REVIEW

Update on neuroimaging in disorders of consciousness

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Purpose of review

Neuroimaging has acquired a prominent place in the assessment of disorders of consciousness (DoC). Rapidly evolving technologies combined with state-of-the-art data analyses open new horizons to probe brain activity, but selecting appropriate imaging modalities from the plethora of available techniques can be challenging for clinicians. This update reviews selected advances in neuroimaging that demonstrate clinical relevance and translational potential in the assessment of severely brain-injured patients with DoC.

Recent findings

Magnetic resonance imaging and high-density electroencephalography provide measurements of brain connectivity between functional networks, assessments of language function, detection of covert consciousness, and prognostic markers of recovery. Positron emission tomography can identify patients with preserved brain metabolism despite clinical unresponsiveness and can measure glucose consumption rates in targeted brain regions. Transcranial magnetic stimulation and near-infrared spectroscopy are noninvasive and practical tools with promising clinical applications.

Summary

Each neuroimaging technique conveys advantages and pitfalls to assess consciousness. We recommend a multimodal approach in which complementary techniques provide diagnostic and prognostic information about brain function. Patients demonstrating neuroimaging evidence of covert consciousness may benefit from early adapted rehabilitation. Translating methodological advances to clinical care will require the implementation of recently published international guidelines and the integration of neuroimaging techniques into patient-centered decision-making algorithms.

Keywords

coma, diagnosis, disorders of consciousness, neuroimaging, prognosis

INTRODUCTION

Disorders of consciousness (DoC) are a group of rare conditions that encompass a wide range of severe acquired brain injuries. DoC affect a heterogeneous clinical population with varying etiologies, degrees of chronicity, and associated neurological deficits, which poses a challenge to the development of diagnostic, prognostic, and therapeutic guidelines [1,2▪▪,3▪▪]. The lack of rehabilitation infrastructures and trained healthcare professionals as well as the intricate ethico-legal issues in their management further contribute to the uncertain status of these vulnerable patients, who are too often neglected by healthcare systems [4,5].

An accurate diagnosis is the first step toward personalized and optimized care. Diagnostic categories have been established based on clinical characteristics displayed by patients, although the consensual nomenclature and the list of behaviors indicating consciousness are continuously evolving in the light of new evidence [6▪,7▪,8▪,9]. The unresponsive wakefulness syndrome (UWS), also known as the vegetative state, describes patients with

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KEY POINTS

- Neuroimaging is essential in the diagnostic and prognostic assessment of patients with disorders of consciousness.
- Multimodal imaging protocols providing complementary data are recommended by current guidelines to reduce misdiagnosis rates and leverage the strengths of each technique.
- Brain imaging and electrophysiology can monitor a treatment's efficacy and provide surrogate biomarkers of early responsiveness.
- Clinically unresponsive patients with a capacity for covert consciousness can be detected with neuroimaging and may benefit from adapted care plans to promote their recovery.
- Future evidence-based decision-making algorithms should guide the clinician in the use of neuroimaging techniques for brain-injured patients, both at the acute and the chronic stages.

preserved arousal (i.e., eye opening) but absent reproducible signs of consciousness [10–12]. The reappearance of unambiguous but low-level signs of consciousness marks the transition to the minimally conscious state minus (MCS−) [13], whereas the presence of residual language-related behaviors defines the MCS plus (MCS+) [14,15]. Emergence from MCS, and therefore from DoC is attained when a patient regains the ability to functionally communicate or use objects [16]. A substantial percentage of those patients experience ongoing cognitive deficits, and diagnostic criteria for the confusional state after traumatic brain injury were defined recently [17]. The recommended clinical scale to assess these behaviors is the Coma Recovery Scale – Revised [18], which substantially reduces misdiagnosis rates compared to clinical consensus [19]. Complementary behavioral tools have been developed to overcome some of its pitfalls (e.g., its long administration duration) or provide additional information at the bedside (e.g., on pain perception or early motor behaviors) [20–25].

As our understanding of the neural networks underlying consciousness progresses, a growing body of evidence suggests that neurophysiological and neuroimaging measures should be taken into account in the diagnosis of DoC, as recommended in the recent guidelines of the European Academy of Neurology (EAN) and the American Academy of Neurology [1,2■■]. Indeed, it has been demonstrated that a substantial fraction of clinically unresponsive patients displays brain activity suggesting the presence of covert consciousness, which has led to the proposal of new diagnostic taxons (e.g., 'cognitive motor dissociation' [26], 'covert cortical processing' [27], 'MCS*' [28]).

Brain imaging paradigms probing consciousness can be divided into 3 categories:

(1) Active paradigms record willful modulation of brain activity by the subject in response to a command, and in rare cases can be used to achieve communication via brain–computer interfaces [29]. These experiments tend to have a high specificity but a low sensitivity to detect conscious awareness, given the many confounding factors, such as aphasia and fluctuating vigilance.

(2) Passive paradigms measure brain responses to external stimuli without the participation of the subject. Although they assess the ability of a primary sensory brain region to process information, these paradigms do not demonstrate the presence of consciousness, which relies on higher-order associative cortical networks [30].

(3) Resting-state measurements study brain activity in the absence of tasks or stimulations. As they do not depend on active participation of the patients or their ability to perceive external stimulations, they mitigate the influence of common confounding factors, such as hearing or vision impairments. However, emerging insights into the interplay between brain networks at rest are only starting to allow the translation of these paradigms into clinically actionable data [31].

The study of activity and connectivity patterns across specific brain regions has reframed the historical search for 'consciousness hotspots' [32,33], which must now account for the influence of interconnected functional networks essential to the generation and maintenance of consciousness (e.g., the default mode, frontoparietal, ventral and dorsal attention networks, as well as corticothalamic feedback loops and the anterior forebrain mesocircuit).

Neuroimaging or neurophysiological exams are not limited to diagnostic uses, as they provide prognostic indicators of recovery [34■,35,36■■,37■,38], surrogate markers of therapeutic efficacy [39■,40,41■,42] and neural benchmarks of clinical assessments [7■,8■,43]. This review highlights a selection of recent original and review articles identified with focused searches of the literature in MEDLINE, associated references and personal libraries. We review common and emerging neuroimaging techniques that are paving the way for future multimodal frameworks and improved care for patients with DoC.

ELECTROPHYSIOLOGY

Electroencephalography (EEG) is an accessible, portable, and noninvasive tool to probe cortical activity with a high temporal resolution. High-density montages in combination with artificial intelligence, source localization or functional connectivity analyses have opened new avenues in EEG signal processing [44]. The plethora of EEG markers available to date allows the development of multivariate classification techniques driven by machine learning algorithms, which may complement and sharpen the clinician's judgment [45▪▪,46].

Nevertheless, well-established methods such as conventional clinical EEG or event-related potentials (ERPs) remain essential in the initial assessment of unresponsive patients when recorded and interpreted correctly, as highlighted in a review endorsed by the International Federation of Clinical Neurophysiology [3▪▪]. Some ERP components perform better than others to detect consciousness, and the 2020 EAN guidelines consider the P300 more contributive than the mismatch negativity to differentiate between UWS and MCS patients, whereas they underline the relatively low sensitivity of all ERPs [2▪▪]. However, recent evidence indicates that using multisensory ERPs as well as single-subject personalized thresholds improves the accuracy of P300 assessments in chronic DoC patients [47▪]. Moreover, ERPs can be combined with dynamic network connectivity analyses to categorize DoC patients, which has revealed impaired top-down processing and frontoparietal connectivity among chronic UWS compared to MCS patients (in line with previous results [48]), associated with altered middle-to-late ERP components linked to higher-order emotional processing (P3a and late positive potential) [49]. This combined approach illustrates the recent shift in experimental design from single-component ERP recordings to multidimensional assessments of cognitive and speech processes, as recently highlighted in a comprehensive review [50▪].

By comparing activity patterns elicited by a passive movie-watching task, EEG may provide a practical and naturalistic bedside tool to detect covert cortical processing in chronic unresponsive patients [51▪]. Most previous EEG-based protocols to identify cognitive motor dissociation have used active tasks requiring willful modulation of brain activity, and this novel individualized paradigm might be less affected by attentional confounding factors [36▪▪,52–54]. Similarly, EEG brain activation to spoken commands can be identified in the acute phase using machine learning and predict functional outcomes at 12 months [36▪▪]. These results highlight the prime importance of language function in the recovery of DoC patients, but common confounding factors such as endotracheal tubes or aphasia represent major hurdles to assess speech in this population. To address this issue, a variety of EEG methods have been developed to record the cortical tracking of speech [37▪,55,56], and support vector machine automated classifiers may provide an unbiased alternative to human-based assessments [57▪].

Additionally, EEG can be used to assess the integrity of sleep-wake cycles over 24-h recordings and identify early polysomnographic signs of recovery [58]. The presence of sleep spindles has been previously associated with neuroimaging evidence of covert consciousness [59], but further advances in sleep data analysis will be necessary to translate this technique to the clinic, as the sleep architecture of DoC patients differs significantly from normal sleep-wake patterns and shows an important heterogeneity [60▪].

Combined with transcranial magnetic stimulation, EEG can be used to characterize the brain's neural response to magnetic perturbation [61]. This diagnostic measure, which reliably distinguishes between different levels of consciousness and detects covert consciousness [62▪], was found to correlate with subcortical atrophy [63]. It also provides a singular opportunity to study mechanistic changes (e.g., decreased evoked slow-activity) induced by concomitant treatment such as transcranial electrical stimulation [39▪].

EEG measures such as alpha power, variability, or reactivity have demonstrated prognostic value in the short-to-medium term, but data on long-term recovery are lacking [38,64▪]. Initial insights indicate that high-density EEG functional connectivity assessments based on graph theory in prolonged DoC could outperform clinical predictions on 2-year outcomes [34▪]. Future diagnostic and prognostic methods may increase their accuracy by integrating complementary spectral, complexity, and connectivity measures into multivariate machine learning models [46].

In summary, a combination of novel personalized paradigms, multisensory stimulations and state-of-the-art data analysis methods are setting the stage for future clinical decision-making pipelines based on sequential complementary neurophysiological assessments [3▪▪] (e.g., as proposed in Fig. 1).

POSITRON EMISSION TOMOGRAPHY

Resting-state fluorodeoxyglucose positron emission tomography (FDG-PET) plays an important role in the multimodal assessment of patients with DoC, as it provides a minimally invasive measure of glucose uptake across the whole brain. It also conveys the

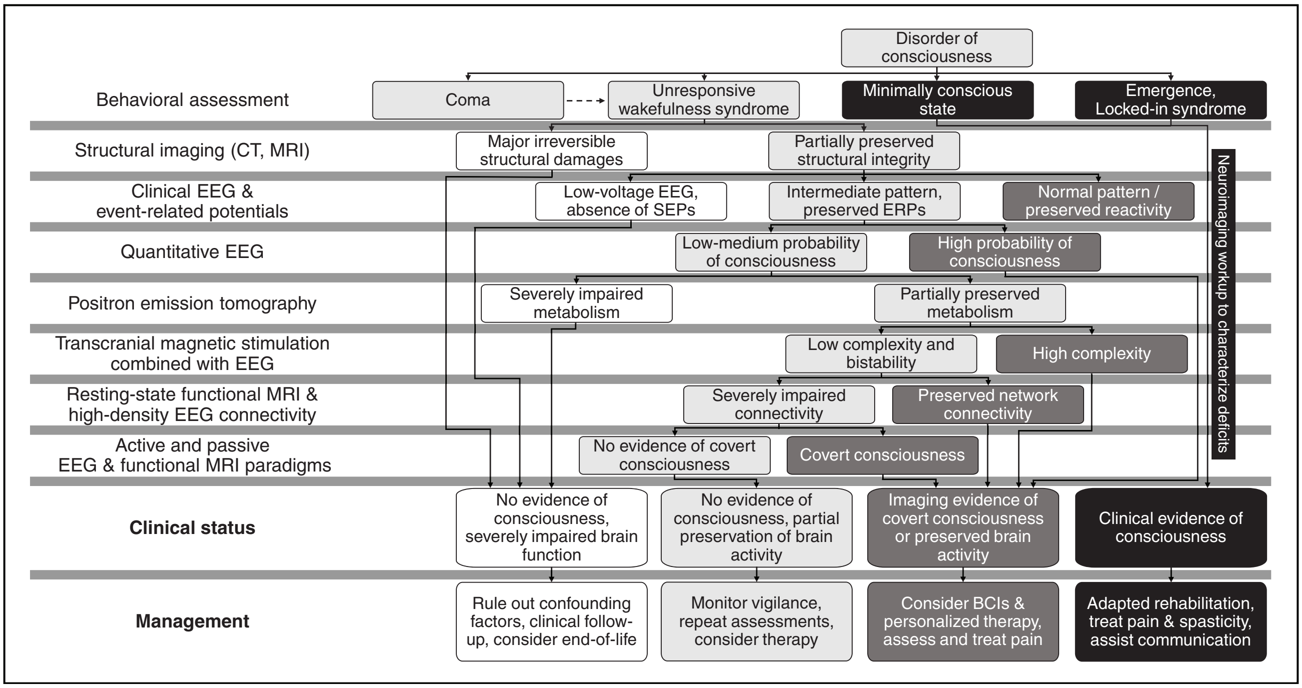

FIGURE 1. Illustrative multimodal decision tree guiding diagnostic exams for patients with disorders of consciousness. A sequential approach is proposed to optimize the allocation of neuroimaging resources, improve the detection rate of covert consciousness and guide the selection of therapies. White boxes indicate patients with severely impaired brain activity and poor prognosis; Light grey boxes indicate patients with uncertain capacity for consciousness, or mismatching neuroimaging results (e.g., unresponsive patient with preserved brain metabolism but impaired connectivity). Dark grey boxes indicate patients with neuroimaging-based evidence of consciousness or preserved brain activity compatible with conscious processing. Black boxes indicate patients with clinical signs of consciousness. CT, computerized tomography; MRI, magnetic resonance imaging; EEG, electroencephalography; SEPs, somatosensory evoked potentials; ERPs, event-related potentials; BCIs, brain–computer interfaces. Inspired by [100] and [3■■].

advantage of reporting brain activity that occurred shortly before the scan, which minimizes the influence of sedation on the interpretability of the data [65].

The recent EAN guidelines underline the high sensitivity and high specificity of FDG-PET to differentiate UWS from MCS patients, when optimal technical conditions are met [2■■]. Emerging evidence also shows that a significant proportion of unresponsive patients demonstrate resting-state cerebral metabolic rates compatible with consciousness, a condition termed ‘nonbehavioral MCS’ or ‘MCS*’ [66,67]. Similar to the terms ‘cognitive motor dissociation’ [26] and ‘covert cortical processing’ [27] (clinically UWS or MCS− patients with appropriate brain response to active and passive paradigms, respectively), this term marks the emergence of a new nomenclature based on neuroimaging criteria, which reflects the growing importance of paraclinical assessments in the appraisal of consciousness [6■]. These considerations call into question the gold-standard status of behavioral diagnosis, as covert cognitive processing missed by standardized clinical scales might be more frequent than previously thought [68]. For instance, the heartbeat-evoked response, an EEG measure of perceptual and self-consciousness, was found to correlate better with FDG-PET-based diagnosis than behavioral diagnosis, which could indicate an ability to probe covert consciousness better than overt consciousness [69].

Although whole-brain metabolism provides a global measure of glucose consumption, FDG-PET data also offer the possibility to perform regional analyses and study local metabolism in key areas for a particular function [70]. Using this approach, a study recently showed higher metabolic rates among MCS+ compared to MCS− patients in the left middle temporal cortex, a key region for semantic language processing [71■].

Beyond its utility to diagnose levels of consciousness, FDG-PET can be used to provide a neural benchmark for clinical observations. UWS patients confirmed by brain hypometabolism systematically obtained low scores on the Nociception Coma Scale

– Revised (a validated clinical scale to assess pain perception in DoC patients), whereas their regional metabolism in the left insula was lower than for patients who displayed a potential capacity to perceive pain [43].

Despite its limited accessibility and its irradiating nature, FDG-PET has become a cornerstone in the assessment of consciousness. By detecting patients with relative preservation of brain metabolism in the early stage, FDG-PET could reduce misdiagnosis rates and lower the risk of premature withdrawal of life-sustaining therapy. In addition, FDG-PET can be used as a pharmacodynamic biomarker of targeted therapeutic interventions [72], thereby facilitating the development of new therapies aimed at promoting recovery of consciousness.

MAGNETIC RESONANCE IMAGING

Structural magnetic resonance imaging (MRI) offers a three-dimensional high-resolution characterization of the grey and white matter alterations following acquired brain injury, whereas functional MRI (fMRI) investigates neural activity at rest or in response to passive and active paradigms. Recent analytic methods have opened new avenues in the characterization of injured brain tissue (e.g., lesion mapping, morphometry, diffusion tensor imaging) and impaired functional connectivity across brain networks [73▪▪]. These methods have evolved from static approaches to dynamic connectivity analyses that measure temporally varying patterns of brain activity at rest [74,75].

The increase in spatial resolution provided by new-generation 7T scanners will allow the future development of new microstructural analyses, high-resolution connectometry and graph-theoretic network topology studies to track disease progression and recovery, as shown in a recent case report [76]. Meanwhile, diffusion tensor imaging has already shown potential as a prognostic marker for unconscious patients after a cardiac arrest, accurately predicting clinical outcomes at 6 months [35]. This technique has also revealed disruption of white matter connections within subcortical and cortical networks in acute and chronic DoC patients, correlating with clinical severity [77,78▪,79,80].

The increasing number of publications reporting resting-state fMRI measures in DoC patients reflects the prolific contribution of this modality to our understanding of the brain properties that are necessary to sustain consciousness. Using cutting-edge functional connectivity analyses, recent studies on DoC patients have measured a number of changes in time-delay latency [81], large-scale network topological properties [82], fractal dimension of networks [83], and variance of network metrics and dynamics [75,84], compared to healthy controls. Decreased dynamic functional connectivity has been observed in the sensory and somatomotor networks, and abnormal network properties correlate with behavioral scores [85,86], which demonstrates the potential clinical relevance of these surrogate biomarkers. Additionally, networks displayed reduced functional diversity and informational capacity in patients with DoC, along with reduced integration of the posterior default mode network with the rest of the brain [87▪▪]. Unconsciousness was also associated with changes in the spontaneous hemodynamic response in the precuneus and posterior cingulate areas. This newly proposed measure allows investigators to study local metabolic changes and reflects the neurovascular coupling mechanism [88▪].

fMRI can also provide insightful information when combined with passive stimulation, recently demonstrating that listening to the patient's favorite music generated increased connectivity compared to rest [89▪]. Finally, fMRI-based active communication paradigms have not reached clinical implementation yet, but a simpler hand-raising motor task was able to detect appropriate brain activation in motor areas among DoC patients whose outcomes were more favorable than fMRI-unreactive patients [90].

MRI has advanced understanding of consciousness processes, through both structural quantitative methods and functional characterization of brain networks. However, its low accessibility, repeatability and its sensitivity to motion artifacts are major hurdles, and it has faced difficulties to translate mechanistic insights into clinically relevant information. The EAN guidelines on neuroimaging recommend the addition of fMRI sequences only in cases where a structural MRI is already indicated, and they highlight sedation and movement as confounding factors. Nevertheless, the guidelines acknowledge that active fMRI paradigms can detect cognitive motor dissociation with a high specificity and a low sensitivity, the latter possibly increased when using salient or familiar stimuli [2▪▪].

FUNCTIONAL NEAR-INFRARED SPECTROSCOPY

Functional near-infrared spectroscopy records the cerebral hemodynamic response in real-time and provides a safe, portable and noninvasive alternative to the logistical constraints of fMRI. It has been proposed as a feasible modality to develop brain-computer interfaces for noncommunicative patients. A recent study has achieved relatively accurate communication with healthy controls instructed to imagine playing tennis for 'yes' and stay relaxed for 'no', by decoding their neural response with support vector machine classifiers [91]. Additionally, concurrent analysis of resting-state near-infrared spectroscopy and clinical EEG allows to measure neurovascular coupling. Using this approach in the intensive care unit, unsupervised learning models were able to distinguish between patients in different states of consciousness and successfully identify those who later failed to recover [92▪]. Functional near-infrared spectroscopy is thus a promising and practical neuroimaging modality that may reveal future groundbreaking applications for patients with DoC, but rigorous assessment of its reliability and further development of its clinical applications are necessary.

MULTIMODAL STUDIES

An increasing number of experimental protocols are using multimodal measures to investigate brain function in DoC. As each imaging modality suffers from inherent limitations, the parallel assessment of DoC patients with different devices increases the diagnostic accuracy and the likeliness to detect covert consciousness [93▪▪]. These multimodal studies also shed light on the intricate relationship between independent neuroimaging biomarkers, as illustrated by the recent finding that EEG power spectra correlate with subcortical atrophy measured by structural MRI [94▪]. Recent studies have also employed combined modalities to pinpoint the neural correlates of a specific behavior. Differences in brain activity between patients with visual pursuit and those with only a reflexive visual blink were demonstrated concurrently by EEG (N2/P2 components), MRI (integrity of optic radiations and primary visual cortex) and FDG-PET (calcarine cortex and lingual gyrus metabolism) [95▪]. Similarly, unresponsive patients able to localize auditory stimuli were found to have increased fMRI connectivity between frontoparietal and visual areas, higher alpha-band EEG connectivity, and higher levels of brain metabolism than those without auditory localization [7▪]. In another study, the presence of increasingly complex auditory behaviors in patients with DoC correlated with graded preservation of brain function in language-related areas, assessed by auditory evoked potentials, FDG-PET, structural and functional MRI measures [96▪].

CONCLUSION

Neuroimaging techniques have become fundamental components of the assessment of a brain-injured patient. Each modality possesses its strengths and limitations, and we advocate the development of multimodal protocols in which complementary data are used to increase diagnostic accuracy, develop prognostic models and identify the neural basis for conscious behaviors [97▪▪]. To translate experimental results into actionable tools for clinicians, we highlight the need to implement recent guidelines and develop decision-making protocols based on sequential or parallel multimodal tests (Fig. 1) [98▪]. We encourage the use of neuroimaging to better characterize brain processes at the acute and chronic stages after injury, which will lead to the elaboration of personalized therapies. Developing these treatments and assessing their efficacy will benefit from neuroimaging biomarkers, which may reveal evidence of therapeutic responses before behavioral effects are observed [40]. Finally, neuroimaging will play a key role in the systematic detection of patients with a capacity for covert consciousness, for which tailored streamlined care plans will need to be implemented in partnership with caregivers and families [99].

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Conflicts of interest

There are no conflicts of interest.

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■■ of outstanding interest

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This landmark paper provides recommendations on the diagnosis of DoC by a guideline taskforce of 10 international experts appointed by the European Academy of Neurology. Twenty statements are issued following a systematic review of the literature and correspond to research questions elaborated with a Patient, Outcome, Comparator, Outcome (PICO) design, related to behavioral, neurophysiological and neuroimaging assessments.

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This study conducted in the intensive care unit employed machine learning on EEG recordings to detect brain activation in response to spoken commands, among clinically unresponsive patients. The authors reported that 15% of patients were able to modulate their brain activity to command in the first week after brain injury, and these patients had improved functional outcomes.

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