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# The neuroethics of disorders of consciousness: a brief history of evolving ideas

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Neuroethical questions raised by recent advances in the diagnosis and treatment of disorders of consciousness are rapidly expanding, increasingly relevant and yet underexplored. The aim of this thematic review is to provide a clinically applicable framework for understanding the current taxonomy of disorders of consciousness and to propose an approach to identifying and critically evaluating actionable neuroethical issues that are frequently encountered in research and clinical care for this vulnerable population. Increased awareness of these issues and clarity about opportunities for optimizing ethically responsible care in this domain are especially timely given recent surges in critically ill patients with prolonged disorders of consciousness associated with coronavirus disease 2019 around the world.

We begin with an overview of the field of neuroethics: what it is, its history and evolution in the context of biomedical ethics at large. We then explore nomenclature used in disorders of consciousness, covering categories proposed by the American Academy of Neurology, the American Congress of Rehabilitation Medicine and the National Institute on Disability, Independent Living and Rehabilitation Research, including definitions of terms such as coma, the vegetative state, unresponsive wakefulness syndrome, minimally conscious state, covert consciousness and the confusional state.

We discuss why these definitions matter, and why there has been such evolution in this nosology over the years, from Jennett and Plum in 1972 to the Multi-Society Task Force in 1994, the Aspen Working Group in 2002 and the 2018 American and 2020 European Disorders of Consciousness guidelines. We then move to a discussion of clinical aspects of disorders of consciousness, the natural history of recovery and ethical issues that arise within the context of caring for people with disorders of consciousness.

We conclude with a discussion of key challenges associated with assessing residual consciousness in disorders of consciousness, potential solutions and future directions, including integration of crucial disability rights perspectives.

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Abbreviations: DoC = disorders of consciousness; MCS = minimally conscious state; PTCS = post-traumatic confusional state

## Introduction

Neuroethical questions raised by recent advances in the diagnosis and treatment of disorders of consciousness (DoC) are rapidly expanding, increasingly relevant and yet underexplored. The aim of this thematic review is to provide a clinically applicable framework for understanding the current taxonomy of DoC and to propose an approach to identifying and critically evaluating actionable neuroethical issues that are frequently encountered in research and clinical care for this vulnerable population. Increased awareness of these issues and clarity about opportunities for optimizing ethically-responsible care in this domain is especially timely given recent surges in critically ill patients with prolonged DoC associated with coronavirus disease 2019 (COVID-19) around the world.[1–3]

Contemporary debates at the crossroads of the neurology and ethics of consciousness have been presaged by centuries of neuroscientific and philosophical inquiry relating to the content and boundaries of consciousness. Questions such as how something as phenomenologically rich as consciousness emerges from our neural repertoire are at the core of efforts to understand what matters most in the human experience. While these two streams of investigation, the neuroscientific and the philosophical, have proceeded largely in isolation from each other, their ultimate epistemic aims are shared, and impactful insights stand to be gained by examining how key findings of each field may meaningfully inform the other.[4] Integration of philosophical and neuroscientific insights is especially critical as conceptual questions and ethical dilemmas have become increasingly commonplace and consequential in clinical practice and research.

In clinical neurology, concepts surrounding consciousness have been defined and operationalized in a way that forms a separate yet complimentary matrix for thinking about the difficult problems that philosophers have been grappling with for ages. Especially in their role as consultants, neurologists are routinely called upon to assess patients' levels of consciousness, to predict outcomes when consciousness is lost or diminished, to identify opportunities for fostering neurorecovery and to counsel families on what they might expect and how to prepare optimally for possible outcomes. In turn, these assessments and recommendations form the dominant axis around which weighty decisions are made regarding the intensity and duration of care that ought to be offered. Assessments of degrees of consciousness and capacities for recovery figure prominently in decisions to limit or continue life-sustaining treatment, speaking powerfully to the centrality of consciousness to the concept of personhood and to what makes life worth living.[5–7] The prolonged utilization of limited intensive or supportive care resources for patients perceived to have no capacity for additional neurological recovery can also cause moral distress among healthcare providers.[8–10] Viewed in this way, the ethical importance of having clarity on how to approach decisions about life-sustaining therapy becomes imminently apparent. Our discussion here will be especially germane of an incisive formulation of neurology and its ultimate aims by Wilder Penfield, which was affixed to the wall of the Montreal Neurological Institute after his death as a homage to his legacy. Penfield remarked that the 'central aim of neurology is to understand man himself'. In designing the ceiling of the Montreal Neurological Institute entrance hall, Penfield chose to feature the aphorism of Galen that 'I have seen the injured brain healed,' a memorialization that refuted the nihilistic Hippocratic view of brain injury and contextualized the vision of a new era in clinical neuroscience and neurotherapeutics.[11,12] Understanding consciousness, its ethical dimensions and philosophical implications, is at the centre of this enterprise.

We begin with an overview of the field of neuroethics. We then explore nomenclature used in DoC, covering categories proposed by the American Academy of Neurology (AAN), the American Congress of Rehabilitation Medicine (ACRM) and the National Institute on Disability, Independent Living and Rehabilitation Research (NIDILRR), including definitions of terms such as coma, the vegetative state, unresponsive wakefulness syndrome, minimally conscious state (MCS) and post-traumatic confusional state (PTCS). We discuss why these definitions matter and why there has been such evolution in this nosology over the years, from Jennett and Plum in 1972 to the Multi-Society Task Force in 1994, the Aspen Working Group in 2002 and the 2018 American and 2020 European DoC guidelines. We then move to a discussion of clinical aspects of DoC, the natural history of recovery and ethical issues that arise within the context of caring for persons with DoC. We conclude with a discussion of key challenges associated with assessing residual awareness in DoC, potential solutions and future directions, including integration of crucial disability rights perspectives.

## Neuroethics in disorders of consciousness: a road map

Neuroethics is the ethics of neuroscience; that is, what is right and what is wrong in the evaluation or manipulation of the nervous system when conducting research or clinical care in the fields of the neurosciences.[5,13–20] In developing a systematic approach to neuroethics in DoC, it is worthwhile to consider issues as they pertain to and emerge from the principles of biomedical ethics. Questions of how to respect autonomy when the capacities that are prerequisite to autonomy are themselves disordered, as they are in DoC, are especially germane. This principle motivates inquiry into how to improve paradigms of consent, testing and counselling in this uniquely vulnerable and incapacitated population of patients. Considering the principles of beneficence and nonmaleficence, questions relating to the perils of misdiagnosis and misprognostication arise. Additional challenges emerge relating to the ethics of brain–computer interfaces, covert consciousness

(consciousness that is not detectable by bedside examination)[21,22] and disclosure of experimental data. The principle of justice prompts further inquiry into topics surrounding stigma of persons with DoC, equity in access to neurorehabilitation, integration of disability rights perspectives and law, fair distribution of limited resources and disparities in care.[5] Virtue ethics animates consideration of how to design systems and standards of research and care for the DoC population that instill the medical-professional ethos of integrity, compassion, accountability, prudence, trust, truthfulness and equity.[23–26] In addition to these principles, contemporary ethical inquiry is informed by analysis of prior instructive cases (casuistry), consideration of expected utility (consequentialism), analysis of normative obligations and duties (deontology), contractarian approaches, and clinical pragmatism.[27–31] Finally, there are a wide range of intriguing philosophical puzzles relevant to this field, relating to the proper classification of border-zone states of consciousness, the relationship of consciousness and personal identity, how to reconcile the subjectivity of consciousness with our conception of an objective reality and the relationship between neural processes and phenomenal experiences.[4,7,32,33]

At the core of cases in which neurologists are consulted for neuroprognostication in DoC are the fundamental questions of: is the patient conscious, if not, will that change, and if so, how can recovery be catalysed, and ultimately, what will the patient's life look like in the future? Therefore, a clear definition of the term consciousness is essential.

Before examining guideline-driven approaches to answering these questions, a particularly insightful comment found in the introduction of Plum and Posner's classic book on the *Diagnosis of Stupor and Coma*, where some of these diagnostic categories were initially defined, is worth mention. Plum and Posner remark that 'the limits of consciousness are hard to satisfactorily define, and we can only infer the self-awareness of others by their appearance and their acts'.[34]

These difficulties were foreshadowed by what is perhaps the first detailed medical treatise on the topic of DoC by Scottish physician and surgeon John Cheyne (1777–1836; eponymously associated with Cheyne-Stokes respirations) in 1812, entitled 'Cases of Apoplexy and Lethargy: With observations upon the comatose diseases'. In the prefatory remarks, Cheyne detailed that 'it is not my intension to offer any definition ... I do not expect to succeed where great masters have failed ... but as, in a medical treatise it is usual ... I shall begin by presenting ... some faithful sketches'.[35] Cheyne presciently later notes,

> 'I cannot be blind to the imperfect classification of the comata ... such are the disease sometimes treated under the names of carus, cataphora, coma and lethargus ... some of the best writers are not perfectly consistent in their application of these terms ... had the genera of this order been less numerous, the subject would have been less embarrassed; for it appears, upon attentively considering the definition, descriptions, and histories and lethargus, or comatedes, and carus, that they differ not in nature but in intensity; that the same class of patients are affected by all these diseases, and that they flow from the same causes ... there may exist cases concerning which we may be in doubt to which genus they ought to be referred'.[35]

## Philosophical framing

From outside in, the limits of consciousness, the boundaries defining its presence or absence, are notoriously fuzzy. This is both due to the nature of the behavioural methods traditionally used to detect consciousness and the ill-defined and fluctuating nature of consciousness itself. With the exception of the first-person case, wherein one may directly access one's own inner thoughts and mental states, historically consciousness was recognized as only inferable by the appearance and behaviours of others.[36,37] This inferential gap between perceptions of behaviours and ascription of conscious states to others has given rise to numerous philosophical puzzles around 'the problem of other minds'. Contemporary inquiry in philosophy of mind distinguishes between approaches to knowing whether or not another being is conscious and approaches surrounding knowing what the content of that consciousness may be. As we will later turn to, a rapidly evolving set of neuroimaging and electrophysiological techniques may provide tools to augment our ability to detect consciousness with greater precision, especially in borderline cases. These techniques are focused primarily on determining the presence or absence of consciousness in settings of uncertainty. One exception to this is the field of implanted brain–computer interfaces, where there is potential to enable rich efferent communication by people otherwise completely locked-in.[38] These same technologies may, in the future, similarly be used diagnostically, as the restoration of reliable and verifiable communication would remove any lingering question about an individual's consciousness.[39] While these technologies remain imperfect and cannot replace behavioural measures, their ability to detect consciousness missed by behavioural measures challenges longstanding historical and categorical reliance on behavioural measures in the ascription of conscious states, both in clinical practice and in philosophical tradition. Similarly, emerging neurotechnologies and methods of data analysis, particularly when they suggest a level of consciousness that exceeds that detected by behavioural measures, create an important research and clinical dilemma for which explicit guidance would be beneficial to clinicians, researchers, families and ultimately, patients. Pragmatic integration of philosophical insights with clinical categories can aid in grounding perspectives and informing taxonomy.

## Consciousness and its disorders: epistemic and historical considerations

How is consciousness defined? Philosophers and other theorists have debated this topic for centuries. Table 1 takes stock of a range of different theories and definitions proposed by key thinkers and neuroscientists over the years, beginning with Hippocrates. In addition to Western conceptions of consciousness, varied conceptions of consciousness are apparent cross-culturally in both historical non-Western philosophic tracts and in the modern psychological literature.[40–46] While it is beyond the present scope to delve into each of these positions and their history or to provide a comprehensive account of all theories of consciousness, the juxtaposition of these definitions highlights their heterogeneity and underscores the inherently elastic and ill-defined nature of the concept of consciousness, alluded to by Cheyne, Plum and Posner. Surveying the landscape of what we have come to learn about consciousness, it becomes clear that it is not a unitary state but rather a cluster concept that includes a number of interdigitated ingredients; in isolation, each is not sufficient but when variably combined produce a range of states that fall on a spectrum of what we call consciousness, and each of which might be variably disordered across the spectrum of conditions that neurologists are called upon to evaluate.[7] Across definitions, consciousness appears to be subjective, related to experience and serves as a grounds for the possibility of other capacities.

An area of philosophical investigation orthogonal to the question of how to characterize consciousness surrounds how to understand the unity of consciousness; that is, how the individual contents of representational experience are joined (temporally and qualitatively) into a coherent whole.[47] Approaches to this question have emphasized the importance of self-consciousness and cognate theories of personal identity to explain the pervasively conjoint phenomenology of consciousness.[48] Pathological alterations in this remarkable capacity for unified experience through consciousness may be occasionally observed in a range of neurological and psychiatric conditions, including anosognosia for hemiplegia, Anton's syndrome, delusional misidentification syndrome, amnestic syndromes, dissociative and dysmorphic disorders, neurodegenerative conditions, neurodevelopmental conditions, epilepsy, traumatic brain injury and sleep-behaviour disorders, highlighting the relevance of this empirically underexplored concept to clinical practice and neuroscientific inquiry.[49–52]

In examining these widely varied perspectives on the character of consciousness, it becomes apparent that rather than a monotonic, fixed entity, consciousness is more aptly characterized as a cluster concept that consists in a wide array of criss-crossing and malleable dimensions and grounds for experience. While many of these dimensions exist on a continuum, in the process of diagnosis and neuroscientific research, clinicians and researchers require discrete categories as instruments for progress, efficient communication and knowledge-generation.[53–55] Despite its practical necessity, creating instrumental categories of consciousness in the derivation of DoC nosology thus carries the epistemic risk of misleading end-users about the nature of the natural phenomena being described; indeed, rather than 'carving nature at its joints',[56] the process of DoC classification is often normatively and pragmatically laden, as is the case with many other diseases.[7,53,54,57–60]

In clinical neurology, consciousness is conceptualized as encompassing two cardinal elements: wakefulness and awareness. 'Wakefulness' refers to the level of arousal, which is often manifested clinically by eye opening. 'Awareness' refers to the 'contents' of consciousness and is clinically assessed by looking for intentional responses to external stimuli; these responses are taken to be our best surrogate measure for some purposeful internal experience. Different states of the brain, both normal and pathological, can be described with respect to these two elements. These ingredients can become dissociated from one another, as in the vegetative state/unresponsive wakefulness syndrome, where there is wakefulness without awareness, and in the case of rapid eye movement sleep, where there may be awareness without wakefulness. Different clinical entities are encountered in mapping the gradual recovery from coma, and may be illustrated as a function of cognitive and motor capacities.

The return of wakefulness, in the absence of volitional motor behaviour, marks the transition from coma to vegetative state/unresponsive wakefulness syndrome. Passage from vegetative state/unresponsive wakefulness syndrome to the MCS is evidenced by reproducible evidence of voluntary behaviour, which has been operationally defined as including: (i) simple command following; (ii) yes/no responses (regardless of the accuracy thereof); (iii) intelligible verbalization; or (iv) motor or emotional responses occurring in contingent relation to relevant stimuli (such as appropriate visual tracking, sustained fixation, hand squeezing, crying, smiling or laughing in contingent relation to appropriate environmental triggers).[61,62] Emergence from the MCS is marked by the return of functional communication or object use. The confusional state is a condition marked by impairments in attention, memory, orientation and symptom fluctuation and may be accompanied by emotional/behavioural dysregulation, disrupted sleep-wake cycling, and confabulation, delusions and perceptual disturbances.[63,64] We will next examine each of these categories (Fig. 1) in greater detail.

## Coma

Coma derives from the Greek term *kōma* meaning trance or deep sleep.[65] It is an unconscious state characterized by lack of both wakefulness and awareness. As Posner observed, 'very few surviving patients ... remain in eyes-closed coma for more than 10 to 30 days';[34] however, cases of longer-lasting coma have been reported, and in one instance lasting up to 1 year.[66] Those who recover from coma may enter or pass through a vegetative state/unresponsive wakefulness syndrome, a MCS or locked-in syndrome. Multiple scales have been devised for classifying patients with coma.[67–70] The value of these is in providing a simple estimate of a person's level of consciousness. The Glasgow Coma Scale (GCS) was devised to categorize patients with head trauma;[67] however, when used by emergency department physicians, inter-rater agreement is only moderate, and so a detailed qualitative description of neurological exam findings may be of greater utility in tracking a patient's course of recovery.[71] The ascending arousal network, also known as the ascending reticular activating system, is instrumental in maintaining arousal, and when disturbed, coma or other DoC ensue.[72,73] The network is composed of key subcortical neurons and their axonal projections in the rostral brainstem tegmentum, diencephalon, basal forebrain and associated cortical networks, which notably exhibit redundancy, [74,75] a characteristic that permits recovery of consciousness depending on lesion location, extent and severity.[76]

## Distinguishing coma from brain death

Importantly, coma should be distinguished from the state of brain death, which in addition to the absence of wakefulness and awareness entails the irreversible cessation of all brainstem functions, including respiratory drive. As such, the state of brain death has been conceptualized by some as an 'irreversible apneic coma'.[77–79] Areas of ongoing ethical and policy debate include whether the diagnosis of brain death requires demonstrable absence of all functions of the brainstem or the entire brain (including neurohormonal functions of the hypothalamus and pituitary gland), whether to distinguish permanent from irreversible dysfunction,[80,81] how to achieve consistency between prevailing definitions and diagnostic schemata and whether brain death should be regarded as biological death or legal death of the human organism in the presence of ongoing cardiopulmonary function supported by mechanical ventilation or extracorporeal membrane oxygenation.[77–79,82,83]

The Uniform Law Commission is meeting in 2021 to decide whether to recommend that the Uniform Determination of Death Act (UDDA), which was approved as model legislation governing death determination in the USA in 1981, should be revised in response to current controversies.[84,85] While the UDDA currently requires the irreversible cessation of all brain function, the AAN guidelines on brain death do not require the loss of hypothalamic function, which is sometimes present in patients who meet the AAN brain death criteria. Likewise, the Academy of Medical Royal Colleges (UK) standards do not require absence of neurohormonal function for declaration of brain death.[86] There is increasing recognition that these possible discrepancies between or within law and clinical guidelines should be addressed.[77–79,82,83]

## From the vegetative state to unresponsive wakefulness syndrome

The vegetative state is one of preserved wakefulness without awareness. It is characterized by recovery of apparent sleep-wake cycles and signalled by the appearance of periods of eye-opening in an unresponsive patient. The use of the term vegetative in this context has been traced to Aristotle's *De Anima*, where a tripartite distinction is drawn between the faculty of organisms that subserve basic physiological functions (vegetative element), the

Table 1 Selected theoretical approaches to consciousness, presented chronologically

| Year | Theorist | Characterization of consciousness |
|---|---|---|
| 460 BCE | Hippocrates | 'The brain, and from the brain only, arise our pleasures, joys, laughter and jests, as well as our sorrows, pains, griefs and tears. Through it . . . we think, see, hear, and distinguish the ugly from the beautiful, the bad from the good, the pleasant from the unpleasant.' |
| ~450 BCE | Majjhima Nikāya | 'With the arising of formations there is the arising of consciousness . . . consciousness is reckoned by the particular condition dependent upon which it arises.' |
| 400 BCE | Aristotle | 'What is (inanimate) is unaware, while what is (animate) is not unaware . . . While asleep, the critical activities, which include thinking, sensing, recalling and remembering, do not function as they do during wakefulness.' |
| ~100–400 BCE | Dīgha Nikāya | 'Consciousness conditions mind and body.' |
| 40 | Philo | 'Where, in what part does this mind lie hid? Has it received any settled habitation? For some have dedicated it to our head, as the principal citadel, around which all the outward senses have their lairs' |
| 175 | Galen | 'the nerves receive the psychic power (faculty) from the brain . . . The usefulness of the nerves, then, would lie in conveying the power of sensation and motion from its source to the several parts.' |
| 762 | Wang Bing Huangdi Neijing Su Wen | 'Consciousness and movement are brought about by the spirit mechanism . . . The five depots store the essence spirit, the hun-soul, the po-soul, the sentiments, and the mind.' |
| 1111 | Al Ghazali | 'only that which inheres in the senses inheres in the mind.' |
| 1479 | Maimonides | Comprised of 'five faculties; the nutritive/vegetative, the sensitive, the imaginative, the appetitive, and the rational . . . which is a unit, and may be compared to matter in that it likewise has a form, which is reason.' |
| 1489 | Da Vinci | 'appears to reside in the seat of judgement, and the judicial part appears to be in that place where all the senses come together, which is called the 'senso comune.' |
| 1624 | Zhang Jie Bin, Su Wen | 'The origin of the generative qi of all animals that have blood, qi, a heart, and consciousness is stored in the five internal [depots].' |
| 1681 | Descartes | 'Cogito ergo sum'; 'Thinking defines consciousness. A nonthinking, nondreaming state is neither conscious nor alive.' |
| 1781 | Kant | 'A manifold of empirical inner intuition: This thoroughgoing synthetic unity of perceptions is the form of experience; it is nothing less than the synthetic unity of appearances in accordance with concepts.' |
| 1888 | Hume | 'nothing but a bundle or collection of different perceptions, which succeed each other with an inconceivable rapidity, and are in perpetual flux and movement.' |
| 1889 | Herzen | 'The intensity of consciousness is in inverse ratio to the ease and quickness of the central translation of stimulus into action.' |
| 1903 | Moore | 'the moment we try to fix our attention upon consciousness and to see what, distinctly, it is, it seems to vanish . . . Yet it can be distinguished if we look attentively enough, and if we know there is something to look for' |
| 1892 | Hill | 'Consciousness is the string upon which the pearls of sense are strung. Break the string, and the pearls are scattered, but they do not cease to be . . . the 'seat' of consciousness is always the higher co-ordinating centre.' |
| 1915 | Jackson | 'not the outcome of a distinct system in the brain. Rather, consciousness emerges from the operation of the association cortices.' |
| 1921 | Russell | 'We say that we are 'conscious' of what we see and hear, of what we remember, and of our own thoughts and feelings . . . we cannot profess to know what we mean by saying that we are possessed of 'consciousness.' |
| 1921 | Jung | 'Consciousness is the function or activity which maintains the relation of psychic contents to the ego.' |
| 1930 | Husserl | 'All consciousness is consciousness of something.' |
| 1940 | Freud | 'The process of something becoming conscious is above all linked with the perceptions which our sense organs receive from the external world.' |
| 1943 | Sartre | 'Consciousness is a being such that in its being, its being is in question insofar as this being implies a being other than itself.' |
| 1953 | Wittgenstein | 'Human beings . . . are their own witnesses that they have consciousness.' |
| 1969 | Plum and Posner | 'The limits of consciousness are hard to satisfactorily define, and we can only infer the self-awareness of others by their appearance and their acts.' |
| 1972 | Tart | 'Awareness resulting from the brain's functioning.' |
| 1974 | Nagel | 'Fundamentally an organism has conscious mental states if an only if there is something it is like to be that organism-something it is like for the organism. . .the subjective character of experience.' |
| 1977 | Thatcher | 'Process in which information . . . is combined into a unified multidimensional representation of the state of the system and its environment, and integrated with information about memories and the needs of the organism.' |
| 1980 | Block | 'Consciousness is a self-scanning mechanism in the CNS.' |
| 1983 | Churchland | 'a battery of monitoring systems, with varying ranges of activity, and with varying degrees of efficiency,' |
| 1991 | Dennett | 'A matter of a representation exceeding some threshold of activation over the whole cortex or large parts thereof' |
| 1994 | Crick | '1. Not all the operations of the brain correspond to consciousness. 2. Consciousness involves some form of memory, probably a very short term one. 3. Consciousness is closely associated with attention.' |
| 1996 | Chambers | 'The subjective quality of experience . . . there is something it feels like to be a cognitive agent. This internal aspect is conscious experience.' |
| 1998 | Searle | 'It is not possible to give a definition of "consciousness" . . . What I mean by 'consciousness' can best be illustrated by examples.' |
| 1999 | Damasio | 'The unified mental pattern that brings together the object and self.' |
| 2004 | Tonini | 'The [integrated information] theory holds that consciousness is a fundamental property possessed by physical systems having specific causal properties . . . is graded [and] is common among biological organisms.' |
| 2006 | Buzsaki | 'There is not even good agreement what the theory about consciousness would be like.' |
| 2011 | Tye | 'Our consciousness of things . . . serves as a ground or warrant for beliefs about what we experience.' |
| 2014 | Dahaene | 'Consciousness is global information broadcasting within the cortex.' |

See also Supplementary Table 1.

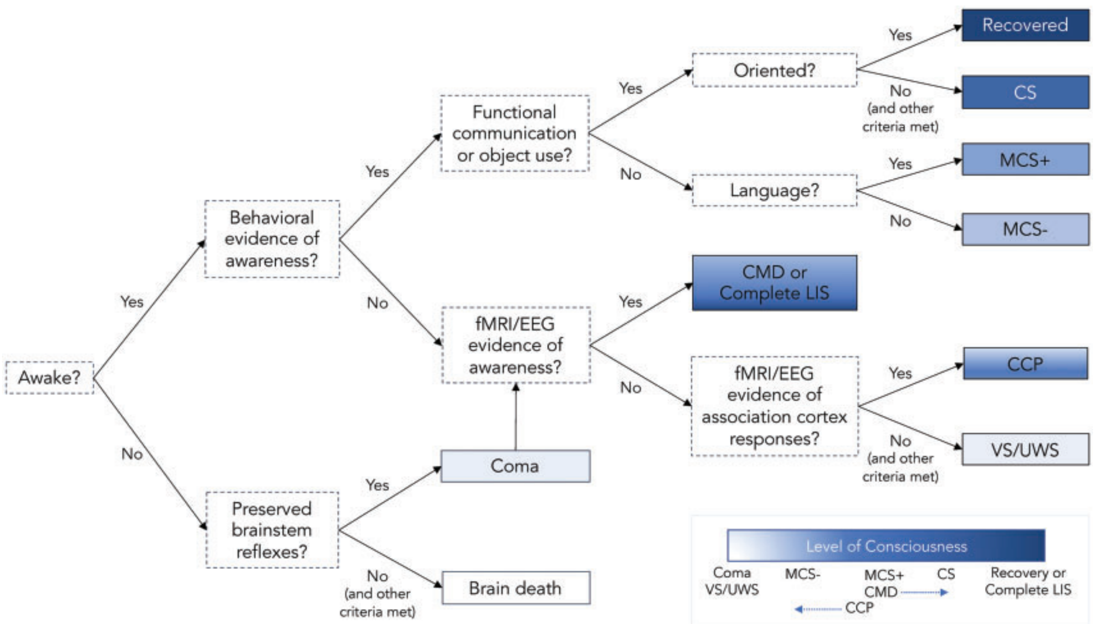


**Figure 1 An operational approach to classifying DoC following brain injury in clinical practice.** Boxes with dashed outline represent decision points in assessment before arriving at a diagnosis. CCP = covert cortical processing; CMD = cognitive motor dissociation; CS = confusional state; LIS = locked-in syndrome; MCS– = minimally conscious state without language function; MCS+ = minimally conscious state with language function; UWS = unresponsive wakefulness syndrome; VS = vegetative state

faculty that subserves emotions and desires (appetitive element) and the faculty that subserves reason (rational element).[53,87] Two milestones in our understanding of vegetative state have been the publication by neurologist Fred Plum and neurosurgeon Bryan Jennett in 1972 that first coined the term vegetative state and the Multi-Society Task Force (MSTF) that in 1994 proposed a consensus definition of vegetative state and its prognosis. The term 'permanent' has now been abandoned, based upon a growing number of reports of late recovery of consciousness in patients who were previously believed to meet criteria for permanent vegetative state.[88–91]

Before 1972, several other terms were used in the medical literature to describe the state of wakefulness without awareness. Beyond mere linguistic preference, choice of language can make profound differences in enabling informed decisions about how to proceed with care.[92] The term apallic syndrome, which is still used in some German-speaking regions[93] (das apallische syndrome), traces back to an article published by German psychiatrist Ernst Kretschmer (1888–1964) in 1940 and derives from 'pallium', meaning cortex.[94,95] This paper suggested that a complete cortical loss is the pathological substrate of this condition (though neuropathological[96] and imaging studies suggest that thalamic injury may also contribute to its pathogenesis).[96–98] Kretschmer described eight patients who had all been exposed to severe cerebral anoxia and survived for varying periods of time. All showed a uniform clinical symptomatology with complete loss of higher capacities but with retention of brainstem functions, including spontaneous breathing. On autopsy, all were found to have widespread cortical atrophy and severe gliosis.[95] In 2010, the European Task Force on DoC, recognizing the possibly misleading connotation of the term vegetative state, proposed a new name for this condition: unresponsive wakefulness syndrome.[99] The task force suggested removing the term 'vegetative', which carries a spuriously pejorative connotation, as well as the term 'state', which erroneously implies a static, immutable condition, when many of these patients may substantially recover.[22,53,89,100–106] Although use of unresponsive wakefulness syndrome in lieu of vegetative state has grown in popularity, it has been suggested that the unresponsive wakefulness syndrome descriptor may be misplaced insofar as it implies absolute unresponsiveness when some patients who appear unresponsive may covertly harbour responsiveness revealed by neuroimaging or electrophysiological tasks,[22] as we examine below. Furthermore, even in the absence of awareness, patients may have stereotyped, reflexive motor responses to noxious or other stimuli. Contrary to what was initially thought to be the neuropathological basis for the vegetative state, many patients who are clinically unresponsive but awake do not suffer complete cortical necrosis as posited by Kretschmer but rather seem to exhibit disconnection of key modules that are part of a widespread cortical network encompassing medial and lateral prefrontal cortices and parietal multimodal associative areas.[107–112]

## The minimally conscious state

Patients in an MCS exhibit preserved wakefulness and reproducible, often fluctuating, signs of awareness. These patients can manifest, albeit inconsistently, behavioural and emotional responses such as responding correctly to verbal commands, manipulating objects, localizing responses to noxious stimulation, visually tracking objects or fixating.[61] In 2002, the Aspen Neurobehavioral Conference Workgroup led by Giacino and colleagues proposed the first consensus based criteria for the diagnosis of MCS, as well as criteria for emergence from the MCS.[61] According to the Aspen criteria, the diagnosis of MCS requires 'clearly discernible evidence of self or environmental awareness' as evidenced by simple command following, gestural or verbal responses, intelligible verbalization and/or purposeful behaviour.[61] Recognizing the 'high rate of misdiagnosis', the Aspen Workgroup recommended that someone 'with experience in neurological assessment of patients with impaired consciousness should be primarily responsible for establishing the diagnosis and prognosis and for coordinating clinical management, [and an] additional opinion of a physician or other professional with particular expertise in the evaluation, diagnosis and prognosis of patients in the vegetative state and MCS is recommended when the assessment will impact critical management decisions.'[61] Given substantial clinical heterogeneity within the population of patients with MCS, Bruno and colleagues in 2011 proposed subcategorizing MCS into MCS+ and MCS–.[113] Patients in an MCS are subdivided into these categories depending on the presence of intelligible speech or intentional communication (MCS+) or absence thereof (MCS–).[114] Some have proposed revising MCS terminology to a 'cortically-mediated state' as a potentially more accurate way to characterize the impairments of patients meeting these criteria.[115] Importantly, vegetative state and MCS differ not only in behavioural criteria but also in the prognosis for recovery that is informed by being in either state.[116,117]

### The confusional state

The confusional state, termed PTCS when following traumatic brain injury, is a condition of disordered neurocognitive functioning with intact wakefulness and awareness that may be observed during transitions to levels of consciousness higher than MCS. Recovery of object use or functional communication indicate emergence from MCS and thus constitutes the lower boundary of PTCS. PTCS is marked by impairments in attention, memory, orientation and cognitive-behavioural consistency. PTCS may be further accompanied by emotional or behavioural dysregulation, disrupted sleep-wake cycling, confabulation, delusions or perceptual disturbances.[63,64] The term PTCS was coined by Stuss and colleagues in 1999[118] and in June 2020 was refined and codified by an ACRM Evidence and Practice Committee.[63,64] In contrast to the historical term 'post-traumatic amnesia', the domain-general term PTCS was formulated to inclusively denote the broader range of multidimensional neurocognitive changes observed during recovery from brain injury. Acute confusional state or delirium are diagnostic categories used to describe non-traumatic cases of confusional emergence from MCS.

### Covert consciousness and the complete locked-in syndrome

Covert consciousness refers to a state of dissociation between cognitive and motor functions, also referred to as cognitive motor dissociation.[21] Despite the absence of overt signs of self-expression or purposeful motoric responses, an individual may still harbour preserved cognition to varying degrees, which are often suggested or detected through task-based functional MRI or EEG paradigms. Odorant-dependent sniff responses have more recently been described as a tool to aid in identifying covert processing and potentially improve diagnosis and prognosis in unresponsive patients with DoC.[119]

The phenomenological significance of intact electrophysiological or neuroimaging responses to tasks is poorly understood, and important questions surround how different forms of subjective experience and processing of stimuli may variably correspond to signatures of neural activity detected through these advanced techniques.[112] Indeed, in many (if not most) cases of cognitive motor dissociation, functional MRI or EEG data may only indicate a binary state of awareness (with the upper limit of cognitive assessment achievable consisting of answering factual/autobiographical yes/no questions)[120,121] without clearly providing immediate information about the subjective state of the individual. The level of subjective experience or qualia implied by different patterns of neural activity may conceivably range from (i) rudimentary subcortical responses; to (ii) primary sensory cortical responses (e.g. Heschl's gyrus response to language); to (iii) association cortex responses disconnected from subjective experience (e.g. Wernicke's area response to language) also known as covert cortical processing[122,123]; to (iv) volitional modulation of thoughts and possible states of locked-in awareness.[124–126] Importantly, the absence of demonstrable brain activity in response to task-based paradigms does not entail evidence of absence of cognitive abilities queried, as highlighted by substantial false negative rates among normal control subjects in functional MRI and EEG studies.[127–129] While the phenomenological significance of individual patterns of covert consciousness remains to be understood, the presence of covert brain activation by EEG portends substantially improved outcomes for behaviourally unresponsive patients after acute brain injury,[130–132] highlighting the potential prognostic relevance of brain activity detected by these advanced neurotechnologies. Efforts to detect covert consciousness have been identified as a moral imperative in light of the consequential impact that this finding may have on clinical decision making, prognosis, family perceptions and neurorehabilitation.[22,106,133,134]

## Ethical challenges in systems of disorders of consciousness care

Having covered key nomenclature in this field, we will now turn to the challenges to current systems of DoC care. Many of the key ethical challenges that arise surrounding DoC involve high rates of misdiagnosis. Approximately 40% of patients diagnosed with vegetative state based on consensus opinion following bedside examination may be in the MCS, a finding that has been replicated across multiple studies.[135–140] Misdiagnosis can lead to dissonant consequences, especially in end-of-life decision-making.[141] Contrary to patients in vegetative state, those who are MCS retain some capacity for potential phenomenological experience, cognitive processing and pain perception.[142] Moreover, the prognosis of patients in MCS is significantly more favorable relative to those in vegetative state.[116,117,143–149]

Why are rates of misdiagnosis so high? There are at least 11 reasons.[5,62,150] These may be classified into patient factors, clinician factors and systems factors (Table 2).[101,151] Patient factors include sensory impairments, motor impairments, fluctuating responsiveness, comorbid conditions or medications that could mask a patient's underlying awareness or capacity to respond to a behavioural command. Clinician factors include evaluator inexperience, confirmation bias and resource utilization bias that may affect the ability of a clinician to rigorously and impartially administer neurobehavioural evaluations. Systems factors include complexity of consciousness assessment scales, training gaps, and prevailing diagnostic schemata that rely on the premise that absence of evidence of awareness should be taken as evidence of absence of awareness. Opportunities to address each of these factors and mitigate misdiagnosis should be recognized and strengthened. Such interventions may include improved education of clinical trainees for evaluating patients with DoC, further research and advocacy highlighting downstream ethical challenges resulting from misdiagnosis, all the way to systemic policy interventions, such as aligning incentives to allow for more time in clinicians' schedules for rigorous neurobehavioural examinations.

Existing nomenclature and diagnostic categories themselves can be conceptually problematic and may underpin the high rates of misdiagnosis. Some descriptions of vegetative state seem to define the syndrome anatomically, others behaviourally and others seemingly tautologically.[152] On the anatomical plane, despite early descriptions, there is wide variation in neuropathology and most do not exhibit loss of the entire neocortex but rather functional disconnection between key neuroanatomic regions. On the behavioural plane, the state of apparent unresponsiveness can be interpreted as unresponsiveness due to unawareness, unresponsiveness due to inattention, unresponsiveness due to impaired drive (e.g. akinetic mutism/abulia) or might reflect unresponsiveness due to covert

**Table 2** Salient classes and examples of factors contributing to misdiagnosis in DoC

| | |
|---|---|
| **Patient factors** | |
| Sensory impairments | Lesions impacting sensation, hearing or vision may confound assessments of responsiveness to relevant sensory or visual stimulation. |
| Motor/Praxis impairments | Lesions impacting motor function or praxis (volitional motor planning) confound assessments of responsiveness to relevant motor commands. |
| Fluctuating responsiveness | As patients with DoC may exhibit inconsistent behaviours that fluctuate over time, capacities or behaviours indicating awareness may evade notice, particularly if formally assessed only once. |
| Comorbid conditions | Toxic-metabolic disturbances or comorbid pain states may impact isolated measures of responsiveness. |
| Medications | Sedating or deliriogenic medications obscure assessments of cognitive capacities. |
| **Clinician factors** | |
| Evaluator inexperience/strain | Many of those tasked with examining persons with DoC, especially in the acute setting, may lack dedicated training in this evaluation or adequate time to rigorously perform it. |
| Confirmation bias | Tendency to seek evidence to support initially presumed diagnosis or prognosis rather than conflicting elements may bias evaluations. |
| Resource utilization bias | Tendency for implicit or explicit bias to affect the interplay between personal views of chronic rehabilitation towards uncertain neurological outcomes and the demand for highly skilled but limited-availability acute or subacute care. |
| **Systems factors** | |
| Complexity | Complexity and length of neurobehavioural DoC assessment scales requires training and time resources that may not be available, especially in acute care settings with high patient censuses. |
| Burden of proof | Behaviour-based diagnostic schemata hinge on the premise that absence of evidence of awareness should be taken as evidence of absence of awareness. As highlighted through cases of cognitive motor dissociation, isolated absence of behavioural responsiveness is not categorical evidence of absence of awareness. |
| Training gap | Clinical training programs often lack dedicated training in the systematic behavioural evaluation of patients with DoC. |

consciousness.[153] Attempts at defining the syndrome in terms of consciousness itself become tautological.[152]

Accompanying shortcomings in misdiagnosis is undue pessimism. The rise of pessimism after brain injury coincided with the evolution of the right to die movement and concomitant overgeneralization of nihilism to all forms of severe brain injury in the wake of Terri Schiavo and other prominent cases.[5,154] Most patients with acute DoC due to brain injury who die in the hospital do so in settings of the redirection of goals of care towards prioritizing comfort measures.[155–157] Such decisions to withdraw life-sustaining therapy are commonly predicated on expectations of poor recovery and cognate attributions of therapeutic futility.[158] Yet, in light of available data, it is not clear what drives these prognostic paradigms. In one cohort study of 50 patients admitted to a rehabilitation centre in vegetative state, 24% recovered responsiveness and 20% of the total sample recovered responsiveness at greater than 1 year (ranging from 14 to 28 months post-onset).[89] For patients in MCS, it is estimated that a third may emerge at greater than 1 year after coma onset.[145] In another study on the natural history of recovery from brain injury after prolonged DoC, 36 patients in a vegetative state or MCS were followed for 4 years during and after rehab. At 4 years, ~50% returned to daytime independence at home; 22% returned to work or school and 17% recovered to at or near pre-injury levels.[146] Considering the total sample, almost two of three patients admitted to acute or chronic rehabilitation settings in vegetative state recovered consciousness, many at time points beyond what former diagnostic guidelines would have dubbed permanent. One group recently found that functional outcomes of patients may continue to progress towards functional independence up to 10 years post-injury.[159] While by design these studies measured outcomes only in persons for whom life-sustaining treatments were continued and could not establish counterfactual outcomes for those where those treatments were withdrawn, the results appear at odds with typical poor prognoses and attributions of futility delivered to the families of patients with acute DoC.[159–162] Because it may be surmised that patients who survive to transfer to rehabilitation facilities may be the least medically and neurologically ill within their respective diagnostic categories, some suspect that prognoses for the patients followed in many neurorecovery studies may be better than for an average patient in an acute care environment with a given DoC. This underscores the need for further study of the natural history of recovery in contexts where withdrawal of life-sustaining treatment is uncommon regardless of perceived prognosis, as is now underway.[163–165] Prior evidence suggesting that factors other than injury severity play an equal or greater role in rehabilitation referral decisions (including involvement of family and a physiatrist in clinical care), together with limitations in data comparing outcomes in DoC patients referred versus not referred to inpatient rehabilitation, confound the attribution of uniform selection bias in rehab referral processes favoring patients with better prognoses.[166–170] Recent prospective, longitudinal evidence from a study of patients enrolled in the Traumatic Brain Injury Model Systems National Database did not suggest systematic severity-based referral bias.[171,172] These points underscore critical opportunities for further empirical investigation. Nonetheless, in light of data highlighting the possibility of meaningful recovery in a substantial percentage of patients, what drives decisions to limit treatment?

## The heavy weight of bias and the limits of certainty

Clinicians, especially those practicing in acute settings, tend to see this population of patients at their worst and often comatose states, which in many other contexts is a justifiable marker of terminal illness and a reasonable trigger for end-of-life discussions.[5,173] In contrast to practices in some regions,[174,175] clinicians in the USA and elsewhere are often trained to protect patients' dignity at the end of life by not unnecessarily prolonging the dying process and often believe that patient advocacy demands directing families to less aggressive care when death is apparently imminent.[158,176–178] However, in settings of acute DoC, reliable prediction of recovery is inordinately challenging.[179] Most clinicians caring for these patients during acute hospitalization do not bear witness to the clinical course of patient recovery during the neurorehabilitation phases, when care is directed by multidisciplinary teams including physiatrists, therapists and psychologists. Attributions of poor prognosis may thereby become self-fulfilling, wherein expectations of poor outcomes drive actions that engender this clinical reality.[156,180,181] In so doing, acts of prognostication slip from the descriptive to the performative, bringing about or transforming states of affairs that they ought only describe.[182] Such decisions therefore carry a high risk of promoting a self-fulfilling prophecy bias that is compounded by a fuzzy nosology and resource constraints that may force premature closure and solidified at times by an erroneous view of disordered consciousness as irreversible.[11]

Apart from self-fulfilling prophecy bias, a range of other cognitive biases weigh heavily on decision making in this population. The disability paradox refers to the fact that many who are living with disabilities report good or excellent quality of life despite external observers' attributions of suffering.[183–185] This paradox and its tendency to unduly influence clinical decision making has been described repeatedly in studies on patients in the locked in syndrome, spinal cord injury, stroke and other conditions, and may stem from a failure to understand how the prudential values or capacities for experience may change with disability.[186–188] The inability to assess quality of life in those who cannot respond, and the pliable, subjective nature of what constitutes a 'meaningful recovery', compounds the difficulty of clinical decision-making in these contexts.

More foundationally, clarity about the value of consciousness for patients and families is needed.[6,189] Whether the state of consciousness is viewed as intrinsically valuable or valuable instrumentally and only insofar as the experiences that it may instantiate will be uniquely influential in determining ethically appropriate and goal-concordant care for patients with DoC. Some theorists have contended that states of reduced consciousness preclude attribution of 'full moral status' or the experience of 'life worth living'.[190–192] While some limited data have been gathered,[193,194] these approaches require further phenomenological and empirical study, particularly including investigation of projected versus actual life satisfaction across a wider range of DoC states, determinants of quality of life and possible evolution over time in those who have improved.[195–200] This may be achieved by surveying the perspectives of patients, surrogates and others whose voices may provide a window through which the phenomenology and moral significance of these states could be empirically understood and rigorously grounded. This could foreseeably vary by culture, context or background.[201–203] Principles of justice and truth-telling support the imperative that clinicians describe such uncertainty with candor and transparency. Such counselling should aim to explain the range of best and worst possible interpretations and outcomes, instead of relying on synthetic or monotonic judgments, avoid disability bias and ensure that care delivered protects patient dignity and preferences to the extent that they may be ascertained.[154,204–206]

## Implications for clinician-family/surrogate communication

While some portion of patients with DoC may make remarkable recoveries, a significant portion will not, despite months or even years of intensive rehabilitation and long-term care. Families of these patients may experience significant financial losses and psychosocial distress, and resources and support systems for family members caring for loved ones with DoC are limited. Some may turn to crowdfunding campaigns to continue aggressive treatments due to gaps in insurance coverage and exhausting all personal resources (a May 2021 search of the largest crowdfunding platform, GoFundMe, revealed over 400 campaigns for patients in a vegetative state or with unresponsive wakefulness syndrome or MCS; while many of these campaigns were USA-based, there were numerous campaigns to raise funds for patients in other regions around the world).[207] For some family members, there may be substantial opportunity costs, such as foregoing educational or professional opportunities because of the need to care for, and be available for, a recovering loved one. Also, for the patient, there is the potential pain, suffering and loss of dignity of continued treatments that ultimately prove to be non-beneficial or without attainment of what the patient would agree to be a minimally acceptable neurological outcome. How to balance these prospects for harm against potential benefits of continuing life-sustaining treatment requires careful ethical and empirical study. With every decision to continue aggressive therapy, surrogates should be counselled that these decisions need not be permanent, and that decisions surrounding goals of care could and should be revisited at regular intervals under the guidance of a clinician who may track relevant progress/stagnation, update prognostic expectations and counsel surrogate decision makers accordingly. Indeed, while counselling surrogate decision makers that a decision to transition to hospice care can be made at any time, clinicians should also recognize that making such a transition many months or years after acute injury is itself accompanied by complexity.

Often, decisions surrounding the intensity and goals of treatment converge on questions of nutritional management (e.g. tube feeding), pulmonary support (e.g. mechanical ventilation), treatment of comorbid medical conditions and management of symptoms or complications of brain injury (e.g. intracranial pressure, dysautonomia, seizures, spasticity and pain). To achieve goal-concordant care, clinicians must work closely with surrogate decision makers to provide education about these categories of management and explain possible treatment pathways (e.g. rehabilitation-focused or comfort/palliative-focused) along with the range of possible outcomes that might be expected through each treatment pathway, and they should diligently identify how patient values and preferences can help guide consistent decisions. While some treatment decisions may be reversible and time-insensitive, others are more critical and may shunt families and patients towards a particular treatment path.[208] Commonly, after several weeks of endotracheal intubation, clinicians become worried about the risk of tracheal erosion and thus a possibly premature pressure is placed on deciding whether to place a tracheostomy (commonly paired with a percutaneous gastrostomy tube). Placement of a tracheostomy for some patients will remove the requirement for mechanical ventilation. But with the course of recovery being easier to predict even a week later, the early forced decision may result in an extended life with DoC that the surrogate might have, a week later, ethically judged to have been more appropriately transitioned to comfort measures via palliative extubation.[209] The perceived limited window of opportunity for certain critical treatment decisions or early palliative care may amplify the psychosocial burden on surrogates faced with these decisions, especially when likely outcomes are uncertain.[210–212] Providing psychosocial support to surrogates through the decision-making process is therefore imperative.[213] Surrogates should be prospectively counselled that if eventual outcomes do not align with prior expectations, overall treatment goals may be revisited and revised as needed. Specialized systems of longitudinal care for patients with prolonged DoC may thus help to ensure alignment of treatment decisions with patient goals across the care continuum.[214]

## The search for covert consciousness and genesis of new guidelines

Recognizing undue pessimism that the previous terminology of permanence invited, recent practice guideline recommendations from the AAN, ACRM and NIDILRR suggest eliminating the term permanent and replacing it with chronic vegetative state.[88] The AAN guideline additionally provides as a level A recommendation that when discussing prognosis with caregivers during the first 28 days post injury, 'clinicians must avoid statements that suggest a universally poor prognosis'. [88] It is important to recognize that this statement does not imply that it is never permissible to prognosticate or limit aggressive treatments for a patient with DoC before 28 days; rather, it encourages clinicians to avoid, during the first 28 days, statements suggesting that one can definitively know that the prognosis for functional recovery is poor. Echoing perceived pitfalls of current diagnostic procedures and prognostic standards for DoC, a 2020 European Academy of Neurology (EAN) guideline encourages 'repeated multimodal evaluations for evidence of preserved consciousness in patients with DoC' rather than predicating clinical decisions or prognostication on isolated assessments.[215] Similarly, the 2020 Royal College of Physicians National Clinical Guidelines for prolonged DoC emphasize that 'the diagnosis of VS (vegetative state) or MCS should only be made by an appropriately experienced assessor, using formal diagnostic tools applied on repeated occasions over an appropriate period of time in conjunction with a detailed clinical neurological assessment' and details that in comparison to the US health system, 'NHS (National Health Service) care allows for a considerably longer period of time over which to evaluate and monitor patients'.[216] In even stronger terms, Norwegian Neurological Society guidelines concerning DoC, updated in 2020, recommend that 'it might be appropriate to consider limitations of LST (life-sustaining therapy) but often not before at least after 1 year observation time for traumatic injuries' and 3 months for non-traumatic brain injuries, echoing the need for rigorous and repeated assessments over time.[209,217]

Ethical and logistical challenges to these guidelines have highlighted the potential resource strain that would likely ensue in intensive care units that choose to continue aggressive therapies for a longer period of time for more patients with severe brain injury.[134,218] Resource constraints during the COVID-19 pandemic magnified these difficulties worldwide.[3,219–222] These challenges are amplified in contexts where intensive care unit beds, ventilators and rehabilitation beds are already scarce, with clinicians facing tragic decisions about how to prioritize and equitably triage patients. Similar situations occur in specialized intensive care units (ICUs) located in tertiary care centres that can provide advanced services not available in community hospital ICUs, but only to the extent that beds in the specialized ICUs remain available. Therefore, increases in ICU and rehabilitation capacities will likely be needed before clinicians can universally meet this need; such increases should be considered in the context of other unmet medical needs and how limited resources should be best allocated. Furthermore, processes to support decision-making after 28 days have not been standardized, and supports to facilitate revisiting individualized goals-of-care decisions longitudinally are limited after discharge from acute or subacute care settings where such processes are increasingly emphasized.[214] Logistical challenges may be compounded by possible psychosocial risks of prolonging patient and family suffering in situations where survival without meaningful recovery is likely yet uncertain.[223]

Where do we go from here? The answer starts with a landmark case report published in 2006, which sparked a paradigm shift in approaches to DoC.[224] This landmark case report described a 23 year-old female who sustained severe brain injury after a motor vehicle accident. Repeated multidisciplinary assessments detected no typical behavioural evidence of responsiveness, and she thus received the diagnosis of vegetative state. However, a functional MRI was performed and when asked to imagine playing tennis, the blood oxygen level-dependent (BOLD) functional MRI signal increased in the premotor cortex, and when asked to relax, the BOLD signal in this region diminished. The patient was then asked to imagine moving from room to room in her house and a different pattern of functional MRI activity emerged that included the parietal cortex and part of the parahippocampal gyrus, two regions known to be involved in spatial navigation. Her pattern of functional MRI activity closely resembled that seen in healthy controls. Based on these findings, it was concluded that she in fact was not vegetative, but rather covertly conscious, even though the paper was entitled 'Detecting awareness in the vegetative state'.[102,224,225] This study opened up a wide area of investigation over the next decade, where investigators started to identify covert awareness in the behaviourally unresponsive. In a follow-up functional MRI study in 2010, 4 of 23 patients who received vegetative state diagnoses on admission appeared covertly aware and able to generate reliable responses on functional MRI.[120] One patient was even able to produce yes/no responses by alternating corresponding spatial or motor imagery tasks,[120] a finding that was subsequently replicated in one additional patient using different language paradigms.[121] These findings indicated that the motor capacity of some patients can be so compromised that bedside evaluations may fail to identify awareness, regardless of how meticulously they are administered.[226] More recently, EEG paradigms have been used to detect command-following in the absence of overt behaviour. Leveraging differences in EEG power spectra during performance of motor and spatial imaging tasks, quantitative analysis of high-density EEG may provide evidence of reliable command-following in patients who are otherwise behaviourally unresponsive through detected changes in the EEG power spectra or other patterns.[128,227,228]

The emerging role of EEG in aiding the diagnosis and prognosis of patients with DoC was emphasized by an International Federation of Clinical Neurophysiology (IFCN) Expert Group opinion statement in August 2020 that proposed a scheme for the integrated neurophysiological assessment of patients with prolonged DoC. The scheme envisions proceeding stepwise from traditional neurophysiological measures including standard EEG and somatosensory evoked potentials to gradually more complex measures including event related potentials, quantitative EEG and paired transcranial magnetic stimulation-EEG to enhance the capture and characterization of covert cognitive abilities not discernible by bedside examination.[229] The IFCN Expert Group suggests that embedding these techniques into multimodal assessments of patients with prolonged DoC 'might help direct behaviourally unresponsive patients towards different lines of evaluation based on objective markers of thalamo-cortical integrity'.[229]

What about in the acute stage? In a cohort of 16 DoC patients with acute traumatic brain injury admitted to the neurointensive care unit, covert consciousness was identified in four patients using functional MRI and EEG paradigms, including three whose behavioural diagnosis suggested a vegetative state.[127] A subsequent study examined a consecutive series of patients in the Neuro-ICU who were unresponsive to spoken commands. Machine learning was applied to EEG recordings to detect brain activation in response to commands for patients to move their hands. Brain activation was detected in 15% of those who were unresponsive to commands and predicted functional independence at 12 months,[130] suggesting that people with covert consciousness carry better prognoses. More recently, passive responses to an EEG protocol probing language function were found to be associated with improved outcomes at 3 and 6 months as measured by the Glasgow Outcome Scale-Extended,[132] adding to a growing body of evidence supporting the clinical role of advanced neurotechnologies in the diagnosis and prognosis of patients with DoC.[132,133,230]

Many groups around the world have used techniques like these to detect covert awareness in patients who appear clinically to be in a vegetative state. A meta-analysis of 37 published studies and over 1000 patients found that in aggregate approximately 20% were misclassified as vegetative when in fact they displayed covert awareness by functional MRI or EEG.[231] These findings raise the daunting possibility that a substantial percentage of patients diagnosed as vegetative worldwide might not be vegetative at all, but simply physically non-responsive with retained awareness. However, the phenomenological nature of the disordered states of consciousness uncovered by these advanced techniques remains unclear and requires further study. Conceivably, the category of cognitive motor dissociation encapsulates a heterogeneous group of states, ranging from complete locked-in awareness to merely reflexive or rudimentary cognitive processing.[232,233] Abundant caution is therefore necessary when counselling surrogates about the significance of these states, particularly what it might be like to be in the state reflected by functional MRI or EEG responsiveness, which is currently unknown.

Recognizing the fundamental diagnostic ambiguity that may be left due to the shortcomings of the bedside exam, the recent AAN DoC Guideline suggested a role for multimodal evaluations including functional imaging or EEG to assess awareness not identified at the bedside, but the guideline does not detail when and how these tools should be optimally used or integrated into clinical decision making. A subsequent 2020 EAN DoC Guideline amplified these sentiments, recommending that '[m]ultimodal assessment and neuroimaging is necessary to avoid misdiagnosis,' and that 'EEG-based techniques and functional neuroimaging (fMRI, PET) should be integrated into a composite reference standard' (Fig. 2) but like the AAN guideline does not clarify at what time point(s) or in which particular clinical contexts these should be used.[215] Each of the paradigms used, including EEG, functional MRI, PET and transcranial magnetic stimulation-EEG, have strengths and limitations, ranging from spatial resolution, temporal resolution, cost, safety and experience required to use them.[226,229] When there is discordance between the level of consciousness detected by different paradigms, the EAN guideline recommends that a patient should be diagnosed with the 'highest level of consciousness' suggested by any of the approaches.[215] This important recommendation implies that in contexts where neuroimaging or neurophysiological measures have not (or cannot) been obtained, the workup remains incomplete, as assessment of the highest level of consciousness relies on knowledge of each of these measures. For the recipients of such incomplete or conflicting information (including surrogates and clinicians) there is potential for greater confusion and compromised decision-making. Possible reasons for discordance between the level of consciousness suggested by different diagnostic modalities include temporal fluctuations in consciousness, evolution of functional status, as well as the inherent limitations of each approach.

Norwegian Neurological Society DoC guidelines also recognize the potential supplementary role of advanced neuroimaging including functional MRI and electrophysiological techniques in the diagnosis and prognosis of patients with DoC.[217] The 2020 Royal College of Physicians National Clinical Guidelines have emphasized that 'advanced brain imaging and electrophysiology techniques have provided valuable insights into this patient group, and will continue to provide an important focus for research' but do not yet recommend their use in routine clinical practice, a position that has recently been critically evaluated.[235] These Royal College of Physicians guidelines also importantly note that 'while it is acknowledged that there is a small cohort of patients who present behaviourally as being in vegetative state but demonstrate covert responses within an fMRI scanner, the prognostic significance of these findings is as yet unclear [and this] raises the ethical dilemma of whether or not and how to disclose this information to clinicians and patients' families'.[235] Of note, it is explicitly specified that 'these UK guidelines do not apply until patients have been in PDOC (persistent DoC) for at least 4 weeks' and thus are not meant to provide guidance during acute stages of DoC or recommendations surrounding the use of advanced neuroimaging or electrophysiological techniques for acute neuroprognostication.[216]

Innovations in detecting consciousness come at an especially exciting time as we are learning more about opportunities to promote neurorecovery in DoC.[236,237] Therapeutic candidates include amantadine, methylphenidate, modafinil, apomorphine, zolpidem, transcranial direct current stimulation, transcranial magnetic stimulation, low intensity focused ultrasound pulsation, deep brain stimulation, vagal nerve stimulation, vestibular stimulation, music stimulation and brain–computer interfaces.[131,236–240] Most available data for these interventions derive from open-label studies and case reports, with the exception of amantadine which shows class I evidence for patients with traumatic brain injury during rehabilitation and is currently the only pharmacological intervention recommended by AAN guidelines for patients with DoC.[88,241] The mechanisms of many of these interventions are thought to converge on the central thalamus[98] and key brainstem networks.[242]

## Towards ensuring access and equity

Despite remarkable advancements in the field of DoC science, these novel tools to potentially improve prognostication and neurorecovery are currently only available at select medical centres around the world.[134] As a result, these technologies may prove untenably inaccessible or unaffordable for many patients, especially those with chronic DoC who are often lost to neurological follow-up.[5,173] Quality DoC care ought to be available to all DoC patients. In contexts where advanced neuroimaging or neurophysiological techniques are not available, covert cognitive states will remain invariably undetected, and evaluations of patients with DoC will therefore be necessarily fraught with disproportionate diagnostic and prognostic uncertainty.

Crucially, the United Nations Convention on the Rights of Persons with Disabilities (CRPD) and Americans with Disabilities Act (ADA) mandate equal treatment of persons with disabilities and prohibits discrimination in the provision of services on the basis of disability.[141,243,244] Specifically, CRPD Article 25 stipulates that 'persons with disabilities have the right to the enjoyment of the highest attainable standard of health without discrimination on the basis of disability ... including health-related rehabilitation ... early identification and intervention as appropriate, and services designed to minimize and prevent further disabilities'. Building upon these imperatives, Article 26 details that parties 'shall promote the availability, knowledge and use of assistive devices and technologies, designed for persons with disabilities, as they relate to habilitation and rehabilitation'. Denying or withholding neurorehabilitative services and therapies from persons with DoC in situations where patients or surrogates desire ongoing support is thus fundamentally inconsistent with the moral and legal obligations that stem from disability rights ethics and

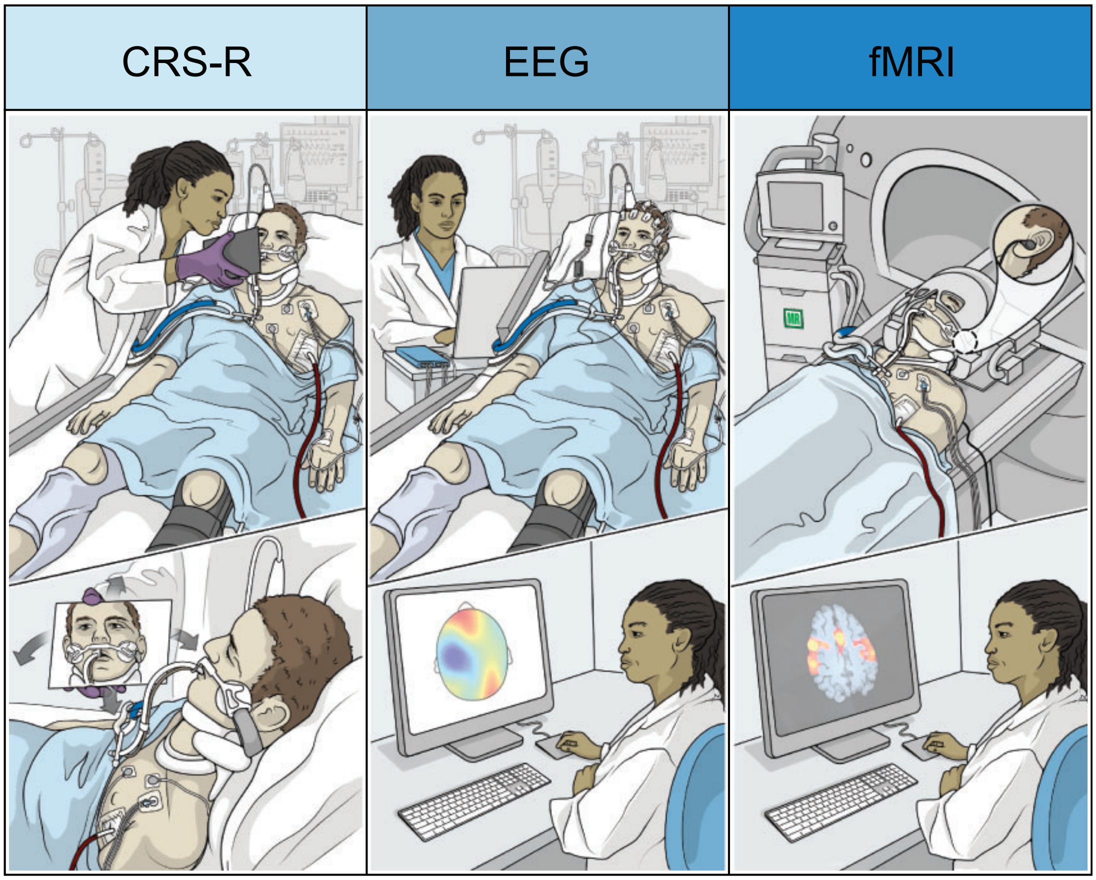


**Figure 2 Expanding the detection of consciousness.** Multimodal assessments, including neurophysiological and neuroimaging techniques such as EEG and functional MRI, can augment the sensitivity of bedside behavioural examinations and aid in the diagnosis and prognosis of DoC. A patient may be diagnosed with the highest level of consciousness assessed by each of these measures. Adapted with permission.[234]

law.[5,141,245–247] Importantly however, these are jurisdiction specific claims and do not necessarily carry legal force in all places where people experience brain injury; for example, the ADA is germane to the USA, which has recognized but has not formally adopted the CRPD, and the adoption of the CRPD across Europe, the UK and elsewhere has been uneven. Opportunities for incorporating the disability rights perspectives of persons who have recovered from DoC and their surrogates into ongoing policy deliberations and research should be recognized and strengthened, along with opportunities to harmonize evidence-based healthcare policy with the ethical and legal imperatives borne of fundamental human rights codified in disabilities rights law.[5,248,249]

Fair mechanisms to improve equitable access and just distribution of these resources as well as opportunities for enrollment in ongoing clinical trials are thus needed to ensure that current disparities are addressed. A hub-and-spoke model of DoC care whereby patients or patient data from remote settings may be referred for specialty evaluation at central hubs of DoC expertise (virtually when appropriate) may be one systematic approach to overcoming geographic and financial impediments to access.[250] Within this model, a network of partnerships with community hospitals and remote care centres would be assembled and leveraged to facilitate bidirectional education and appropriate triage of patients. This model may foreseeably entail remote collection of neuroimaging or electrophysiological data, which can then be transmitted to a centre of DoC expertise for analysis and input. Hub-and-spoke model systems have been successfully used to improve patient access in other areas of medicine including cardiac care, stroke, radiology, neurology and cancer care.[251–257] In settings where data acquisition cannot be completed because of lack of neurotechnologies or support staff, appropriate patients may be selected for triage to regional hubs equipped with a more complete diagnostic armamentarium for specialized evaluation. Such systems redesign efforts should proceed in tandem with advocacy and education at community, institutional and legislative levels to raise awareness about the prevalence of DoC, increase availability of ICU and rehabilitation beds, and illuminate and overcome disparities in access to specialized care.[258]

## Open questions in disorders of consciousness: COVID-19 and beyond

Unprecedented research advances in the field of DoC have generated a complex set of novel ethical, societal and clinical challenges (Box 1). Many patients are incorrectly labelled as unaware either due to insufficient evaluation, confounding medical states or because they are covertly conscious without discernible behavioural markers of awareness. These issues are magnified by shortcomings in prevailing diagnostic criteria in which absence of behavioural responsiveness is erroneously equated to absence of awareness, a premise challenged by the discovery of covert consciousness. Presumptions of poor prognosis and biased quality of life projections rooted in ableism may lead to unduly pessimistic decisions, including premature limitation of life-sustaining treatments or denial of access to rehabilitation.[5,214] On a systems level, economic and resource constraints may motivate early triage or treatment limitation to maintain an available supply of already

**Box 1 Salient ethical challenges in DoC care**

Should definitions and diagnostic criteria surrounding consciousness be clarified and why?
What are the meaningful outcomes, and for whom are they meaningful? Are they achieved by identifying patients who are covertly conscious?
How should emerging philosophical and neuroscientific theories of consciousness be reconciled with instrumental clinical categories?
Should research data be shared with families/clinicians and how?
How to ensure equitable access to technologies, research and specialty care, without unduly straining healthcare systems, especially in the context of the additional strains imposed by COVID-19 pandemic?
How to implement new DoC guidelines while protecting patients and families from increased suffering in situations where meaningful recovery is unlikely yet possible?
Is the state of consciousness itself intrinsically valuable or only instrumentally valuable?
At what point should research tools to evaluate consciousness justifiably be introduced into clinical practice?
How can neuroethics in DoC be studied empirically to inform the above questions?

limited ICU beds, as keeping more neurocritical ill patients on life-support pending recovery for prolonged periods of time may further strain care structures and magnify family burden (psychosocial and financial).[223,259] Moreover, systems of post-acute care and neurorehabilitation are underequipped to adequately and equitably accommodate those with chronic DoC.[173,178] These issues have been highlighted during the COVID-19 pandemic, with increasing recognition of delayed recovery of consciousness after COVID-19 critical illness and of the unique ethical issues pertaining to this growing population, including special sensitivity to nosology and methods of neuroprognostication.[1,3,219–222] Novel neuroimaging and electrophysiological tools carry promise to improve evaluations of consciousness and neuroprognosis, but raise a challenging set of ethical questions surrounding uncertainty about when to use them, what the significance of the data they yield is, how to ensure equity in access, and whether and how to disclose imperfect and at times conflicting data to surrogates and families. There is also great uncertainty about how to translate these techniques into pre-existing clinical decision-making paradigms, challenges amplified by recent society guideline recommendations encouraging clinical implementation.

Given the increasingly apparent limitations of current systems of diagnosis and management, ethical obligations depend upon clinicians and professional societies to refine our nosology of impaired consciousness and associated guidelines based on emerging data. Diagnostic categories ought to be revised in a way that can be informed by novel neuroimaging and EEG paradigms, wherever such technologies are readily available.[123] These efforts should include revision of the International Classification of Diseases 10th Revision (ICD-10), which while containing codes for locked-in syndrome (G83.5), persistent vegetative state (R40.3), somnolence, stupor and coma (R40), currently lacks codes for MCS and cognitive motor dissociation. This should proceed in tandem with ongoing research identifying improved strategies to detect consciousness, characterize its neural correlates (as well as those of self-consciousness) and predict neurorecovery, along with ongoing development of neurotherapeutics and brain–computer interfaces to facilitate societal reintegration and ethically resilient care in this vulnerable population. Approaches to caring for patients and supporting surrogates should be personalized to be as precise as possible in diagnostic assessments, while recognizing and conveying degrees of uncertainty.[260] During goals-of-care conversations, balance is needed between the recognized right to die with supporting the right to care for those who want it, and recognition of the cognitive biases that may influence assessments in this process is crucial.[91,178,261] Clinical paradigms and healthcare policies should seek to uphold and protect the moral and legal rights of persons with DoC that stem from international disability law and bioethics, and practice deficiencies should be identified and corrected.[141] To these ends, advocacy for improved training, care-systems redesign and optimized resource-allocation to longitudinally support this population are imperative.

As technologies for assessing consciousness continue to mature and proliferate, clinicians, families of patients with DoC and ethicists will be faced with increasing data of evolving diagnostic and predictive value; those data will be accompanied by both increased insight into the state of consciousness and, often, heightened dilemma in clinical decision-making. Recognizing the daunting road ahead, further empirical study is needed to clarify how to ethically translate emerging neurotechnologies to detect consciousness in patients with severe brain injuries. Salient perspectives of key stakeholders and end-users should be captured and studied, and aligned insights may be used to inform an empirically-grounded framework for the responsible research and translation of novel neurotechnologies to guide clinicians and researchers through these formidable settings of diagnostic and prognostic uncertainty.

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The authors report no competing interests.

## Supplementary material

Supplementary material is available at *Brain* online.

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