chatelle C, Majerus S, Whyte J, *et al*. A sensitive scale to assess nociceptive pain in patients with disorders of consciousness. *J Neurol Neurosurg Psychiatry* 2012; **83:** 1233–1237.
83. Riganello F, Cortese MD, Arcuri F, *et al*. A study of the reliability of the Nociception Coma Scale. *Clin Rehabil* 2014; **29:** 388–393.

84. Chatelle C, Hauger SL, Martial C, *et al*. Assessment of nociception and pain in participants in an unresponsive or minimally conscious state after acquired brain injury: the relation between the Coma Recovery Scale – Revised and the Nociception Coma Scale – Revised. *Arch Phys Med Rehabil* 2018; **99:** https://doi.org/10.1016/j.apmr.2018.03.009.
85. Vink P, Eskes AM, Lindeboom R, *et al*. Nurses assessing pain with the Nociception Coma Scale: interrater reliability and validity. *Pain Manag Nurs* 2014; **15:** 881–887.
86. Vink P, Lucas C, Maaskant JM, *et al*. Clinimetric properties of the Nociception Coma Scale (– Revised): a systematic review. *Eur J Pain* 2017; **21:** 1463–1474.
87. Formisano R, Contrada M, Aloisi M, *et al*. Nociception Coma Scale with personalized painful stimulation versus standard stimulus in non-communicative patients with disorders of consciousness. *Neuropsychol Rehabil* 2019; 1–12: https://doi.org/10.1080/09602011.2019.1614464.
88. Bagnato S, Boccagni C, Sant'Angelo A, , *et al*. Pain assessment with the revised Nociception Coma Scale and outcomes of patients with unresponsive wakefulness syndrome: results from a pilot study. *Neurol Sci* 2018; **39:** 1073–1077.
89. Ely EW, Margolin R, Francis J, *et al*. Evaluation of delirium in critically ill patients: validation of the confusion assessment method for the intensive care unit (CAM-ICU). *Crit Care Med* 2001; **29:** 1370–1379.
90. Bergeron N, Dubois MJ, Dumont M, *et al*. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. *Intensive Care Med* 2001; **27:** 859–64.
91. Sherer M, Nakase-Thompson R, Yablon SA, Gontkovsky ST. Multidimensional assessment of acute confusion after traumatic brain injury. *Arch Phys Med Rehabil* 2005; **86:** 896–904.
92. Larsen LK, Frokjaer VG, Nielsen JS, *et al*. Delirium assessment in neuro-critically ill patients: a validation study. *Acta Anaesthesiol Scand* 2019; **63:** 352–359.
93. Annen J, Blandiaux S, Lejeune N, *et al*. BCI performance and brain metabolism profile in severely brain-injured patients without response to command at bedside. *Front Neurosci* 2018; **12:** 370.
94. Stender J, Mortensen KN, Thibaut A, *et al*. The minimal energetic requirement of sustained awareness after brain injury. *Curr Biol* 2016; **26:** 1494–1499.
95. Demertzi A, Gómez F, Crone JS, *et al*. Multiple fMRI system-level baseline connectivity is disrupted in patients with consciousness alterations. *Cortex* 2014; **52:** 35–46.
96. Kondziella D, Fisher PM, Larsen VA, *et al*. Functional MRI for assessment of the default mode network in acute brain injury. *Neurocrit Care* 2017; **27:** 401–406.
97. Soddu A, Vanhaudenhuyse A, Bahri MA, *et al*. Identifying the default-mode component in spatial IC analyses of patients with disorders of consciousness. *Hum Brain Mapp* 2012; **33:** 778–96.
98. Crone JS, Schurz M, Höller Y, *et al*. Impaired consciousness is linked to changes in effective connectivity of the posterior cingulate cortex within the default mode network. *NeuroImage* 2015; **110:** 101–109.
99. Rosazza C, Andronache A, Sattin D, *et al*. Multimodal study of default-mode network integrity in disorders of consciousness. *Ann Neurol* 2016; **79:** 841–853.
100. Crone JS, Ladurner G, Höller Y, *et al*. Deactivation of the default mode network as a marker of impaired consciousness: an fMRI study. *PLoS One* 2011; **6:** e26373.
101. Bekinschtein TA, Manes FF, Villarreal M, *et al*. Functional imaging reveals movement preparatory activity in the vegetative state. *Front Hum Neurosci* 2011; **5:** 5.
102. Coleman MR, Rodd JM, Davis MH, *et al*. Do vegetative patients retain aspects of language comprehension? Evidence from fMRI. *Brain* 2007; **130:** 2494–2507.
103. Coleman MR, Davis MH, Rodd JM, *et al*. Towards the routine use of brain imaging to aid the clinical diagnosis of disorders of consciousness. *Brain* 2009; **132:** 2541–52.
104. Fernandez-Espejo D, Junque C, Vendrell P, *et al*. Cerebral response to speech in vegetative and minimally conscious states after traumatic brain injury. *Brain Inj* 2008; **22:** 882–890.
105. Heelmann V, Lippert-Grüner M, Rommel T, Wedekind C. Abnormal functional MRI BOLD contrast in the vegetative state after severe traumatic brain injury. *Int J Rehabil Res* 2010; **33:** 151–7.
106. Kremer S, Nicolas-Ong C, Schunck T, *et al*. Usefulness of functional MRI associated with PET scan and evoked potentials in the evaluation of brain functions after severe brain injury: preliminary results. *J Neuroradiol* 2010; **37:** 159–66.
107. Li L, Jiang W, Xiong L, *et al*. Brain response to thermal stimulation predicts outcome of patients with chronic disorders of consciousness. *Clin Neurophysiol* 2014; **126:** 1539–1547.
108. Nigri A, Nava S, Sattin D, *et al*. Central olfactory processing in patients with disorders of consciousness. *Eur J Neurol* 2015; **23:** 605–612.
109. Nigri A, Catricalà E, Ferraro S, *et al*. The neural correlates of lexical processing in disorders of consciousness. *Brain Imaging Behav* 2017; **11:** 1526–1537.
110. Okumura Y, Asano Y, Takenaka S, *et al*. Brain activation by music in patients in a vegetative or minimally conscious state following diffuse brain injury. *Brain Inj* 2014; **9052:** 1–7.
111. Qin P, Di H, Liu Y, *et al*. Anterior cingulate activity and the self in disorders of consciousness. *Hum Brain Mapp* 2010; **31:** 1993–2002. https://doi.org/10.1002/hbm.20989.
112. Sharon H, Hassin D, Giladi N, *et al*. Emotional processing of personally familiar faces in the vegetative state. *PLoS One* 2013; **8:** e74711.
113. Wang F, Huang W, Nie Y, *et al*. Cerebral response to subject's own name showed high prognostic value in traumatic vegetative state. *BMC Med* 2015; **13:** 1–13.
114. Bardin JC, Schiff ND, Voss HU. Pattern classification of volitional functional magnetic resonance imaging responses in patients with severe brain injury. *Arch Neurol* 2012; **69:** 176–181.
115. Bardin JC, Fins JJ, Katz DI, *et al*. (2011) Dissociations between behavioural and functional magnetic resonance imaging-based evaluations. *Brain* **134:**769–82.
116. Bick AS, Leker RR, Ben-Hur T, Levin N. Implementing novel imaging methods for improved diagnosis of disorder of consciousness patients. *J Neurol Sci* 2013; **334:** 130–138.

117. Braiman C, Conte MM, Schiff ND, *et al*. Cortical response to the natural speech envelope correlates with neuroimaging evidence of cognition in severe brain injury. *Curr Biol* 2018; **28:** 3833–3839.e3.
118. Chennu S, Finoia P, Kamau E, *et al*. Dissociable endogenous and exogenous attention in disorders of consciousness. *NeuroImage Clin* 2013; **3:** 450–61.
119. Forgacs PB, Conte MM, Fridman EA, *et al*. Preservation of electroencephalographic organization in patients with impaired consciousness and imaging-based evidence of command-following. *Ann Neurol* 2014; **76:** 869–79.
120. Gibson RM, Gonzalez-Lara LE, FernÃ¡ndez-Espejo D, *et al*. Multiple tasks and neuroimaging modalities increase the likelihood of detecting covert awareness in patients with disorders of consciousness. *Front Hum Neurosci* 2014; **8:** 1–9.
121. Gibson RM, Chennu S, Fernández-Espejo D, *et al*. Somatosensory attention identifies both overt and covert awareness in disorders of consciousness. *Ann Neurol* 2016; **80:** 412–423.
122. Haugg A, Cusack R, Gonzalez-Lara LE, *et al*. Do patients thought to lack consciousness retain the capacity for internal as well as external awareness? *Front Neurol* 2018; **9:** 1–13.
123. Monti MM, Rosenberg M, Finoia P, *et al*. Thalamo-frontal connectivity mediates top-down cognitive functions in disorders of consciousness. *Neurology* 2015; **84:** 167–73.
124. Rodriguez Moreno D, Schiff ND, Giacino J, *et al*. A network approach to assessing cognition in disorders of consciousness. *Neurology* 2010; **75:** 1871–8.
125. Vogel D, Markl A, Yu T, *et al*. Can mental imagery functional magnetic resonance imaging predict recovery in patients with disorders of consciousness? *Arch Phys Med Rehabil* 2013; **94:** 1891–1898.
126. Huang Z, Dai R, Wu X, *et al*. The self and its resting state in consciousness: an investigation of the vegetative state. *Hum Brain Mapp* 2014; **35:** 1997–2008.
127. Curley WH, Forgacs PB, Voss HU, *et al*. Characterization of EEG signals revealing covert cognition in the injured brain. *Brain* 2018; **141:** 1404–1421.
128. Golkowski D, Merz K, Mlynarcik C, *et al*. Simultaneous EEG–PET–fMRI measurements in disorders of consciousness: an exploratory study on diagnosis and prognosis. *J Neurol* 2017; **264:** 1986–1995.
129. Kirsch M, Guldenmund P, Ali Bahri M, *et al*. Sedation of patients with disorders of consciousness during neuroimaging: Effects on resting state functional brain connectivity. *Anesth Analg* 2017; **124**(2)**:** 588–598. https://doi.org/10.1213/ANE.0000000000001721
130. Estraneo A, Loreto V, Guarino I, *et al*. Standard EEG in diagnostic process of prolonged disorders of consciousness. *Clin Neurophysiol* 2016; **127:** 2379–2385.
131. Cologan V, Drouot X, Parapatics S, *et al*. Sleep in the unresponsive wakefulness syndrome and minimally conscious state. *J Neurotrauma* 2013; **30:** 339–46.
132. de Biase S, Gigli GL, Lorenzut S, *et al*. The importance of polysomnography in the evaluation of prolonged disorders of consciousness: sleep recordings more adequately correlate than stimulus-related evoked potentials with patients' clinical status. *Sleep Med* 2014; **15:** 393–400.
133. Landsness E, Bruno M-A, Noirhomme Q, *et al*. Electrophysiological correlates of behavioural changes in vigilance in vegetative state and minimally conscious state. *Brain* 2011; **134:** 2222–2232.
134. Malinowska U, Chatelle C, Bruno M-A, *et al*. Electroencephalographic profiles for differentiation of disorders of consciousness. *Biomed Eng Online* 2013; **12:** 109.
135. Cruse D, Chennu S, Chatelle C, *et al*. Relationship between etiology and covert cognition in the minimally conscious state. *Neurology* 2012; **78:** 816–22.
136. Boly M, Garrido MI, Gosseries O, *et al*. Preserved feedforward but impaired top-down processes in the vegetative state. *Science* 2011; **332:** 858–62.
137. de Tommaso M, Navarro J, Ricci K, *et al*. Pain in prolonged disorders of consciousness: laser evoked potentials findings in patients with vegetative and minimally conscious states. *Brain Inj* 2013; **27:** 962–72.
138. Faugeras F, Rohaut B, Weiss N, *et al*. Event related potentials elicited by violations of auditory regularities in patients with impaired consciousness. *Neuropsychologia* 2012; **50:** 403–18.
139. Fischer C, Luaute J, Morlet D. Event-related potentials (MMN and novelty P3) in permanent vegetative or minimally conscious states. *Clin Neurophysiol* 2010; **121:** 1032–1042.
140. Perrin F, Schnakers C, Schabus M, *et al*. Brain response to one's own name in vegetative state, minimally conscious state, and locked-in syndrome. *Arch Neurol* 2006; **63:** 562–569.
141. Risetti M, Formisano R, Toppi J, *et al*. On ERPs detection in disorders of consciousness rehabilitation. *Front Hum Neurosci* 2013; **7:** 775.
142. Rohaut B, Faugeras F, Chausson N, *et al*. Probing ERP correlates of verbal semantic processing in patients with impaired consciousness. *Neuropsychologia* 2015; **66:** 279–292.
143. Schnakers C, Perrin F, Schabus M, *et al*. Voluntary brain processing in disorders of consciousness. *Neurology* 2008; **71:** 1614–20.
144. Kotchoubey B, Lang S, Mezger G, *et al*. Information processing in severe disorders of consciousness: vegetative state and minimally conscious state. *Clin Neurophysiol* 2005; **116:** 2441–2453.
145. Sergent C, Faugeras F, Rohaut B, *et al*. Multidimensional cognitive evaluation of patients with disorders of consciousness using EEG: a proof of concept study. *NeuroImage Clin* 2017; **13:** 455–469.
146. King JR, Faugeras F, Gramfort A, *et al*. Single-trial decoding of auditory novelty responses facilitates the detection of residual consciousness. *NeuroImage* 2013; **83:** 726–38.
147. Casali AG, Gosseries O, Rosanova M, *et al*. A theoretically based index of consciousness independent of sensory processing and behavior. *Sci Transl Med* 2013; **5:** 198ra105.
148. Casarotto S, Comanducci A, Rosanova M, *et al*. Stratification of unresponsive patients by an independently validated index of brain complexity. *Ann Neurol* 2016; **80:** 718–729.
149. Rosanova M, Gosseries O, Casarotto S, *et al*. Recovery of cortical effective connectivity and recovery of consciousness in vegetative patients. *Brain* 2012; **135:** 1308–20.

150. Ragazzoni A, Pirulli C, Veniero D, *et al*. Vegetative versus minimally conscious states: a study using TMS-EEG, sensory and event-related potentials. *PLoS One* 2013; **8:** e57069.
151. Bodart O, Fecchio M, Massimini M, *et al*. Meditation-induced modulation of brain response to transcranial magnetic stimulation. *Brain Stimul* 2018; **11:** 1397–1400.
152. Azabou E, Navarro V, Kubis N, *et al*. Value and mechanisms of EEG reactivity in the prognosis of patients with impaired consciousness: a systematic review. *Crit Care* 2018; **22:** 184.
153. Pavlov YG, Gais S, Müller F, *et al*. Night sleep in patients with vegetative state. *J Sleep Res* 2017; **26:** 629–640.
154. Wielek T, Lechinger J, Wislowska M, *et al*. Sleep in patients with disorders of consciousness characterized by means of machine learning. *PLoS One* 2018; **13:** e0190458.
155. Claassen J, Doyle K, Matory A, *et al*. Detection of brain activation in unresponsive patients with acute brain injury. *N Engl J Med* 2019; **380:** 2497–2505.
156. King JR, Sitt JD, Faugeras F, *et al*. Information sharing in the brain indexes consciousness in noncommunicative patients. *Curr Biol* 2013; **23:** 1914–1919.
157. Goldfine AM, Bardin JC, Noirhomme Q, *et al*. Reanalysis of 'Bedside detection of awareness in the vegetative state: a cohort study'. *Lancet* 2013; **381:** 289–91.
158. Cruse D, Chennu S, Chatelle C, *et al*. Reanalysis of 'Bedside detection of awareness in the vegetative state: a cohort study' – authors' reply. *Lancet* 2013; **381:** 291–292.
159. Steppacher I, Eickhoff S, Jordanov T, *et al*. N400 predicts recovery from disorders of consciousness. *Ann Neurol* 2013; **73:** 594–602.
160. Stoll J, Chatelle C, Carter O, *et al*. Pupil responses allow communication in locked-in syndrome patients. *Curr Biol* 2013; **23:** R647–R648.
161. Vassilieva A, Olsen MH, Peinkhofer C, *et al*. Automated pupillometry to detect command following in neurological patients: a proof-of-concept study. *PeerJ* 2019; **7:** e6929.
162. Trojano L, Moretta P, Masotta O, *et al*. Visual pursuit of one's own face in disorders of consciousness: a quantitative analysis. *Brain Inj* 2018; **32:** 1549–1555.
163. Mélotte E, Maudoux A, Delhalle S, *et al*. Is oral feeding compatible with an unresponsive wakefulness syndrome? *J Neurol* 2018; **265:** 954–961.
164. Blume C, Lechinger J, Santhi N, *et al*. Significance of circadian rhythms in severely brain-injured patients. *Neurology* 2017; **88:** 1933–1941.
165. Wilhelm B, Jordan M, Birbaumer N. Communication in locked-in syndrome: effects of imagery on salivary pH. *Neurology* 2006; **67:** 534–5.
166. Raimondo F, Rohaut B, Demertzi A, *et al*. Brain–heart interactions reveal consciousness in noncommunicating patients. *Ann Neurol* 2017; **82:** 578–591.
167. Riganello F, Larroque SK, Bahri MA, *et al*. A heartbeat away from consciousness: heart rate variability entropy can discriminate disorders of consciousness and is correlated with resting-state fMRI brain connectivity of the central autonomic network. *Front Neurol* 2018; **9:** 1–18.
168. Giacino JT, Katz DI, Schiff ND, *et al*. Practice guideline update recommendations summary: Disorders of consciousness. *Neurology* 2018; **91:** 450–460.
169. Formisano R, Giustini M, Aloisi M, *et al*. An international survey on diagnostic and prognostic protocols in patients with disorder of consciousness. *Brain Inj* 2019; **33:** 974–984.