REVIEW ARTICLE

Functional neuroimaging in disorders of consciousness: towards clinical implementation

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Abstract

Functional neuroimaging has provided several new tools for improving both the diagnosis and prognosis in patients with DoC. These tools are now being used to detect residual and covert awareness in behaviourally non-responsive patients with an acquired severe brain injury and predict which patients are likely to recover. Despite endorsement of advanced imaging by multiple clinical bodies, widespread implementation of imaging techniques such as functional MRI (fMRI), electroencephalography (EEG), and positron emission tomography (PET) in both acute and prolonged disorders of consciousness patients has been hindered by perceived costs, technological barriers, and lack of expertise needed to acquire, interpret, and implement these methods. In this review we provide a comprehensive overview of neuroimaging in DoC, the different technical approaches employed (i.e. fMRI, EEG, PET), the imaging paradigms used (active, passive, resting state) and the types of inferences that have been made about residual cortical function based on those paradigms (e.g., perception, awareness, communication). Next, we outline how these barriers might be overcome, discuss which select patients stand to benefit the most from these neuroimaging techniques, and consider when during their clinical trajectory imaging tests are likely to be most useful. Moreover, we make recommendations that will help clinicians decide which advanced imaging technologies and protocols are likely to be most appropriate in any particular clinical case. Finally, we describe how these techniques can be implemented in routine clinical care to augment current clinical tools and outline future directions for the field as a whole.

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Introduction

Disorders of consciousness (DoC) are characterized by disruptions in arousal and/or awareness following a severe brain injury and affect millions of people worldwide.[1,2] These conditions include coma, the vegetative state (VS) (also known as unresponsive wakefulness syndrome)[3], and the minimally conscious state (MCS), each characterized by different levels of behavioural responsiveness and cognitive function. The clinical management of DoC patients in both acute and prolonged settings is marked with uncertainty due to the complexity and heterogeneity of these conditions, making accurate diagnosis and prognosis clinically, ethically, and scientifically challenging.[4,5] Behavioural assessments, long considered the gold standard for evaluating DoC patients, often provide unreliable diagnostic and prognostic information, and fail to capture the full spectrum of responsiveness and preserved cognitive function that some DoC patients may retain covertly.[5] In recent years, functional neuroimaging methods, including functional MRI and electroencephalography, have been used to detect preserved awareness in around 20% of non-responsive DoC patients.[6–10] In this condition, a patient's behavioral presentation does not align with their level of awareness measured using functional neuroimaging,[11] a phenomenon that has been referred to as 'covert awareness' (in the case of entirely non-responsive patients who appear coma or vegetative) and termed 'cognitive motor dissociation' (CMD) (which also includes lower level minimally conscious state patients who can neurally command follow).[12–14] An even larger proportion of patients appear to have some preserved cortical function, inferred through a positive neural response to passive neuroimaging tasks that assess sensory processing, or so-called 'resting state scans', that measure the overall functioning of the brain.[15–22] In some instances, these markers have been shown to be related to functional and neurological recovery from DoC.[15–19,23–25]

Despite clinical endorsement of these techniques by multiple international bodies,[26,27] implementation in both acute and prolonged settings has been hindered by concerns about prohibitive costs, access to the necessary technology, lack of the required personnel, and clinical inertia.[28,29] Regarding the latter, a pervasive sense of nihilism within the medical community—stemming from a belief that these advanced diagnostics will not significantly benefit patient assessments—has hindered broader acceptance and integration.[30,31] In this article, we outline the current state of the science and provide comprehensive recommendations for how the latest advances in functional neuroimaging may be practically applied in a clinical setting. We highlight which patients stand to benefit the most from neuroimaging, including those with ambiguous behavioural examination results, those for whom traditional diagnostic methods have proven inconclusive, and ambiguous prognostic results. We also discuss the appropriate timing and selection of neuroimaging tasks and paradigms to maximize diagnostic and prognostic accuracy. Finally, we propose a practical framework for implementing these techniques, addressing common logistical challenges, and offering solutions that will allow clinicians and researchers to integrate neuroimaging into their standard care practices.

Clinical Overview

Disorders of Consciousness

Acute and prolonged DoC following a structural or metabolic brain injury are characterised by a continuum of impairment in arousal and awareness and present unique management, assessment, and prognostic challenges throughout the trajectory of care.[2,32] We, along with most others, refer to acute DoC as the period of emergency care and intensive care unit (ICU) management that occurs within the initial 28 days following a severe brain injury.[33] The terms 'sub-acute' and 'prolonged' DoC are used to describe patients who remain with impairments in arousal and/or awareness beyond 28 days and who are often cared for in non-critical inpatient facilities, rehabilitative centres, long term care centres, or at home by caregivers and nursing staff.

Acute Disorders of Consciousness

Acute DoC are critical medical emergencies that often require admission and management to an ICU for various life-sustaining measures.[34] These interventions may include endotracheal intubation and mechanical ventilation to ensure adequate oxygenation and ventilation, continuous monitoring of intracranial pressure to prevent secondary brain injury, and administration of pharmacological agents to mitigate cerebral edema and prevent seizures. The most common acute DoC is coma, which is characterized by a complete absence of arousal and awareness.[35,36] Coma is a transient state of unconsciousness, and in general, patients who survive begin to awaken within 2–4 weeks. Recovery may never progress beyond a VS/MCS, or may involve complete recovery of awareness.

Medical teams must perform a series of assessments to detect signs of awareness and evaluate the chances of long-term recovery after brain injury, which often informs decisions regarding the trajectory of care. These assessments are often fraught with uncertainty, because although there are tools available for predicting a *poor* outcome (that is, death or prolonged DoC), few tools exist for predicting a *good* functional and neurological outcome.[37,38] This makes decisions regarding the continuation or withdrawal of aggressive life-sustaining measures extremely challenging for both medical teams and families.[39–41] Prognostic uncertainty is also influenced by diagnostic uncertainty; in particular, how it relates to a patient's level of awareness following a severe brain injury. Most commonly, crude behavioural measures such as the Glasgow Coma Scale (GCS) are used but they fail to capture signs of awareness in up to 20% of patients in the ICU.[8,42,43]

Prognostication after acute DoC

Prognostication following acute brain injury is a complex and uncertain process.[4] Despite advancements in care, overall survival rates remain low, and only a small percentage of survivors achieve a favorable neurological outcome.[34,40,44] Recent guidelines emphasize the importance of multimodal approaches to neuroprognostication, incorporating clinical, biochemical, electrophysiological, and neuroimaging markers.[45,46] In cardiac arrest, indicators of poor prognosis include absent pupillary and corneal reflexes, bilateral absence of the N20 cortical response in somatosensory evoked potentials, elevated neuron-specific enolase levels, unreactive burst suppression on EEG, amongst others.[47] While predictors of favorable recovery remain limited, evidence suggests early motor responses, normal blood values of neuron-specific enolase, positive somatosensory evoked potentials, continuous background on EEG, and absence of diffusion restriction on MRI findings may be indicative good outcomes.[38] While DoC resulting from TBI generally carries a more favorable prognosis than that from cardiac arrest, prolonged recovery periods are common, and the absence of awareness after one month does not necessarily indicate a poor outcome.[48] Factors associated with poor recovery include advanced age, loss of pupillary reflexes, the presence of hypotension, hypoxia, and uncontrolled intracranial hypertension, the bilateral absence of the N20 cortical components of somatosensory evoked potentials, and elevated serum levels of glial fibrillary acidic protein and S100B,[48,49] whereas predictors of favourable recovery in severe TBI include younger age, preserved motor reflexes, and lower CT grades in the acute phase of brain injury.[50,51]

Prolonged Disorders of Consciousness

If disruptions to the neural systems responsible for arousal and awareness are not reversed, it can lead to a prolonged DoC, such as VS or MCS. The VS is characterized by periods of wakefulness but no signs of awareness or responsiveness. Those in a VS may retain basic reflexes, spontaneous eye opening, and sleep wake cycles, yet lack any purposeful behaviour. Reports of 'late' recovery or discovery of awareness (that is, > 1 year after injury), have led the latest DoC guidelines to abandon the term 'permanent' when describing patients with VS.[52,53]

The MCS describes patients who show limited but clear evidence of awareness of themself or their environment.[54,55]. Two types of MCS have been identified: MCS- (minus) and MCS+ (plus). In the MCS- state, patients demonstrate at least one of the following behaviours: visual fixation, object localization, object manipulation, automatic motor responses, non-functional communication, or visual pursuit, but lack any evidence of command following or language function. The MCS+ state describes patients who demonstrate signs of language function through the ability to either command follow, recognize objects, or produce intelligible verbalization.[56] However, these patients cannot consistently engage in complex communication or object use. Finally, emergence from MCS (eMCS) refers to patients who have transitioned from a DoC to a condition where they reliably and consistently exhibit functional communication or purposeful use of objects. Some level of recovery from MCS is more likely than it is from the VS.[33] However, some patients may remain in a MCS indefinitely.

Prolonged DoC often require ongoing care strategies focused on improving quality of life and maximizing functional outcomes over time. While acute DoC demand rapid assessment and intervention due to their emergent nature, prolonged disorders require sustained, often multidisciplinary care to address evolving needs and support patients and families through extended periods of disability.[57] Patients with prolonged DoC are at a high risk of developing medical comorbidities that directly relate to their brain damage (e.g. epilepsy, spasticity) or to their prolonged immobility (e.g. respiratory comorbidities, metabolic abnormalities).[58]

Behavioural Assessments

The most recommended behavioural assessment for detecting signs of awareness along the DoC continuum is the Coma Recovery Scale — Revised (CRS-R), which, has been shown to detect signs of awareness in up to 40% of patients that appear to be unresponsive.[59–61] However, the results of the CRS-R can be confounded by motor deficits, examiner biases in interpreting subtle responses, and a patient's sensory impairments. While the CRS-R remains the most widely used behavioural assessment of awareness, it fails to detect it (when it exists) in approximately 20% of unresponsive patients.[7,62] The CRS-R is also time-intensive and often not practical as a daily assessment tool for patients in the ICU but is commonly used in patients with prolonged DoC. Other behavioural examinations that have been validated for DoC patients include the Simplified evaluation of CONsciousness disorders (SECONDs),[63] the revised Motor Behavior Tool (MBT-r),[64] and CRS-R Fast.[65] Of important note, the habituation of the startle reflex (hASR) is a simple and accurate bedside measure to distinguish MCS from VS/UWS.[66,67] The hASR enlarges the MCS behavioral repertoire, correlates with the functional and structural integrity of a brain-scale fronto-parietal network, and predicts 6-month recovery of awareness making it an attractive tool to use with DoC patients. Moreover, validated analogical scales used by caregivers[68] and pain anticipation signs are other novel tools that have been validation and should be considered valued additions to the repertoire of DoC assessment tools.

Functional neuroimaging in DoC: An historical perspective

Functional neuroimaging in DoC already has a long and scientifically rich history, spanning more than three decades. This history can be characterized in terms of the different technical approaches employed (i.e. fMRI, EEG, PET), the imaging paradigms used (active, passive, resting state) and the types of inferences that have been made about residual cortical function based on those paradigms (e.g., perception, awareness, communication).[69–71] With this in mind, it is useful to review the major milestones in this field, in terms of when they occurred and how they shaped its trajectory (Fig 1).

Neuroimaging first emerged as a potential assessment tool for DoC patients in the 1980s-1990s, when the majority of neuroimaging centres used either fluorodeoxyglucose PET (FDG-PET) or single photon emission computed tomography (SPECT) to measure cerebral blood flow and glucose metabolism.[72–74] Typically, widespread reductions in metabolic activity of up to 50% were reported in prolonged DoC, although in a few cases normal cerebral metabolism and blood flow were found.[75–77] However, it was only when $H_2^{15}O$ PET activation studies became more commonplace in the mid-1990s, that it became possible to relate such changes in neural activity to specific underlying cognitive processes. In the first of such studies, regional cerebral blood flow was measured in a post-traumatic patient who had been diagnosed as being in a VS, while the patient's mother read him a story.[78] These and similar studies using faces, speech and non-speech sounds, and pain helped to establish that many DoC patients retain a greater level of cognitive processing than is apparent when they are tested behaviourally.[79–83]

$H_2^{15}O$ PET activation studies involve radiation, which might preclude essential longitudinal or follow-up investigations in many patients or even a comprehensive examination of multiple cognitive processes in any one session.[84] A key development in this rapidly evolving field was the relative shift of emphasis in the early 2000s to fMRI studies. Not only is fMRI more widely available than PET, but it also offers increased statistical power, improved spatial and temporal resolution, and does not involve radiation. This switch in methodology, and the uptick in studies of DoC patients that it promoted allowed for more direct connections to be made between patterns of neural activity and preserved cognitive function, including speech perception, speech comprehension, emotion, and sensory processing, revealing that many behaviourally non-responsive patients retain a greater level of cognitive function than appeared to be the case from standard bedside examination.[85–89] However, for many years, it was entirely unclear what these preserved cortical responses might represent in terms of awareness. Many types of stimuli, including faces, speech and pain, will elicit relatively 'automatic' responses from the brain; that is, they also occur in the absence of awareness.[90] This fact exposes a central conundrum in the study of awareness and in particular, how it relates to DoC: if responses to stimuli such as faces and speech *can* occur automatically in the brain, does it mean that they *are* occurring automatically in DoC patients?

The solution to this conundrum came in 2006, when it was shown for the first time that a patient who presented as VS, was unequivocally aware, despite showing no behavioural signs to support that contention.[11] The patient was able to modulating her fMRI activity during two mental imagery tasks (imagine playing a game of tennis and imaging walking through her home) in response to external commands. Since overt command-following, demonstrated through behavior, is recognized as definitive evidence of awareness in brain-injured patients, covert command-following, identified through intentional changes in brain activity, can be used to draw the same conclusion.[12,91] In a follow up study in 2010, the same team showed that almost 4/23 (17%) of patients who were diagnosed as VS could willfully modulate their brain activity in this way, suggesting that a significant minority of this population retain a level of awareness that is entirely undetectable using traditional bedside assessment.[9] In 2011, it was shown that EEG could provide information that was comparable to that acquired previously using fMRI, again confirming that around 20% of patients who cannot reliably follow commands behaviourally are, in fact, aware. [10] The prevalence of this phenomenon, which has been referred to as 'covert awareness' and labelled 'cognitive motor dissociation',[13] has now been confirmed by numerous follow-up studies in hundreds of patients diagnosed as VS and MCS-.[9,10,92]

Over the next few years, there was a relative explosion of advanced neuroimaging and electrophysiological techniques for patients with DoC, and significant progress was made in understanding how they might best be deployed to improve both diagnosis and prognosis.[93] A growing number of patients were studied, making it possible to demonstrate that intact neural responses were associated with better chances of some recovery.[15–17,24,94–97] Studies with larger sample sizes also enabled more robust conclusions to be drawn, while advancements in data processing and machine learning techniques allowed for detailed analyses of brain dynamics, facilitating the development of improved diagnostic and prognostic models for DoC.[21,98–106] Moreover, a notable milestone during this era was the development of fMRI technology to allow some behaviourally non-responsive patients to answer simple "yes" and "no" questions by modulating their brain activity in the scanner in real time.[9,12]

Between 2010 and 2020, a key question that emerged was whether these techniques could be used to assess ICU patients with acute DoC. In this group, prognosis is even more uncertain than in prolonged DoC, and the diagnosis is often entirely unclear. In 2017, task-based fMRI and EEG in an ICU population to identify awareness and passive responses to auditory stimuli in the first few days after a brain injury.is study demonstrated that task and stimulus-based neuroimaging in the ICU is feasible, and that they may have an important role to play alongside traditional methods of clinical assessment. In 2019, covert command-following detected with EEG in the ICU in 15% patients with severe brain injury out of a group of 104 patients were covertly aware, and that these patients were more likely to have a good functional recovery (and recover more quickly) than those who were not covertly aware.[43] These studies, along with others demonstrated that advanced neuroimaging can provide reliable indicators of recovery in the ICU,[18,19,107–110] as shown prior in chronic DoC literature[15,111]. Most recently, new bedside imaging techniques like functional near-infrared spectroscopy have emerged, and have been used successfully to detect covert awareness and passive processing in both acute and prolonged DoC patients.[112–114]

In summary, the culmination of 25 years of research have revealed two critical insights. First, it has been consistently demonstrated that around 20% of both chronic and acute DoC patients who cannot behaviourally command follow remain covertly aware, challenging diagnostic gold standards in a significant minority of cases.[6–10,16,42,43] Second, these techniques can predict short and long-term recovery in patients with DoC and can provide critical information that has the potential to alter/shape the trajectory of care.[8,16,17,23,24,43,94,95,111,115] As a result, this body of work has prompted calls for a reassessment of existing diagnostic categories and guidelines for the treatment and assessment of behaviorally non-responsive patients. In response, clinical bodies in the United States and Europe now advocate for the incorporation of advanced neuroimaging into the management of DoC patients.[26,27]

The clinical importance of neuroimaging

Prolonged Disorders of Consciousness

Using advanced neuroimaging to assess residual and covert awareness in patients with prolonged DoC has significant clinical implications.[12] First, it fundamentally alters the diagnosis and understanding of a patient's cognitive condition, which has profound ethical and medical consequences. This reclassification can lead to changes in care plans, including the introduction of tailored rehabilitation programs aimed at enhancing communication and cognitive function. Second, identifying covert brain activity can enhance the accuracy of prognostic assessments, offering families and healthcare providers more precise information about the patient's potential for recovery and long-term outcome.[15,97] In fact, one of the largest studies to date in prolonged DoC found that over two-thirds of unresponsive individuals in whom functional neuroimaging detected covert awareness, later regained behavioural signs of awareness.[16] This finding is further supported by two recent EEG studies showing that patients who were able to complete a neural command-following task and those with neural responses to language stimuli showed improvement.[94,97] While it is important not to conflate improvement with recovery, this is nonetheless encouraging, and confirms that functional neuroimaging has a role to play in predicting which prolonged DoC patients are more likely to improve over time. Finally, legal proceedings surrounding decisions about the withdrawal of nutrition and hydration in this patient group often hinge on two critical questions: 1) Does the patient have any awareness of their condition? 2) Do they have any prospects for recovery? Functional neuroimaging can provide valuable information that addresses both of these questions, offering insights into the patient's level of awareness and, by extension, their potential for recovery.

Acute Disorders of Consciousness

In the acute setting, the need for advanced imaging arguably becomes more pressing, as detecting covert brain activity in acute DoC may impact clinical decision-making. If a patient is known to be covertly command following, or have neural activity similar to that of a healthy individual in response to passive stimuli, discussions regarding aggressive rehabilitative care versus the withdrawal of life-sustaining measures are likely to be entirely different compared to situations in which the patient is assumed to have no residual cognitive function. Moreover, the presence of preserved awareness has direct prognostic implications, as these patients have more chance of recovering behavioral awareness and doing so more quickly than those without such signs.[8,43] Given that the majority of deaths in brain injured patients in the ICU result from the withdrawal of life-sustaining measures, correct assessment of awareness is crucial to avoid inappropriate or premature decisions being made.[40,116,117]

In recent years, neuroimaging in acute DoC has emerged as a reliable predictor of long-term recovery.[5] Many decisions to withdraw treatment following severe brain injury occur within the first 72 hours and can change on an hour-to-hour basis, often influenced by prognostic pessimism and the belief that many patients will have poor outcomes.[116,118,119] Recent advances in neuroimaging techniques have challenged the status quo by demonstrating both higher sensitivity and specificity than standard clinical tools when predicting recovery.[23,43] To this end, neuroimaging has a critical role to play in the decision-making process for acute DoC patients. The fact that it is not more widely used may deprive some patients of precise and reliable predictors, thereby adversely affecting their outcomes, increasing the length of hospital stays, increasing healthcare costs, and possibly leading to erroneous decisions to withdraw life-sustaining measures.

How to increase adoption, given endorsement

One important change in recent years has been that various international regulatory bodies have now endorsed the use of functional neuroimaging in DoC. Recent guidelines by the American Academy of Neurology, the American Congress of Rehabilitation Medicine, and the US National Institute on Disability, Independent Living, and Rehabilitation Research, recommend that advanced neuroimaging may be used to probe for preserved awareness in patients who are unresponsive to serial behavioural assessments and classified as VS/UWS 28 days after brain injury.[27] The European Academy of Neurology guidelines advocate a broader approach, suggesting that task-based, stimulus, and resting-state paradigms using fMRI, EEG, and PET should be used to evaluate any patient who lacks command following at the bedside.[26] It is important to note, however, that the current UK guidelines argue that these more sophisticated neuroimaging techniques do not form part of routine clinical evaluation for patients with DoC and are best reserved for research purposes.[30,120]

Despite being endorsed by several medical bodies; neuroimaging techniques have not been widely implemented as standard clinical assessment tools. Recent surveys indicate that only a fraction of medical centers (between 8% to 20%), utilize advanced neuroimaging for diagnostic and prognostic purposes.[28,29] However, these figures likely underestimate the global adoption rate with a selection bias in responses, highlighting significant barriers to integration. While the majority of centres surveyed expressed that, in theory, it would be possible for them to integrate advanced neuroimaging into the assessment of patients with DoC, three key barriers remain: cost, difficulties in accessing necessary technology, and lack of sufficient expertise to conduct such assessments.[29]

Cost

While the initial investment required to acquire advanced neuroimaging technologies can be high (e.g. to purchase an MRI scanner), the following points should be kept in mind. First, advanced neuroimaging (whether that be fMRI, EEG or PET) is not excessively costly, when compared to the enormous costs of acute and long-term care of patients with DoC.[121,122] Second, the costs should not be considered in isolation, but rather as a function of the potential benefits to patients.[123,124] By analogy, kidney dialysis is extremely expensive, but keeps people alive.[125] If a DoC patient will benefit from an assessment tool that can provide novel diagnostic and prognostic information (especially when other tools fail to do so), the cost can be more reasonably justified. Third, the main reason that advanced neuroimaging is often perceived as expensive is because historically, these approaches were only used in research centres where cost recovery models were in place to pay for the initial equipment purchase. Most hospitals acquire imaging equipment for a variety of purposes, not directly related to DoC, making the operational costs of running them relatively low. Furthermore, in countries with private health care systems, such as the United States, insurance companies are already beginning to reimburse costs for techniques like fMRI and EEG.[126] Of course, lack of insurance coverage may be a barrier to access for many, but that is not a problem that is unique to functional neuroimaging.

Lack of technology

We acknowledge that in certain situations—particularly in remote or low-income areas—access to MRI, PET, and EEG may be significantly restricted, and initiating a neuroimaging program may be financially prohibitive. As a result, patients in these areas may have limited access to these advanced diagnostic tools, which will impact the quality of care they will receive. Addressing these disparities requires innovative solutions, such as mobile imaging units and telemedicine consultations to ensure equitable access to essential diagnostic services. Most MRI scanners now come equipped with functional neuroimaging capabilities (which may already be used for other clinical purposes, such as epilepsy surgery mapping), while clinical grade EEG montages (arguably the most accessible technology in this context) are widely available and already in use in many settings. In most cases, existing MRI technology can be repurposed so that functional imaging sequences can be acquired at both 1.5T and 3T.[127] While it is often believed that hospitals lack the technology to perform sophisticated neuroimaging studies, this is an historical misconception. For example, there are more than 7800 MRI scanners in the United States alone, and most are capable of performing fMRI.[128]

Personnel

Here, we concede that specialized knowledge is crucial for the accurate analysis and interpretation of neuroimaging results, especially because no widely accepted automated pipelines currently exist. While administering neuroimaging paradigms may be relatively straightforward, setting up protocols and analyzing and interpreting the data may be more challenging. While guidelines exist for using neuroimaging techniques in DoC, they often fail to i) describe which paradigms and technologies should be used for specific types of cases ii) identify which patients will benefit most iii) recommend the optimal timing for imaging, iv) describing *how* to integrate these methods into clinical practice. In the following sections we will seek to rectify this by offering a pragmatic framework for effectively utilizing these techniques, specifying when to apply which methods, and providing practical guidance for their incorporation.

Overview of techniques and paradigms

Imaging techniques

fMRI

Functional MRI is a neuroimaging technique used to measure and map brain activity by detecting changes associated with local blood oxygenation. In most contexts, the blood oxygen level dependent (BOLD) signal is measured, which reflects alterations in the levels of oxygenated and deoxygenated blood in the brain. When a brain area is more active, it consumes more oxygen, which can be detected by fMRI. Often considered the gold standard of neuroimaging, fMRI provides unparalleled spatial resolution that can allow for precise localization of activity.[129] On the one hand, in acute DoC, access to MRI is relatively straightforward as most hospitals are already equipped with scanners, and patients often only need to be transported short distances within the hospital to receive a scan. On the other hand, acute patients may be hemodynamically unstable, unable to lie flat in a scanner due to raised ICP, or heavily sedated, which would prohibit the acquisition of a functional sequence. Transporting acute patients to MRI also carries inherent risks. To mitigate this, we recommend conducting fMRI scans when a clinically required structural scan has been requested e.g., for brain injury prognostication and structural diagnosis.[37] Where prolonged DoC patients are concerned, access to MRI can be more problematic because many patients are cared for in non-hospital settings. Nevertheless, given that fMRI has been shown to significantly change the diagnosis of awareness for a substantial minority of patients,[7] we would argue that such efforts are well justified in most cases.[123,124] As in acute DoC, efforts should be made to organize functional and structural scans at the same time to minimize risks and maximize the information that can be acquired during a single hospital visit.

PET

18F-FDG-PET is a functional imaging technique that measures glucose metabolism in the brain. By using a radiolabeled glucose analog, PET scans provide detailed images that reflect the metabolic activity of brain tissue. This technique is particularly valuable for identifying regions of increased metabolic activity, which can reliably differentiate between states of awareness.[16,17,130,131] In many cases, fMRI and PET share similar medical and practical considerations. One advantage of FDG-PET is that sedation does not significantly alter the metabolic demands of the brain when administered after tracer uptake, making it a reliable option even when patients require sedation during the imaging phase. However, it's important to note that administering sedation during the tracer uptake phase may affect the PET signal, as sedation could alter the metabolic activity being measured. On the other hand, while fMRI can be used to confirm awareness, PET only measures the metabolic integrity of cortical networks that are necessary for awareness, rather than confirming that the patient is aware *per se*. Put simply, fMRI can be used to establish covert command following, because neural 'command following' (willful or intentional neural modulation) whereas results of 18F-FDG PET scans can be suggestive of awareness but cannot guarantee it.

EEG

Electroencephalography (EEG) is a neuroimaging technique that measures electrical activity in the brain using electrodes placed on the scalp. Importantly, EEG has high temporal resolution but limited spatial resolution. Its portability, widespread accessibility, and relative ease of use make it suitable for DoC patients along the temporal continuum. Most ICUs are equipped with standard-grade EEG montages that monitor for seizure activity. These montages can also be used to detect covert brain activity associated with awareness as well as changes in electrical signals in response to passive tasks, or at rest[132]. For prolonged DoC patients, EEG is a more convenient and accessible technique that can be brought to the patient rather than having them visit a hospital. However, the technique's sensitivity to external artifacts and motion can pose challenges. Despite this, EEG remains an attractive and ideal tool to use with DoC patients due to the low-cost, non-invasiveness, the ability to continuously record patient brain activity. Moreover, EEG can be coupled to cognitive paradigms, to brain-computer interfaces, and can be used as a dedicated device for each patient in a continuous fashion (in sharp contrast with current fMRI devices).[8,10,99,133]

Emerging Technologies

Functional near-infrared spectroscopy (fNIRS) is portable neuroimaging is considered an optical equivalent to fMRI with the advantage of being a relatively inexpensive that enables patient monitoring at the bedside.[113,114,134–136] fNIRS infers inferring brain activity through neurovascular coupling by estimating concentration changes in oxygenated and deoxygenated (HbR) hemoglobin.[137–139] Recently, fNIRS has been shown to be effective at detecting commonly studied resting state networks, sensorimotor processing, speech-specific auditory processing and volitional command driven brain activity.[114] Moreover, fNIRS has been used to identify acute and prolonged DoC patients with covert awareness, establishing its diagnostic utility.[114,140] Whether fNIRS is useful for prognostication in DoC remains to be determined.[141]

Both fNIRS and fMRI have been used to *communicate* with behaviourally non-responsive patients in acute and chronic settings.[9,12,142,143] Nevertheless, a true 'brain-computer interface' (BCI) for routine communication with brain injured patients has yet to be developed.[144–146] In large part, this reflects the enormous technical hurdles that need to be overcome in developing BCIs that are sensitive enough to detect covert brain activity and facilitate reliable communication in real-time, yet progress is being made.[147] In future, BCIs have the potential to allow DoC patients to communicate about their well-being, pain, or end-of-life preferences (i.e. medically assisted death), thereby offering patient autonomy in the medical decision-making process. Both EEG and fNIRS are ideal tools in this regard due to their simplicity of use and portability. This is particularly crucial for patients with covert awareness/CMD, who clearly retain cognitive capabilities but are unable to communicate through conventional means. The ethical mandate for the field is straightforward: increased investment in BCI technologies is essential to empower patients who are otherwise unable to communicate or take part in crucial decisions, giving them a voice in their care.

Transcranial Magnetic Stimulation paired with EEG (TMS-EEG) combines brain stimulation using magnetic pulses with the recording of electrical brain activity.[148] As a result, neural complexity measures can be obtained via the perturbational complexity index (PCI). TMS-EEG can directly measure neural activity, enabling a precise assessment of brain dynamics with high specificity and sensitivity for differentiating states of awareness and avoids relying on cognitive processes like language, attention, or memory. [149,150] Importantly, TMS-EEG cannot directly measure awareness but rather the capacity for it. While the use of TMS-EEG remains limited, it remains a promising potential diagnostic and prognostic tool in acute and prolonged DoC.

Types of neuroimaging tasks

Command following

In command-following tasks, patients are instructed to engage in a mental imagery paradigm that requires intentional control of brain activity in response to external prompts. In this context, positive neuroimaging outcomes rely on the patient's active participation, which is absent if they lack awareness.[12] The two most commonly used command following paradigms are motor imagery (whereby patients are instructed to imagine playing tennis or imagine opening and closing your hand) and spatial navigation (whereby patients are instructed to imagine walking through your home).[42,151,11] While these tasks are able to directly detect preserved awareness, a positive result also reveals intact language comprehension, working memory, and executive processing.[12] Thus, from a positive result one can draw high-level conclusions about a patient's level of awareness as well as the preservation of an array of cognitive functions. It is important to note that a negative result in command following tasks cannot be used to rule out awareness.[30] For example, a patient may fail to hear or comprehend the instructions, be delirious, have confounding medications, or not have the cognitive capacity to complete the task, despite retaining some level of awareness. Nevertheless, the risk of such 'false negatives' does not diminish the utility of such approaches because it is positive, not negative, results that influence action.[30]

Passive paradigms

Passive paradigms examine neural activity to in response to external sensory stimuli (i.e. language, music, somatosensory). There stimuli allow for precise measures of cortical function and, by proxy, may indicate the extent of brain injury.[15] Importantly, passive paradigms require no active participation from the patient. Passive paradigms can provide important diagnostic and prognostic information. For example, a positive result in the absence of a behavioral response can indicate that a patient has preserved cortical function in response to a particular type of stimulus, such as a face or a voice.[15,152] Moreover, the extent to which passive stimuli are processed (as inferred from neuroimaging results) has been shown to be related to the extent of recovery.[15,18,19,97] However, one cannot assume that such responses are accompanied by any phenomenological experience of those stimuli. Put simply, awareness is not necessarily required for a positive response to occur, as similar neural signatures have been observed in healthy individuals during anesthesia or sleep .[90,153] Nevertheless, a positive result in a passive paradigm can at least indicate that the cortical areas responsible for the underlying cognitive functions are intact.

EEG based measures of cognition have also been commonly used to assess for residual cognition, namely the P3 response (or P300), which is a component of an event-related potential (ERP) that reflects cognitive processes related to awareness and attention.[132] The widely used "local-global" event related potential (ERP) paradigm, incorporates two layers of auditory regularity and presence of a P3b global effect has been shown in early studies to be associated with improved prognosis, serving as a predictor for transitioning from a MCS to full consciousness.[154] Event related potentials have been studied in many contexts with DoC patients, and have emerged as a reliable assessment tool for states of awareness and preserved cognitive function.[155] Such studies have shown that deviant tones,[156] somatosensory stimuli,[157] hierarchical levels of auditory linguistic processing (i.e. perceptual and semantic)[97,158] and spatial attention[159] can be leveraged to assess preserved cognitive functions in DoC patients with EEG.

Moreover, recent studies utilizing inter-subject synchronization under ecological stimulation conditions have provided novel insights into assessing preserved cognitive function.[98,160–162] These studies present DoC patients with stimuli and examine whether their neural[98,160,162] and cardiac[161] activity synchronizes with the stimuli in a manner comparable to that of healthy controls. Inter-subject synchronization studies offer a sensitive and naturalistic approach to assess preserved cognition in DoC patients by examining how their neural and physiological responses align with complex stimuli, such as speech or narratives, compared to healthy controls. This method provides insights into higher-order cognitive functions that traditional stimulus-response paradigms may miss.

Stimulus-free paradigms

Stimulus free paradigms (otherwise known as resting-state) measure spontaneous synchronized patterns of brain activity in the absence of external stimulation. Resting-state fMRI can reveal networks linked to different brain functions, including those underlying various aspects of cognition and awareness[163], whereas resting-state EEG can be organized into distinct frequency bands that correspond to different states of mental activity.[164] In fMRI and EEG, there is strong converging evidence that resting state techniques can accurately predict levels of awareness (e.g., VS vs. MCS),[21,99,165] as well as long-term recovery from severe brain injury with high precision.[23–25,95,133,166–175] Moreover, quantitative EEG metrics that examine power spectral density measures through the median or mean frequency have demonstrated to be highly promising metrics to assess DoC patients.[99,133] It is crucial to note that, while these measures can detect networks that support and sustain awareness and various higher order cognitive processes, it is not a direct measure of awareness and so whether it is preserved or absent cannot be deduced from stimulus free measure alone.

Moreover, measuring brain activity at rest using PET has been reliably used to differentiate between different states of awareness and uncover preserved brain activity in VS patients that resembles that of MCS patients.[16] In fact, up to 67% of patients behaviorally diagnosed as VS have been shown to retain at least partial preservation of a pattern of brain metabolism that resembles MCS patients (i.e., minimally conscious state, MCS*).[17] Of note, MCS* is a diagnostic category that broadly encompasses any patient who has neural activity from any imaging modality and paradigm that is comparable to conscious individuals.[17]

Summary of Paradigms to use with DoC Patients

It is evident from the discussion above that a wide range of imaging techniques and paradigms are available for assessing covert brain activity in DoC. A pressing question then, is which advanced imaging technologies and paradigms are most appropriate for answering specific clinical questions? With this in mind, the following conclusions can be drawn with respect to the discussed literature, notwithstanding the fact that which techniques and paradigms are used will ultimately depend on technological availability and analysis expertise:

1. Command following tasks (using either fMRI or EEG) should be used to look for signs of awareness in both acute and prolonged DoC patients. The results can inform both diagnosis and prognosis.
2. Passive stimuli (using either fMRI or EEG) such as auditory sounds can be used to look for evidence of covert cortical processing in response to external stimuli in both acute and prolonged DoC patients. The extent of neural processing observed can inform prognosis.
3. PET can be used in patients with prolonged DoC to measure preserved metabolism, which has some diagnostic and prognostic implications.
4. Resting-state fMRI and EEG can be used for diagnostic and prognostic purposes in both acute and prolonged DoC patients.

Patient selection criteria and timing for neuroimaging application

A significant shortcoming in neuroimaging guidelines is the absence of specific recommendations about which patients stand to benefit most from advanced neuroimaging techniques. Although almost any DoC patient can theoretically undergo a functional neuroimaging sequence (barring medical and physical contraindications), it does not necessarily mean that all patients should. Given the practical bottlenecks of staffing, limited availability on scanners, and EEG use, it is important to select patients who stand to benefit the most from these techniques. Moreover, there are unique considerations in both a prolonged and acute setting, as follows.

Acute DoC

In acute DoC, neuroimaging should be considered for any patient who does not demonstrate behavioral command following through serial, standardized neurological assessments (i.e. coma, VS, MCS-), except in cases where brain death has been confirmed or when clear markers of a poor prognosis are present. Given the wide scope of patients in an ICU setting, decision trees have been established for selecting patients that may benefit most from advanced neuroimaging, while considering common medical and environmental confounds.[5] A strict timeframe may not always be feasible due to the variable nature of medical contraindications; however, neuroimaging should ideally begin once patients are hemodynamically stable, and for those treated with hypothermia for hypoxic-ischemic brain injury, after rewarming is completed. Additionally, since decisions about continuing or withdrawing life-sustaining therapy often occur within the first 10-14 days post-injury—sometimes even sooner [116,118]—we recommend conducting advanced neuroimaging before these critical discussions with families and surrogate decision-makers.

Prolonged DoC

Similar to acute DoC, advanced neuroimaging should be considered in any DoC patient who does not show behavioural evidence of command following. Decision trees have been established to identify *which* patients with a prolonged DoC may benefit from advanced imaging for diagnostic purposes, while taking into account medical and environmental factors. Such decision trees are very useful in selecting out of a large number of patients, which stand to benefit most from advanced neuroimaging.[176] However, it is important to note that these guidelines reflect AAN recommendations, which only endorse imaging with fMRI and EEG to look for evidence of covert command following in VS patients, and not MCS patients. Increasing evidence shows that some MCS patients, who only exhibit basic signs of awareness such as visual tracking or localization to painful stimuli, can follow commands in neuroimaging tests.[7] This suggests that they have more responsiveness and cognitive processing than is suggested from behavioral observation alone. Therefore, as recommended by European guidelines, functional neuroimaging should be used for MCS- patients who do not show command following or language function during behavioral assessments.

It is widely recognized that the likelihood of recovery decreases the longer a patient remains in a DoC. Nevertheless, it is crucial to acknowledge that delayed recovery remains possible and has been widely reported.[52] Recent evidence suggests that the length of time a patient spends in a DoC relates to the likelihood of covert awareness; that is to say, the longer a person remains in a DoC, the more likely they are to be able to follow commands using fMRI or EEG.[7] For example, one patient who had been repeatedly diagnosed as VS for 12 years and was completely unresponsive was later found to be covertly aware and capable of communication using fMRI.[12] Thus, it is not possible to recommend a definitive temporal cut-off for advanced neuroimaging in unresponsive patients who are beyond the post-acute phase. In fact, the longer a patient remains in this condition, the greater the imperative to understand their true cognitive state. Therefore, we recommend that advanced neuroimaging is used to assess covert brain activity as a routine clinical assessment for patients with prolonged DoC. One scenario where advanced neuroimaging would be particularly timely in prolonged cases of DoC is in legal situations involving a petition to withhold nutrition and hydration. In such circumstances, it seems essential to understand the true cognitive state of the patient prior to a decision to discontinue life-sustaining measures being made.[122]

Multi-modal and repeated testing in DoC

Finally, consistent with European guidelines we suggest that a multi-modal imaging approach be used to probe for awareness and preserved cortical processing, as multiple techniques and paradigms can improve detection accuracy and provide patients with their best chance of demonstrating preserved cognitive abilities.[177] Similarly, combining multiple techniques predicts recovery from a DoC more effectively than individual methods alone.[95,177,178] Wherever feasible, we suggest testing on multiple occasions to reduce the possibility of false negative findings – given that behavioural studies have demonstrated that assessments at a single time point are prone to false negatives.[179]

A recent clinical outline proposes a hierarchical framework for deploying multimodal neurophysiological techniques in patients with DoC.[132] This graded approach is designed to streamline the evaluation of patients, beginning with less complex methods and advancing to more sophisticated tools as needed. The workflow starts with conventional neurophysiological measures such as standard EEG and evoked potentials (SEPs). These are followed by more advanced techniques, such as ERPs and, finally, quantitative EEG analysis (TMS/EEG, and active EEG paradigms). The importance of this framework lies in its structured, stepwise approach, which helps clinicians decide which tools to deploy based on the complexity of the case and the patient's responsiveness. The general scheme is designed to guide behaviorally unresponsive patients toward different lines of evaluation depending on objective markers of thalamocortical integrity. By adopting this structured approach, clinicians can make informed decisions, ensuring that simpler tests are exhausted before moving to more complex, resource-intensive methods. Thus, using systematic and evidence-based progression model through increasingly sophisticated diagnostic tools may optimize the use of resources while maximizing the likelihood of identifying covert awareness or residual brain activity in patients with DoC.

Implementation of neuroimaging

Up to this point, we have outlined which patients stand to benefit from advanced neuroimaging techniques, when they should be used, and which approaches are most appropriate for answering specific diagnostic and prognostic questions. However, a major barrier to translating these specialized research techniques into widespread clinical practice is the lack of practical knowledge regarding the acquisition, analysis, and interpretation of functional neuroimaging data.[29] Successfully integrating advanced imaging techniques from research into clinical settings for DoC patients will require a collaborative effort among clinicians, radiologists, medical staff, and scientific researchers. Thus, we have outlined in **Table 1** a series of steps that can be taken to practically implement these techniques by outlining common considerations for neuroimaging set up, acquisition, analysis, and interpretation. In brief, interpreting neuroimaging data requires a nuanced approach. It is important to ensure that imaging data is of high quality, free from artifacts and noise, and correctly preprocessed to account for motion, spatial normalization, and other factors. Clinical teams must also consider the heterogeneity of the DoC population, as variations in brain injury etiology, extent of damage, and patient-specific factors can influence the neuroimaging results.[180] Results should be interpreted with caution and reported in electronic medical records. Medical teams should review results before conveying them to families of loved ones.[181]

If centres do not have the personnel to analyze data, the hub and spoke model may be an effective approach to promoting the implementation of advanced neuroimaging techniques in DoC.[182] According to this model, regional centers (spokes) are responsible for collecting neuroimaging data from patients, which is then sent to specialized centers (hubs) for analysis and interpretation. This structure ensures that patients across various regions benefit from advanced imaging technologies. By centralizing the expertise for data analysis and interpretation at the hubs, the model promotes timely assessments, consistent care standards, and collaborative care efforts. This approach may ultimately lead to improved and more efficient utilization of healthcare resources.

In clinical practice, similar approaches are commonly used in other contexts. For example, in the field of epilepsy, EEGs are often acquired at regional or local centers for seizure monitoring. These recordings are then sent to specialized epilepsy centers for detailed analysis and interpretation by clinical experts in the field.

Another implementation model that has been proposed for the care of DoC patients in France is a structured, two-tiered system designed to address the varying complexities of diagnosis.[183] This model envisions local (Tier-1) and regional (Tier-2) centers working in tandem, supported by centralized electronic databases and algorithmic hubs to enable systematic and equitable access to expertise. By tailoring the level of diagnostic rigor to individual patient needs—ranging from minimal data for straightforward cases to advanced behavioral and neuroimaging measures for more complex ones—this framework ensures efficient resource allocation. Furthermore, the proposal includes establishing a national registry of DoC patients to facilitate evidence-based monitoring, optimize performance, and support rational decision-making, making it a realistic and highly promising approach for widespread implementation. [183]

Future directions

There are several initiatives that the DoC field could adopt to facilitate the transition of neuroimaging procedures from a research tool to a routinely available clinical assessment. First, there is a need for publicly available imaging paradigms that will enable standardized and streamlined acquisition of imaging data. This is complemented by the necessity for automated preprocessing pipelines, which can simplify the complex process of data processing. Establishing ‘industry standards’ for fMRI, EEG, and PET protocols is crucial, as the lack of uniformity can lead to results that are difficult to compare across centres. A consensus for a standardised approach to reporting and interpretation of results would further ensure that data is presented in a consistent manner. In some instances, “possible” “probable” and “indeterminate” terminology has been adopted to report imaging findings.[184] To support these efforts, comprehensive educational resources, including training modules, tutorials, and workshops, should be developed to educate clinicians and researchers on the fundamentals and advancements in fMRI/EEG /PET analysis. Endorsement and support from clinical bodies for these educational initiatives may significantly enhance their uptake and impact. Additionally, defining common data elements for future research is essential to facilitate data sharing, aggregation, and comparison of results.[185]

Moreover, it is crucial to evaluate the economic implications of implementing neuroimaging techniques for diagnosis and prognosis in DoC patients – especially in the acute stage. Medico-economic studies could provide valuable insights into cost savings associated with improved diagnostic accuracy, more tailored treatment plans, and potentially shorter ICU stays. Such analyses would not only guide clinicians and policymakers in resource allocation but also help demonstrate the value of these techniques to regulatory authorities, fostering broader adoption. Future research in this area should prioritize quantifying the economic benefits alongside clinical outcomes to build a comprehensive case for integrating multimodal neuroimaging diagnostics into routine care.

There is an imperative to continue to explore low-cost tools such as electromyography and cardiac monitoring techniques that have been shown to be indicative of preserved cognitive processing, as they offer potential for more accessible diagnostic approaches in neuroimaging.[161,186,187] Emerging pupillometry techniques capable of detecting covert brain activity may offer a more accessible alternative in settings lacking advanced fMRI or EEG and be used with a broader patient population where neuroimaging is unsuitable.[188] Similarly, olfactory sniff responses provide a non-invasive and accessible biomarker, effectively distinguishing between unresponsive and minimally conscious states, predicting recovery of awareness, and correlating with long-term survival, further advancing the tools available for assessing awareness and recovery after severe brain injury.[189] Taken together, these tools, if validated effectively, could democratize access to critical neurological assessments and improve patient care globally. Lastly, incorporating nursing staff's assessments offers a valuable perspective that may enhance diagnostic accuracy.[68]

Conclusion

Translating advanced imaging techniques from a research perspective to a clinical setting will require the collaborative effort of clinicians, radiologists, medical staff, and scientific researchers. This unified approach is essential to bridge the gap between cutting-edge research and practical application, ensuring that the latest imaging advancements translate into tangible benefits for patients. As outlined in this review, integrating these technologies into clinical practice can profoundly enhance the accuracy of assessments, providing a clearer understanding of preserved awareness and improving prognosis. Patients with DoC deserve the most comprehensive and precise evaluation from the tools available, as their quality of life and potential for recovery hinge on accurate diagnoses and prognosis. Notwithstanding the fact that existing behavioural tools are well known to be limited and fallible in a significant proportion of DoC patients, neuroimaging stands to provide information that is otherwise unattainable via any other means. Only by bridging the existing gap between cutting-edge research and practical application, will we ensure that the latest imaging advancements translate into tangible benefits for all patients with DoC.

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Competing interests

The authors declare no conflicts of interests.

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Figure Legend

Figure 1 Historical Timeline of Seminal Neuroimaging Findings in Disorders of Consciousness. Historical timeline of seminal neuroimaging findings in disorders of consciousness from 1997 to 2024. Key discoveries[8-11,15,42,43,78,80] and advances include the identification of neural activity and cognitive function in DoC patients using PET, fMRI, and EEG, establishing the presence of covert awareness/CMD and its prognostic value for recovery. Highlights include the first documented case of covert awareness (2006),[11] guidelines endorsing imaging techniques in clinical practice (2020),[26] and a multi-national study confirming covert awareness in 25% of DoC patients (2024).[7] Abbreviations: AAN = American Academy of Neurology; CMD = cognitive motor dissociation; DoC = disorders of consciousness; EAN = European Academy of Neurology.

Table 1 Practical Recommendations for Implementation of Neuroimaging as an Assessment Tool in Disorders of Consciousness

Step	Recommendation
Imaging set up	Acquisition sequences will need to be set up on imaging devices for scanner-based techniques (fMRI, PET). One structural T1 (MPRAGE) sequence is also required to overlay the functional sequence to the structural image. Specific acquisition parameters may vary based on the manufacturer of a scanner. Detailed acquisition parameters for BOLD sequences and associated T1s are reported in the methods section for every functional neuroimaging paper and can be used to set up scanner protocols. Set up for EEG involves a standard channel EEG montage that is routinely used for clinical purposes.
Acquisition of data	For resting state sequences, data must be collected in the absence of any external stimuli. Stimuli will be required for task-based sequences (command following and passive tasks). Active command-following tasks to assess for awareness and passive auditory stimuli to assess for covert cortical processing. For both fMRI and EEG sequences, MRI-compatible headphones, an amplifier, and a laptop to deliver the stimuli are necessary. A comprehensive tutorial for PET acquisition can be found here: https://indico.giga.uliege.be/event/260/timetable/#20211002.detailed
Analysis of data	Analysis of data should follow standard protocols that follow strict statistical considerations. Neuroimaging toolboxes or publicly available code can be used to can be used to process data semi-automatically with extensive online tutorials to help guide the user. Well established regions of interest that tend to activate in response to specific stimuli during active and passive tasks should be considered.
Interpretation of data	Training should be available by societies who endorse neuroimaging on how to interpret data "probable", "possible", or "indeterminate" evidence guidelines has been proposed.[153] Integrate neuroimaging findings into existing electronic health records systems for a seamless workflow.

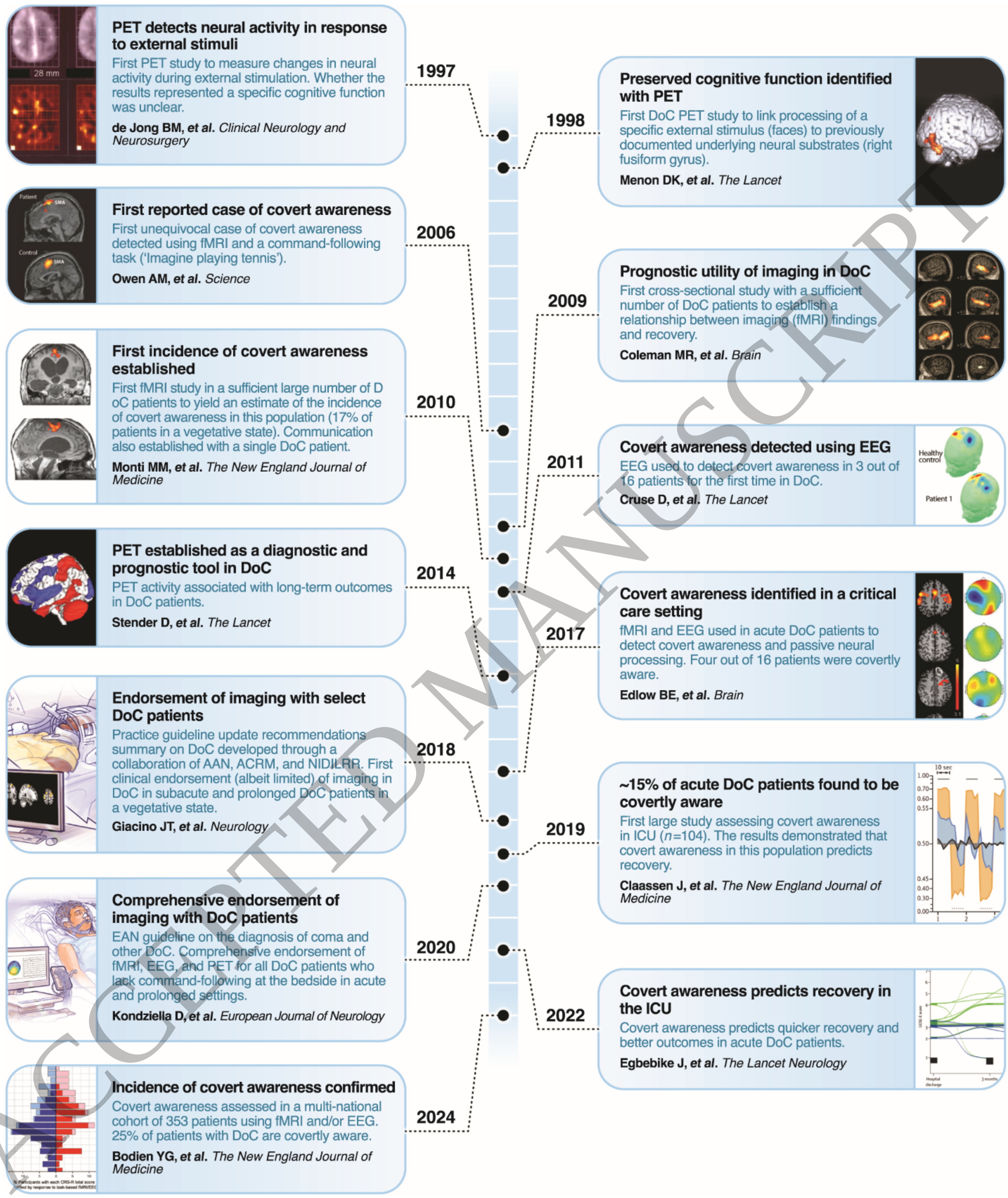

Figure 1
182x216 mm (DPI)