Advances in neuroimaging in disorders of consciousness

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Abstract

Disorders of consciousness (DoC) are a heterogeneous spectrum of clinical conditions, including coma, unresponsive wakefulness syndrome and minimally conscious state. DoC are clinically defined on the basis of behavioral cues expressed by the patients, on the assumption that such behavioral responses of the patient are representative of the patient's degree of consciousness impairment. However, many studies have highlighted the issues arising from formulating a DoC diagnosis merely on behavioral assessment. Overcoming the limitations of behavioral assessment, neuroimaging provides a direct window on the cerebral activity of the patient, bypassing the motor, perceptual or cognitive deficits that might hamper the patient's ability to produce an appropriate behavioral response. In this chapter, we will provide an overview of available molecular, functional and structural neuroimaging evidence in patients with DoC. We introduce the neuroimaging tools available in the clinical settings of nuclear medicine and neuroradiology, and present the evidence on the role of neuroimaging tools to improve clinical management of DoC patients, from the standpoint of differential diagnosis and prognosis. Last, we outline the open questions in the field, and point at actions that are urgently needed to fully exploit neuroimaging tools to advance scientific understanding and clinical management of DoC.

Keywords

Disorders of consciousness, Positron Emission Tomography, Computed Tomography, Functional Magnetic Resonance Imaging, Structural Magnetic Resonance Imaging, Diffusion Weighted Imaging, Diagnosis, Minimally Conscious State, Unresponsive Wakefulness Syndrome, Vegetative State

Rationale

Disorders of consciousness (DoC) include a heterogeneous spectrum of disorders. *Coma* is a transient state characterized by continuous absence of eye-opening (either spontaneous or following stimulation) persisting for more than one hour. Patients exit coma (usually after hours, days or typically not more than 4 weeks) when they regain spontaneous or stimulus-induced eye opening. After coma, patients might progress to *unresponsive wakefulness syndrome/vegetative state (UWS/VS),* where reflexive motor behaviors are present, while purposeful motor behavior and evidence of cognitive functions are absent. They might also progress to *minimally conscious state (MCS)*, when non-reflexive, purposeful behavior appears, pointing at a recovery of perceptual awareness (MCS-) and language comprehension (MCS+). If and when patients re-establish functional communication or functional use of objects, they are diagnosed as having *Emerged from the MCS (EMCS)*. EMCS patients do not fall within the spectrum of DoC, while still retaining significant cognitive and motor impairments.

As of now, the diagnostic categories of coma, UWS/VS and MCS are intrinsically defined on the basis of behavioral cues expressed by the patients. Conventional assessment of the degree of consciousness impairment in suspected DoC patients heavily relies on the assumption that the motor response of the patient is representative of the degree of consciousness impairment. Still, several studies highlight the issues arising from formulating a DoC diagnosis merely on behavioral assessment (e.g., Boly et al., 2013; Monti et al., 2010; Owen et al., 2007; Schnakers et al., 2009), as bedside assessment of consciousness is intrinsically gated by behavioral responsiveness (Perri et al., 2016).

Accordingly, increasing evidence recognizes that the absence of non-reflexive, contextual behaviors cannot serve as proof of lack of consciousness, and that a diagnosis relying on behavioral assessment alone risks mistaking lack of responsiveness for lack of consciousness. This point is well exemplified by the case of *locked-in syndrome (LIS)* (Smith and Delargy, 2005), where partial to total behavioral unresponsiveness coexists with intact consciousness and cognition. More recently introduced on the spectrum of DoC are *cognitive motor dissociation (CMD)* (Schiff, 2015) and *minimally conscious state* (MCS*)* (Gosseries et al., 2014; Thibaut et al., 2021), where lack of behavioral responsiveness coexists with covert command following for the former and cerebral function usually associated with consciousness for the latter. The identification of patients with partial to no consciousness impairment in a behavioral framework of complete unresponsiveness owes a great deal to neurophysiological and neuroimaging tools (Perri et al., 2016). These tools allow clinicians and researchers to get direct access to the presumed cerebral substrates of consciousness, bypassing the motor, perceptual or cognitive deficits that might hamper the patient's ability to produce an appropriate behavioral response. These considerations, together with a growing body of evidence, suggest that neuroimaging tools should be part of the diagnostic assessment of DoC, as also recommended in the recent guidelines of the European Academy of Neurology (EAN) (Kondziella et al., 2020) and the American Academy of Neurology (Giacino et al., 2018).

In this chapter, we will provide an overview of the molecular, functional and structural neuroimaging evidence in patients with DoC. We will first introduce the neuroimaging tools available in the clinical settings of nuclear medicine and neuroradiology, describing their biological targets of interest and the different levels of analysis and of interpretation that can be obtained from each tool. We will then present the evidence on the role of neuroimaging tools to improve clinical management of DoC patients, from the standpoint of (i) differential diagnosis and (ii) prognosis. Last, we will outline the issues and open questions in the field, and point at actions that are urgently needed to fully take advantage of neuroimaging to advance the understanding of DoC, promote accurate patient stratification and tailored care.

Neuroimaging tools: basics

Neuroimaging tools allow to get access to several aspects of brain structure and function. Some neuroimaging tools (Computed Tomography (CT), Positron Emission Tomography (PET) and single-photon emission computed tomography (SPECT)) are available within nuclear medicine departments; other tools (Structural and Functional Magnetic Resonance Imaging, sMRI and fMRI) are available within neuroradiology departments. Altogether, these tools allow to assess the degree of impairment of several parameters related to brain structure and function (Figure 1).

CT, PET and SPECT

Neuroimaging tools available in nuclear medicine settings allow to measure both brain structure (CT) and function (PET and SPECT). All these tools require exposure of the subject to a limited amount of radioactivity, as they rely on X- or gamma-rays for measurement.

CT – CT combines X-rays images taken from different angles and uses them to compute a comprehensive *structural* image of the brain (Buzug, 2011). The different degree of attenuation exercised by the different tissues on the X-rays allows to obtain brain images with very high spatial resolution (≈0.5 mm) and sufficient contrast between gray and white matter, the latter being however inferior to that of magnetic resonance imaging (MRI) (Balakrishnan, 2019).
In patients with DoC, CT represents the method of election to investigate the underlying etiology of DoC in *emergency* settings, thanks to its fast execution (scan duration: 5-10 minutes), general availability, low cost and compatibility with metallic implants and pacemakers (Damiani, 2019). Image quality is only marginally affected by patient movement.
PET – PET allows to measure biochemical processes via labelling a biological target of interest by means of a radiopharmaceutical, administered via venous injection. Localization of the radiotracer in the tissue is based on detection of gamma rays emitted by annihilation of the positrons released by the radiotracer (Turkheimer et al., 2014). Detection of gamma rays is used to reconstruct a *functional/molecular* brain image by means of computed-based algorithms, with good spatial resolution (≈4.5mm) and a sensitivity to the biological target of interest in the nano- to pico-molar range (Varnäs et al., 2013). As CT, the exam is compatible with metallic implants and pacemakers.
PET was one of the first neuroimaging tools used to investigate brain function in DoC patients, (see e.g., Bewermeyer et al., 1985; Levy et al., 1987). Traditionally, PET scans required long acquisition protocols, and invasive procedures to quantify the biological parameters of

interest (Heurling et al., 2017; Mintun et al., 1984). As of today, PET acquisitions have become faster, while advances in modelling have allowed to simplify quantification, avoiding invasive procedures (Guedj et al., 2022). These advances have made the exam much better tolerated by the patients. It is also worth mentioning that, thanks to improvements in scanner design and image reconstruction algorithms, the dose of radioactive tracer required for the exam is much lower than in the past. For the most used tracer, i.e., [18F]Fluorodeoxyglucose ([18F]FDG), the injected dose is 2-3 times lower than it used to be ≈20 years ago, corresponding to a radiation exposure similar to a person's yearly exposure to natural sources of radioactivity (Kaushik et al., 2015).
PET studies to assess brain functional/molecular integrity in DoC have mainly focused on two biological targets of interest, i.e. glucose metabolism and blood flow (Boly et al., 2008). Only a limited amount of evidence focused on investigation of neurotransmitter alterations, such as GABA-A and Dopaminergic, type 2 receptors, in DoC patients (Fridman et al., 2019; Qin et al., 2015b; Rudolf et al., 2002).

Glucose metabolism, the main source of energy production in the brain, can be measured by PET with the radiotracer [18F]FDG (Sokoloff, 1981, 1977). [18F]FDG-PET allows to track the trapping of glucose via phosphorylation by hexokinase, an extremely important, "gate-keeping" step of glycolysis, determining the rate at which all subsequent reactions can occur. Since ≈75% of brain energy expenditure is dedicated to neurotransmission (Howarth et al., 2012), tracking glucose metabolism is an indirect way to track neuronal activity; glucose phosphorylation is coupled in particular to glutamatergic neurotransmission (Stoessl, 2017), so that glucose metabolism can be considered as a proxy for excitatory neuronal communication.
[18F]FDG-PET studies typically use resting-state paradigms, with the subject not receiving any particular stimulation nor being involved in any particular task during the PET assessment. Traditionally, [18F]FDG-PET protocols involved a 60-minute acquisition with arterial blood sampling, allowing absolute quantification of brain glucose metabolism by means of cerebral metabolic rate of glucose (CMRglu). Currently, simplified protocols involving [18F]FDG are used with DoC patients, requiring a 10-15 minutes image acquisition to start 30 to 60 minutes post tracer injection; [18F]FDG uptake is determined based on the brain status from injection up to 30 minutes post-injection (the so-called "uptake" phase). This protocol design is particularly advantageous for DoC patients: in case the patient needs to be sedated during scanning, to limit movement and ensure good image quality, the sedation will not affect uptake of the tracer in the brain, as the latter takes place for the most part prior to sedation. When using these simplified procedures, glucose metabolism can be quantified using indices such as the standardized uptake vale (SUV) (Boellaard, 2009). Alternative methods for glucose quantification have also been recently developed in DoC (Stender et al., 2015). When an absolute measure of glucose metabolism is not needed (e.g., in studies interested in assessing *local* differences in glucose metabolism) relative measures can be used. The most common relative measure is the SUV ratio (SUVr), typically obtained via scaling on tracer uptake in the whole brain (e.g., Stender et al., 2014; Thibaut et al., 2012).

Blood flow, the main mean of glucose and oxygen delivery to neurons, can be measured by PET with the radiotracer [15O]H2O. [15O]H2O allows to track the water molecules that make up to 51% of the blood volume and that diffuse through the capillaries irrorating the brain parenchyma, providing a measure of blood flow. As increases in blood flow are normally

coupled to local neuronal activity by a specific spatio-temporal relationship (the hemodynamic function) (He et al., 2020), blood flow is deemed an indirect index of neural activity.
While [15O]H2O-PET is the method of election to study cerebral blood flow, its use is now less widespread because of the availability of less invasive neuroimaging techniques based on MRI. Acquisitions after administration of [15O]H2O is extremely fast, with a scanning time of 90-120 seconds. The signal is affected by the eventual administration of sedatives to the patients. [15O]H20-PET studies can use resting-state, passive-stimulation or active-task protocols. Resting-state protocols are mainly used to investigate co-fluctuations in brain perfusion across time or across subject, as a proxy for synchronized neural activity, also known as "functional connectivity" (Friston et al., 1993). Passive-stimulation and active-task paradigms are commonly used to assess the degree of brain activation during non-resting conditions, by quantifying the differences in perfusion between brain at rest and during sensorial/pain stimulation or during cognitive/motor tasks, that, under normal conditions, would elicit significant neural activations in relevant brain regions.

SPECT - Like PET, SPECT allows to measure biochemical processes by labelling a biological target of interest by means of a radiopharmaceutical, administered via venous injection. Differently from PET, localization of the radiotracer in the tissue is based on direct detection of individual (single) gamma rays emitted directly by the tracer. Detection of single gamma rays is used to reconstruct a *functional/molecular* brain image by means of computed-based algorithms, achieving a spatial resolution of around 12-15mm (Driessen et al., 2017), with an acquisition time of around 30 minutes. Differently from PET, the images obtained from SPECT are in general qualitative, i.e., they do not provide an absolute measure of the biological target of interest; methods for absolute quantification have been developed for more than a decade (Seret et al., 2012), their applications remaining still limited to research settings (De Schepper et al., 2021). These limitations have not hampered the use of SPECT in clinical settings, thanks to the lower cost of the scanners and easier methods of production of its radiopharmaceuticals. As CT and PET, the exam is compatible with metallic implants and pacemakers (Warwick, 2004). SPECT studies typically use resting-state paradigms, the subject not receiving any particular stimulation nor being involved in any particular task during the SPECT assessment.

MRI

Neuroimaging tools available in neuroradiological settings allow to measure both brain structure (sMRI) and function (fMRI), with minimally invasive procedures. Both sMRI and fMRI rely on the manipulation of the orientation of protons contained in the water molecules within brain tissue via application of a powerful magnetic field (DiProspero et al., 2022). MRI scanners typically available in general clinical settings are capable of generating magnetic fields with a strength of 1.5 Tesla, of 3 Tesla in selected clinical settings and research settings, and 7 Tesla in selected research centers. The strength of the magnetic field determines the signal-to-noise ratio of the resulting images but does not affect the spatial resolution. Different pulse sequences generate images with different contrasts and intensities, that allow to highlight certain properties of the tissue over others. MRI is generally well tolerated by DoC patients thanks to the relatively short acquisition times (about 30 minutes to include optimized sMRI and fMRI sequences), the major contraindications being claustrophobia and

presence of ferromagnetic implants in the patient body (pacemakers, clips, artificial valves and implants or foreign objects). sMRI and fMRI images are moderately sensitive to motion artifact so that acquisition of good quality images might require sedation of the patient. Patient sedation affects signal of fMRI sequences like BOLD and ASL, but not of sMRI sequences.

sMRI - sMRI allows to visualize morphology and density of brain grey and white matter, with a typical resolution of around 1 and 2mm, respectively. sMRI studies in DoC are performed generally for the purpose of either (i) visual inspection by a neuroradiologist, (ii) assessment of gray matter atrophy, or (iii) assessment of white matter integrity.

Visual Inspection – Conventional MRI sequences include different T1-weighted and T2-weighted images, allowing to detect brain edema, contusion, hematomas, herniation, hemorrhage, hydrocephalus, or hemorrhagic shearing lesion due to diffuse axonal injuries (Perri et al., 2016). While MRI is not the method of election in *emergency* settings, due to longer scanning time than CT and necessity of *ad hoc* antimagnetic equipment (e.g., respirator), neuroradiological assessment of conventional MRI is used (after CT has been performed), to assess if? possible intracranial injuries went undetected, taking advantage of the wide range of tissues contrasts available (Yuh, 2017). Conventional sequences include T1-weighted images, optimized to ensure maximum contrast between gray and white matter, providing relevant morphological information on atrophy, axonal injury, and enlarged ventricles. T2-weighted images (including T2* sequences) are optimized to ensure maximum contrast between brain tissue and lesions. Fluid-attenuated inversion recovery (FLAIR) images, based on T2-weighted imaging with suppression of cerebrospinal fluid (CSF) signal, further enhance lesion visualization.

Assessment of gray matter atrophy – aside from conventional neuroradiological assessment, T1-weighted images are most commonly used to measure and assess changes in volumes and/or cortical thickness across brain regions. Changes in gray matter volume can reflect neural loss or decrease in dendritic spine density (Keifer Jr et al., 2015).

Assessment of white matter integrity – on top of conventional MRI sequences, specific sequences exist to evaluate the structural integrity of the brain white matter. These sequences, i.e., diffusion weighted imaging (DWI), are optimized to measure water motility, and allow to make inferences on white matter integrity based on the molecular diffusion principle. In white matter tracts, water is constrained by the axons membranes and diffuses anisotropically, i.e., mostly along the axons. Variations in anisotropy can indicate alterations in the axon membranes, and hence point at reduced structural integrity or damage. Such variations can be assessed visually or quantified with specific metrics. Such metrics are obtained by first modelling the information on fiber orientation via fiber orientation distribution functions (fODF) to reconstruct the individual white matter tracts of the patients, an approach called diffusion tensor imaging (Huisman et al., 2006; Jones et al., 2000). The integrity of each tract is then quantified, voxel-by-voxel, using metrics like fractional anisotropy (FA) or mean diffusivity (MD).

fMRI - fMRI allows to measure blood oxygenation and blood flow with a spatial resolution of around 3-4mm. fMRI studies in DoC are performed generally based on two functional

measures (i) blood oxygenated-level dependent (BOLD) signal, and (ii) arterial spin labelling (ASL).

BOLD – fMRI measurement of BOLD signal relies on the different magnetic susceptibility properties of deoxygenated vs. oxygenated hemoglobin (being paramagnetic and diamagnetic, respectively), to infer differences in blood oxygenation. The latter is coupled to neural activity through the hemodynamic response function, a neurovascular mechanism regulating blood flow to cover the energy demands of local brain activity, the response being observed for around 20 seconds post neural activation, with a peak after around 6 seconds (Hillman, 2014; Wald and Polimeni, 2015). BOLD-fMRI allows to study blood oxygenation, as an indirect index of neural activity, with a spatial resolution of around 3mm. Since the measurement does not require exposure of the subject to ionizing radiations, it is now the most commonly used technique to investigate neural activity. Quality of BOLD signal can be affected by the presence of blood artefacts, which are commonly found in severely brain-injured patients. fMRI studies can use resting-state, passive-stimulation or active-task protocols. Resting-state protocols are mainly used to investigate co-fluctuations in brain BOLD signal across time, as a proxy for synchronized neural activity, also known as "functional connectivity" (Biswal et al., 1997); the configuration of collections of functionally connected brain regions, called "resting-state brain networks" (Greicius et al., 2003), can also be investigated. Passive-stimulation and active-task paradigms are commonly used to assess the degree of brain activation during non-resting conditions, by quantifying the differences in BOLD signal between brain at rest and during sensorial/pain stimulations or during cognitive/motor tasks, that, under normal conditions, would elicit significant neural activations in relevant brain regions.

ASL- ASL-fMRI allows measurement of resting-state cerebral blood flow by tracing the water molecules contained in the blood. This is done by tagging the water molecules in the blood within the carotid and vertebral arteries at the basis of the skull with a radiofrequency inversion pulse and then following the tagged molecules as they flow up into the brain (Bambach et al., 2022). ASL-fMRI allows absolute quantification for blood flow, although with lower dynamic range and accuracy, especially at subcortical level, compared to [150]H2O-PET (Fahlström et al., 2021). ASL-fMRI studies typically use resting-state paradigms.

Image Analysis

Data derived from neuroimaging acquisitions can be analyzed and interpreted using extremely different strategies. While a thorough overview of such approaches goes beyond the scope of this chapter, we describe below some of the most common strategies adopted in DoC.

Visual assessment – In DoC assessment, CT and sMRI images are often inspected visually by a neuroradiologist, to provide an evaluation of macroscopic morphological abnormalities (e.g., enlarged ventricles or midline shifts), pathological events (e.g., bleeding) and extent/severity of brain damage.

Quantitative analysis - PET, SPECT, sMRI and fMRI data are most commonly analyzed further to quantitatively measure the extent of brain damage or dysfunction, via statistical comparison with a reference group of healthy controls. Quantitative analysis of neuroimaging data follows typically three steps:

1) Data pre-processing:
For the quantitative comparison to take place, a series of pre-processing steps are required, e.g., filtering, co-registration, normalization and smoothing. One of the most crucial aspects of pre-processing is co-registration/normalization of patient's and healthy controls images into the same space, so that each 'location' in the patient's brain can be compared with the corresponding location in the healthy controls' brain. A common approach to achieve spatial co-registration/normalization is to match the patient (and healthy controls) image to a standard template in common standardized space. While DoC-specific templates have been developed to make the process smoother (e.g., Phillips et al., 2011), this step can be challenging in patients with DoC where spatial normalization algorithms can fail due to the huge brain deformations. Alternative approaches have been proposed that avoid the pitfalls of standard spatial normalization, either based on automated procedures (e.g., https://surfer.nmr.mgh.harvard.edu/) or on the manual delineation of the regions of interest to be analyzed; such approaches however allow to perform analyses at regional level-only and necessarily require availability of an sMRI-T1 image. Alternative approaches based on the low-dose CT images (typically acquired during PET scanning) have been proposed (Presotto et al., 2018) but not applied in DoC.

2) Data analysis:
Once the previous steps (i.e., pre-processing) are completed, statistical or quantitative analysis can take place. These can require computation of additional metrics of interest and/or comparison with the reference group of healthy controls via a statistical test. Data analysis can be either univariate or multivariate. *Univariate* analyses use information contained in each *individual* voxel or region of interest, to evaluate local changes in, e.g., glucose metabolism (FDG-PET), perfusion (H2O-PET, SPECT, ASL-fMRI), gray matter volume (T1-sMRI), white matter integrity (DWI-sMRI) or hemodynamic response (BOLD-fMRI, with passive-stimulation or active-task protocols). *Multivariate* analyses integrate information *across* multiple voxels or regions of interest. The most common multivariate metric in the literature is the so-called "brain connectivity", declined in *structural* (Hagmann et al., 2008a), *functional* (Friston et al., 1993) and *molecular* (Hahn et al., 2019; Lee et al., 2008) connectivity, relying on BOLD-fMRI, H2O- and FDG-PET and DWI-sMRI data, respectively. Whole-brain descriptions of structural, functional and molecular connectivity are defined as 'connectomes' (Sala et al., 2023; Sporns et al., 2005; van den Heuvel and Sporns, 2019). Structural brain connectivity assesses the number of white-matter tracts between brain regions, to infer the strength of regional interconnection (Hagmann et al., 2008b). Functional/molecular brain connectivity assesses co-variations in functional signal across brain regions/voxels, assuming them as proxies for functional brain communication (Friston et al., 1993). Brain regions/voxels that display strong tendencies to co-vary together form the so-called "resting-state brain networks" (Biswal et al., 1995; Greicius et al., 2003), detectable even at rest using methods such as seed-based analysis or independent component analysis (Sala and Perani, 2019) applied to BOLD-fMRI and FDG-PET data (Savio et al., 2017). Several of these resting-state networks have been identified (Dworetsky et al., 2020) and their functional significance

asserted in relation to cognitive, perceptual and motor tasks. For instance, a salience network, a language network, a visual network and motor network, have been identified (Smith et al., 2009). Two of these brain networks are of particular interest in the field of DoC, i.e., the internal awareness network, including the precuneus, cingulate and angular gyri, and external awareness network, including the lateral fronto-parietal areas (Thibaut et al., 2012; Vanhaudenhuyse et al., 2011). These networks, supporting awareness of the self and of the environment (Vanhaudenhuyse et al., 2011), are also known as default mode and executive control networks, respectively (Doucet et al., 2019; Dworetsky et al., 2020). Other metrics of interest can be derived from the quantitative analysis of neuroimaging data (e.g., Evans, 2013; Faskowitz et al., 2020; Margulies et al., 2016) but have not yet been applied to DoC patients.

3) Results interpretation: visual vs. quantitative evaluation

Once the metrics of interest are computed and/or the statistical comparison has taken place, results can be interpreted once again either visually or quantitatively. *Visual* evaluation of statistical maps obtained from comparison with healthy controls is fairly common in the case of [18F]FDG-PET images, where a rater visually assesses the location of statistical differences in internal and external awareness networks (e.g., Thibaut et al., 2012; Stender et al., 2014; see also example in Figure 2). *Quantitative* evaluation is generally performed on global or regional metrics (e.g., gray matter volume (T1-sMRI), number of tracts arising from a given brain region (DWI-fMRI), centrality or other graph theory measures of functional connectivity (BOLD-fMRI)); results can be interpreted following binary classification (pathological/normal index) after identification of a suitable cut-off (ideally in an independent sample of patients/healthy controls)(e.g., Stender et al., 2016). Global or regional metrics can also be further evaluated quantitatively by means of automated classification approaches that weight the information provided by each metrics and/or region of interest to achieve the best predictive accuracy (e.g., Annen et al., 2018b).

Diagnosis of DoC patients aided with neuroimaging

Several studies have been conducted to assess the value of neuroimaging for the differential diagnosis of DoC, with a main focus on distinguishing UWS/VS from MCS patients. Guidelines promoted by the American Academy of Neurology (Giacino et al., 2018), UK Royal College of Physicians (Royal College of Physicians, 2020), and European Academy of Neurology (Kondziella et al., 2020) have been published in the last five years, building on this evidence. An overview of the literature, and of the recommendations of the different guidelines, is provided in the following paragraphs and in Table 1.

In general, the overwhelming consensus is that brain imaging and electrophysiology techniques provide valuable insights into DoC, with some differences across guidelines. UK guidelines report that, while more work is needed for integration of *advanced* neuroimaging markers into routine clinical practice, more common neuroimaging examinations are recognized as valuable and recommended; US guidelines highlight that not enough evidence is available to support or discourage the use of neuroimaging for differential diagnosis (but not for prognosis, see next paragraph); on the contrary, EU guidelines recommend several neuroimaging assessments for the purpose of differential diagnosis. These differences can be

partially ascribed to the different procedures used to reach consensus across the different guidelines. Most importantly:
(i) UK guidelines are based on consensus meetings among experts convening up until October 2019 and *not* of a systematic review of the literature;
(ii) US guidelines are based on a systematic review of the literature up until February 2017; these guidelines are based on limited evidence, as only studies where 100% of the patients had prolonged DoC and/or results for 100% prolonged DoC were provided, were included. Quality of each study was established based on the methodological standards classification established by the American Academy of Neurology (Gronseth et al., 2011).
(iii) European guidelines are based on a systematic review of the literature from 2002 (year of the introduction of the category of MCS) up until October 2018. Studies including patients with acute or prolonged DoC were included. Quality of each study was established based on the GRADE methodological standards classification (Balshem et al., 2011).

CT, PET, SPECT

CT - Thanks to its high sensitivity to density changes in tissue and acute hemorrhages (Haupt et al., 2015), CT allows to ascertain DoC etiology in terms of hemorrhagic and ischemic strokes, intracranial and subarachnoid hemorrhage, brain edemas, herniations and acute hydrocephalus (Damiani, 2019) and skull fracture (14).
The use of CT imaging for the differential diagnosis of DoC is not addressed by *US or European guidelines*. CT imaging is recommended by *UK guidelines* (Royal College of Physicians, 2020) during the acute phase of care and for patients with prolonged DoC, only in case there is suspicion of undiagnosed or new specific, structural and operable causes of DoC, or at the doctor discretion, if a repeated examination is expected to provide more accurate prognosis. CT is especially recommended for the exclusion of hydrocephalus (Royal College of Physicians, 2020).

PET, glucose metabolism- Resting brain glucose metabolism is drastically diminished in DoC patients (Usami et al., 2022), the degree of decrease often associated to the degree of consciousness impairment (Figure 3, top panel); it was estimated that a minimum of 42% of the average global glucose metabolism is necessary to produce a conscious state (Stender et al., 2016). As global glucose metabolism does not necessarily return to pre-insult levels after recovery of consciousness (Laureys et al., 1999b), it is believed that the association between global glucose metabolism and consciousness is not absolute (Perri et al., 2016). Rather, consciousness impairment seems to be associated to decreased glucose metabolism (i.e., hypometabolism) in specific brain areas encompassing the internal and external awareness networks (Figure 3, bottom panel) (Laureys et al., 2004b, 1999a; Stender et al., 2014; Thibaut et al., 2012).
When it comes to international guidelines, *US guidelines* (Giacino et al., 2018) do not recommend nor discourage the use of PET for the differential diagnosis of prolonged UWS/VS and MCS, on the grounds of insufficient evidence available (Giacino et al., 2018). The statement is based on only one previous study that investigated whether glucose metabolism in regions of the internal awareness (default mode) network could help distinguish UWS/VS and MCS patients, reporting an AUC of 0.75 in a sample of 85 patients (Rosazza et al., 2016). *UK guidelines* do not considered PET as part of the routine clinical examination of patients with prolonged DoC, due to its unclear utility over and above clinical assessment and lack of

widespread availabilities in clinical settings (Royal College of Physicians, 2020). Still, they foresee a greater applicability of resting-state protocols, as used in [18F]FDG-PET studies, over more complex protocols involving active tasks in clinical and non-specialist settings (Royal College of Physicians, 2020). More recently, and taking advantage of a wider evidence base, the *European guidelines* have recommended the use of resting state [18F]FDG-PET to complement behavioral assessment in unresponsive patients. This recommendation is based on five studies with a total of 341 patients[1] (Annen et al., 2018a; Bodart et al., 2017; Chennu et al., 2017; Stender et al., 2016, 2014), overall showing that glucose metabolism (either in internal and external awareness networks (Annen et al., 2018a; Bodart et al., 2017; Chennu et al., 2017; Stender et al., 2014) or globally (Stender et al., 2016) allows to distinguish UWS/VS/coma patients from MCS patients with a 95% sensitivity and 70% specificity (Kondziella et al., 2020). The guidelines note that it is necessary that data acquisition follows high technical standards to be reliable, most importantly ensuring adequate levels of blood glycemia at the moment of injection and arousal of the patient during the uptake phase of the tracer (Kondziella et al., 2020). In line with these findings, a more recent study in 57 patients with prolonged DoC showed that absolute glucose metabolism can differentiate between UWS/VS and MCS patients with a 87% sensitivity and 76% specificity, resulting in an AUC of 0.82 (Hermann et al., 2021)

PET, blood flow - In DoC patients, [15O]H2O-PET is typically used in studies contrasting multiple rest and stress images, acquired within a single scanning session - something possible thanks to the short half-life and lower radiation dose of 15O tracers. [150]H2O-PET studies using passive-stimulation paradigms, where blood flow is studied at rest and during perceptual or pain stimulation, have been pivotal in showing that blood flow increases in primary cortices during external stimulation in post-comatose UWS/VS patients, while higher-order multimodal areas only activate in MCS patients (Boly et al., 2008, 2004; Laureys et al., 2002b, 2000a). In simple words, cortical activation is present but isolated and dissociated from higher-order associative cortices, suggesting a residual cortical processing that is probably insufficient to attain a normal degree of awareness (Laureys et al., 2002a).
None of the *guidelines* has made any recommendation for the use of [150]H2O-PET, for the quantification of blood flow in the differential diagnosis of DoC.

SPECT, blood flow - Brain SPECT studies in DoC are limited and have mainly focused on one biological target of interest, i.e., blood flow, using tracers such as Technetium 99m ethyl cysteinate dimer (99mTc-ECD), 99mTc- hexamethylpropyleneamine oxime (HMPAO), ^{123}I-N-isopropyl-p-iodo-amphetamine (IMP), or ^{133}Xenon (Hannawi et al., 2015). Studies have shown general decreases in brain blood flow in coma patients (Roine et al., 1991; Sato et al., 1989; Shiina et al., 1998) with stronger decreases in frontal areas in patients who later did not regain consciousness vs. patients who did (Roine et al., 1991).
None of the *guidelines* has made any recommendation for the use of SPECT, for the quantification of blood flow in the differential diagnosis of DoC.

MRI

[1] A certain overlap in the patients' samples of these studies is possible, as noted in Kondziella et al., 2020

Visual Inspection - In DoC patients, studies performing visual MRI assessment have focused mainly on coma patients, reporting a correlation between number of lesions at FLAIR and T2* sequences and score at the Glasgow Coma Scale, the presence of lesions in the corpus callosum and dorsal midbrain associated with reduced chances of recovery (Hoelper et al., 2000; Kampfl et al., 1998).
US guidelines (Giacino et al., 2018) do not recommend nor discourage visual MRI assessment for the purpose of differential diagnosis of prolonged UWS/VS and MCS, on the grounds of insufficient available evidence (Giacino et al., 2018). This statement is based on one previous study that investigated whether severity of gross anatomical and signal abnormality, as measured by visual rating of T1-sMRI images on a 5-points scale by two expert neuroradiologists in regions of the internal awareness (default mode) network could help distinguish VS/UWS and MCS patients, reporting an AUC of 0.73 in a sample of 85 patients (Rosazza et al., 2016). More recently, the same group published a similar study, extending visual assessment to gross anatomical and signal abnormalities of several low-order and high-order resting-state networks (Medina Carrion et al., 2023). The authors reported an AUC of 0.83, for visual rating of all low-order and high-order resting-state networks combined, to distinguish prolonged UWS/VS and MCS in a sample of 99 patients (Medina Carrion et al., 2023).
Like CT, visual MRI assessment is recommended by the *UK guidelines* (Royal College of Physicians, 2020) during the acute phase of care; for patients with prolonged DoC, visual MRI assessment is recommended only in case there is suspicion of undiagnosed or new specific, structural and operable causes of DoC, or if a repeated examination is expected to provide additional information of clinical utility. MRI is especially recommended for visualizing localized damage or late atrophy (Royal College of Physicians, 2020). *European guidelines* have not made any recommendation for the use of visual MRI assessment in the differential diagnosis of DoC.

Assessment of gray matter atrophy – In general, after brain injury, gray matter atrophy takes place, accompanied by an increase in volume of the cerebrospinal fluid and increases in the ventricles and in the intra-sulci spaces (Di Perri et al., 2016). In DoC patients, limited studies are available, showing diffuse cortical and subcortical atrophy (Guldenmund et al., 2016; Lutkenhoff et al., 2015; Annen et al., 2018b). Gray matter loss in the thalamus and in the basal ganglia have been related, respectively, to awareness and wakefulness in prolonged DoC patients (Lutkenhoff et al., 2015). More severe atrophy in medial prefrontal cortex and precuneus has also been reported in UWS compared to MCS patients (Guldenmund et al., 2016). A recent study in 102 DoC patients, assessing changes in regional gray matter volume, found that UWS/VS and MCS patients could be distinguished with an AUC of 0.96 when using an automated classifier: the result was replicated in an additional dataset encompassing 55 DoC patients, for which an AUC of 0.79 was obtained (Annen et al., 2018b). Another recent study in 99 DoC patients attempted to asses changes in gray matter volume in a series of low-order and high-order resting-state networks (Medina Carrion et al., 2023). The study reported however negative findings, imputable to technical difficulties in performing a quantitative analysis of structural MRI data, producing usable data only in a minority (13%) of cases (Medina Carrion et al., 2023).
Currently, none of the *guidelines* has made any recommendation for the use of sMRI T1 images combined with approaches for voxel-based morphometry or cortical thickness (for the quantification of local or global atrophy) in the differential diagnosis of DoC.

Assessment of white matter integrity - In DoC patients, DWI applications have mainly focused on patients with traumatic brain injury, revealing diffuse axonal injury after brain trauma (Huisman et al., 2003). Damage to several white matter connections within subcortical and cortical networks has been reported in both acute and prolonged DoC patients, the degree of structural derangement correlating with clinical severity (Fernández-Espejo et al., 2012, 2011; Gerdes et al., 2014; Snider et al., 2020, 2019; Stafford et al., 2019; Tan et al., 2022). Differences have been reported for DoC of traumatic vs. non-traumatic etiology, with white matter abnormalities in the brainstem typically present only in the former (Newcombe et al., 2010). Evidence also exists for the utility of DWI-sMRI in the differential diagnosis of DoC patient. One small study including 25 UWS/VS and MCS patients reported that measures of white matter structural integrity (MD) in subcortical and thalamic regions can distinguish between the two diagnostic groups with an accuracy of 0.95 (Fernández-Espejo et al., 2011). A more recent study in 102 DoC patients, assessing changes in regional white matter volume, found that UWS/VS and MCS patients could be distinguished with an AUC of 0.98 when using an automated classifier: the result was replicated in an additional dataset encompassing 55 DoC patients, for which an AUC of 0.70 was obtained (Annen et al., 2018b).
US and European guidelines do not provide any recommendation concerning DWI-sMRI as well. Based on *UK guidelines*, DWI-sMRI is not considered to be part of the routine clinical examination of patients with prolonged DoC, due to its unclear utility over and above clinical assessment and lack of widespread availabilities in clinical settings (Royal College of Physicians, 2020). Still, *UK guidelines* do acknowledge the encouraging results obtained in some studies (e.g., Fernández-Espejo et al., 2011).

BOLD-fMRI - Resting-state studies have shown a massive and multifaceted alteration of function connectivity in DoC (Perri et al., 2016), with extensive functional connectivity alterations within regions of the internal awareness/default mode network (Laureys et al., 2004a; Vanhaudenhuyse et al., 2010). Likewise, alterations were reported for the external awareness/executive control network and sensory networks (Demertzi et al., 2015; Qin et al., 2015a; Wang et al., 2022), and across networks (Threlkeld et al., 2018).
More recent studies have measured a number of alterations in global metrics derived from functional connectivity, reporting alterations in for instance time-delay latency (Rudas et al., 2020), brain topological properties (Martínez et al., 2020), fractal network dimensions (Varley et al., 2020), and variability of network metrics and dynamics (Crone et al., 2020; Demertzi et al., 2018), all indicative of a deeply altered brain functional organization in DoC patients. Passive-stimulation and active-task BOLD-fMRI studies have shown evidence of neural response to passive-stimulation in some DoC patients, with e.g., increases in functional connectivity in response to the favorite patient's music (Carriere et al., 2020). Active-task fMRI has also shown evidence of neural response to command, in the form of increased BOLD signal compared to rest, pointing at the possibility to use BOLD-fMRI as a brain-computer interface (Monti et al., 2010).

In *UK guidelines*, (rest, passive-stimulation and active-task) fMRI is not considered to be part of the routine clinical examination of patients with prolonged DoC, due to: (i) it is not widespread available in general clinical settings, (ii) lack of sufficient clinical evidence, (iii) no applicability to patients with metal implants, tracheostomy and presenting involuntary

movements. A greater applicability of resting-state protocols over activation studies is recognized in clinical and non-specialist settings (Royal College of Physicians, 2020).

US guidelines (Giacino et al., 2018) do not recommend nor refute the use of *resting-state* BOLD-fMRI for the differential diagnosis of prolonged UWS/VS and MCS, on the grounds of insufficient available evidence (Giacino et al., 2018). This statement is based on one previous study that investigated default mode network identifiability, as measured by the visual rating (a 3-point scale) of BOLD-fMRI functional connectivity maps, for the differential diagnosis of prolonged DoC (Rosazza et al., 2016). The study reported an AUC of 0.57 for distinguishing prolonged UWS/VS and MCS patients in a sample of 85 patients overall (Rosazza et al., 2016). More recently, and taking advantage of a wider evidence base, the *European guidelines* (Kondziella et al., 2020) have recommended the use of resting-state BOLD-fMRI whenever a standard clinical structural MRI is already planned for the patient. The recommendation is based on six studies with 218 patients[2] (Crone et al., 2015; Demertzi et al., 2015, 2014; Kondziella et al., 2017; Rosazza et al., 2016; Soddu et al., 2012), investigating brain functional connectivity of brain networks, with a particular focus on the default mode network. These studies overall showed that resting-state BOLD-fMRI allows to distinguish between UWS/VS/coma and MCS patients with a 72% sensitivity and 71% specificity. The guidelines recommend to assess functional connectivity not only in the default mode network, but considering other networks such as the auditory, salience, executive and fronto-parietal (Kondziella et al., 2020; see also Figure 4). No specific indication is provided on which analytical methods to use for functional connectivity assessment. Caution is advised in interpreting findings in patients showing involuntary movements and/or under sedation (Kondziella et al., 2020).

US guidelines (Giacino et al., 2018) do not recommend nor refute the use of *passive-stimulation* BOLD-fMRI for differential diagnosis of prolonged DoC, based on one study comparing brain activity in response to the presentation of factually correct and factually incorrect sentences in a sample of 29 patients (Kotchoubey et al., 2014); differences in activation between the two conditions allowed to differentiate between UWS/VS and MCS with a 19% sensitivity and 62% specificity only (Kotchoubey et al., 2014). The *European guidelines* (Kondziella et al., 2020) have recommended the use of passive-stimulation BOLD-fMRI paradigms within research contexts only, due to reported small effect and heterogeneity of the tested paradigms, across a corpus of 17 studies and 313 patients[3] (Bekinschtein et al., 2011; Coleman et al., 2009, 2007; Crone et al., 2011; Di et al., 2007; Edlow et al., 2017; Fernández-Espejo et al., 2008; Heelmann et al., 2010; Kremer et al., 2010; Li et al., 2015; Nigri et al., 2017, 2016; Okumura et al., 2014; Qin et al., 2010; Sharon et al., 2013; Wang et al., 2015), resulting overall in a sensitivity of 71% and 58% specificity of in distinguishing UWS/VS/coma and MCS patients. These guidelines recommended to prefer salient stimuli and/or familiar activities in such protocols (Bick et al., 2013; Coleman et al., 2009; Di et al., 2007; Edlow et al., 2017; Nigri et al., 2017; Okumura et al., 2014; Qin et al., 2010; Sharon et al., 2013; Wang et al., 2015).

US guidelines (Giacino et al., 2018) do not recommend *active-task* BOLD-fMRI using word-counting tasks, while they do not recommend nor refute the use of *active-task* fMRI using

[2] A certain overlap in the patients' samples of these studies is possible, as noted in Kondziella et al., 2020

[3] A certain overlap in the patients' samples of these studies is possible, as noted in Kondziella et al., 2020

command-following tasks for differential diagnosis of prolonged DoC, due to limited available evidence; these recommendations are based on two studies overall, namely: (i) one *active-task* BOLD-fMRI study contrasting a word-counting task vs. a control passive listening task in a sample of 17 patients; differences in activation between the passive and active conditions allowed to differentiate between prolonged UWS/VS and MCS with a 50% sensitivity and 40% specificity only (Monti et al., 2015); (ii) one *active-task* BOLD-fMRI study using a motor imagery paradigm to assess covert command-following in 20 patients and allowing to differentiate between prolonged UWS/VS and MCS with a 21% sensitivity and 100% specificity (only 3/14 MCS patients had evidence of covert command following) (Forgacs et al., 2014a). Still, the same guidelines point at the importance of task-based fMRI as a tool to detect covert consciousness in patients who are behaviorally unresponsive (Giacino et al., 2018). The same point is made by the *European guidelines*, that recommend the use of active-task fMRI paradigms as part of multimodal assessments in behaviorally unresponsive patients (Kondziella et al., 2020). The recommendation is based on data pooled from twenty studies and 343 patients[4], overall reporting 43% sensitivity and 73% specificity in differentiating between UWS/VS/coma and MCS patients (Bardin et al., 2012, 2011; Bekinschtein et al., 2011, 2009; Bick et al., 2013; Braiman et al., 2018; Chennu et al., 2013; Curley et al., 2018; Edlow et al., 2017; Forgacs et al., 2014b; Gibson et al., 2016, 2014; Haugg et al., 2018; Huang et al., 2014; Monti et al., 2015, 2010; Rodriguez Moreno et al., 2010; Sharon et al., 2013; Stender et al., 2014; Vogel et al., 2013). In conclusion, both US and European guidelines recognize the value of active-task fMRI paradigms to identify an important group of patients who can follow commands despite appearing unresponsive at the bedside (see Box 1 for further details).

ASL-MRI - In coma patients, ASL-fMRI is used to investigate total absence of cerebral blood flow, when the patient displays failed brainstem reflexes and apnea, and brain death is suspected (Bambach et al., 2022). In DoC patients, after coma, the limited available ASL-fMRI studies have provided evidence for decreased blood flow especially at the level of anterior midline structures (Liu et al., 2011; Wu et al., 2018) and putamen (Liu et al., 2011), the decrease being more severe in UWS/VS than in MCS patients (Liu et al., 2011).
None of the *guidelines* has made any recommendation for the use of ASL-MRI, for the quantification of blood flow in the differential diagnosis of DoC.

Summary - Overall, evidence for the utility of neuroimaging in supporting the differential diagnosis of DoC is increasing, as reflected by the recommendations of the most recent clinical guidelines. While use of structural (visual assessment of CT and sMRI), molecular (FDG-PET) and functional (BOLD-fMRI) imaging is being recommended for differential diagnosis of UWS/VS and MCS, evidence is also emerging for the utility of the quantitative evaluation of brain atrophy and white matter integrity (sMRI) for differential diagnosis. The importance of both resting-state (BOLD-fMRI and FDG-PET) and passive-stimulation/active-task (BOLD-fMRI) neuroimaging for the detection of covert consciousness in behaviorally unresponsive patients is also becoming a topic of major interest (see Box 1). A summary of the extensive evidence provided in this paragraph is provided in Table 1.

[4] A certain overlap in the patients' samples of these studies is possible, as noted in Kondziella et al., 2020

BOX 1: Detection of awareness in behaviorally unresponsive patients

Neuroimaging has a special role in the detection of awareness in behaviorally unresponsive patients. Some of the patients diagnosed as UWS/VS can present a disconnection between motor and cognitive functions, appearing behaviorally unresponsive while retaining fully or partially intact awareness. The former is the case of patients with locked-in syndrome that cannot move or talk to express their cognitive capacity (Vanhaudenhuyse et al., 2018) . The latter is the case of patients with MCS star (MCS) (Gosseries et al., 2014; Thibaut et al., 2021) or cortically mediated state (CMS), type 3a (Naccache, 2018), terms that include the diagnostic categories of cognitive motor dissociation (CMD) (Schiff, 2015) and high-order cortex motor dissociation (HMD) (Edlow et al., 2017). These patients all present a behavioral diagnosis compatible with UWS/VS but functional neuroimaging (at rest, passive-stimulation or active-task) compatible with a diagnosis of MCS (Thibaut et al., 2021). Landmark studies in the 2000s (Monti et al., 2010; Owen et al., 2007) have demonstrated the feasibility to detect covert consciousness in -some- behavioral UWS/VS patients using active-task BOLD-fMRI. Other neuroimaging modalities, like resting-state [18F]FDG-PET, have more recently been explored for the same purpose.*

Interestingly, while European guidelines acknowledge the importance of identifying awareness in this "specific and important group of patients" (Kondziella et al., 2020) with active-task BOLD-fMRI, UK guidelines argue against it, highlighting that there is only a "small cohort of patients who present behaviorally as being VS but demonstrate covert responses within an fMRI scanner". US guidelines (Giacino et al., 2018) do not support nor refute the use of BOLD-fMRI nor [18F]FDG-PET to detect awareness in patients diagnosed as VS/UWS, due to insufficient available evidence; still, they note that while neuroimaging show promise in increasing the chances to detect awareness in unresponsive patients, negative findings are nevertheless to be expected in the majority of patients diagnosed with UWS/VS, the latter point arguing against the widespread use of neuroimaging in such cases. While factually correct, the claim is quite surprising considering that a minor but substantial proportion of UWS/VS patients has been shown to present covert consciousness: a systematic review and meta-analysis reported brain activation consistent with awareness in 14% of cases, based on six studies using different active-task BOLD fMRI protocols in 102 UWS/VS patients; the proportion increases to 21% when passive-stimulation protocols are considered, based on three studies in 63 UWS/VS patients (Kondziella et al., 2016)*. Another study including 41 sub-acute and prolonged UWS/VS patients reported evidence of brain activity at resting-state [18F]FDG-PET in 33% of UWS/VS patients (Stender et al., 2014). In spite of the heterogeneity of the findings, due to use of different methods and protocols, overall, these results suggest that neuroimaging findings compatible with partially preserved consciousness, are a relatively frequent occurrence in patients that are behavioral unresponsive.*

It is debated whether such results should be disclosed to clinicians and families (Royal College of Physicians, 2020), given that the exact link between MCS-like neuroimaging findings in behaviorally unresponsive patients and consciousness is still unclear (Giacino et al., 2018; Royal College of Physicians, 2020). Encouragingly, one recent study (Thibaut et al., 2021) has shown that MCS patients have a more positive prognosis than UWS/VS patients, the majority*

progressing to MCS or emerging from MCS (compared to 100% negative outcomes in 'true' UWS/VS patients). Prognostic studies in these patients are urgently needed to confirm this positive evidence.
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Prognosis of DoC patients aided with neuroimaging

Prognostic studies have assessed "recovery" in patients with DoC mainly in terms of (i) return to functional independence, (ii) recovery of consciousness, or (iii) progression from one diagnostic category to the next (Royal College of Physicians, 2020). Overall, the available longitudinal evidence suggests that up to two thirds of the patients admitted to rehabilitation will regain signs of consciousness in the long term, while 20-50% will regain functional independence and 20% will go back to work or education (Estraneo et al., 2022, 2010; Hammond et al., 2019; Katz et al., 2009; McCrea et al., 2021; Nakase-Richardson et al., 2012; Nekrasova et al., 2022; Whyte et al., 2013). Patient stratification for the purpose of prediction of prognostic outcomes is extremely relevant for patient management, tailored treatment plans and appropriate communication with the families. Recommendation for the utility of neuroimaging for prognostic prediction is provided by the US and UK guidelines for prolonged DoC. The topic of prognosis is not addressed in the European guidelines, which focus only on diagnosis. An overview is provided in the following paragraphs and in Table 2.

In general, both guidelines recommend the use of neuroimaging for the purpose of improving prognostication. Recommendations of the UK guidelines are based on experts' consensus (Royal College of Physicians, 2020), whereas US guidelines are based on a systematic review of the literature on prognosis of DoC patients (Giacino et al., 2018), as detailed above.

CT, PET, SPECT

CT – One CT study in patients with prolonged post-traumatic coma reported that hydrocephalus after one-month post injury is associated with a worse prognosis, with only 17 out of 54 patients (31%) with hydrocephalus recovering awareness (Sazbon and Groswasser, 1990). Based on this study, the *US guidelines* deem CT imaging, specifically for the detection of hydrocephalus in prolonged DoC, as *probably* associated with a worse prognosis in traumatic prolonged UWS/VS (Giacino et al., 2018). Of note, this study was performed before the formal introduction of the diagnostic category of MCS. *UK guidelines* also recommend structural imaging for DoC prognostication, suggesting nevertheless to prefer sMRI to CT whenever possible.

PET, glucose metabolism – A previous study in subacute and prolonged DoC patients showed that deficits in brain glucose metabolism in internal and external awareness networks are able to predict outcome at 12-month follow-up with an accuracy of 74% in 102 DoC patients (Stender et al., 2014). Another study including 119 subacute and prolonged DoC patients showed that global brain glucose metabolism predicted patient outcomes (diagnostic change) at 12-month follow-up with an 88% accuracy. In details, 8 out of 11 UWS/VS patients (73%) with less impaired glucose metabolism, i.e., above the minimal requirement for consciousness of 42%, recovered consciousness at follow-up, against only 1 out of 3 UWS/VS

(33%) patients with more impaired glucose metabolism (Stender et al., 2016). In a very recent study, it was shown that prolonged UWS/VS patients with relative preservation of glucose metabolism in areas of the internal and external awareness networks (MCS*) had significantly better outcome (recovery) than UWS/VS patients with no such preservation, with 7 out of 23 MCS* patients (30%) progressing to MCS or EMCS as opposed to 0 out of 12 UWS/VS (0%) (Thibaut et al., 2021). Another study including 57 prolonged DoC patients showed that absolute glucose metabolism, when combined with electroencephalography (EEG), significantly predicted recovery of command-following at 6-month follow-up (Hermann et al., 2021). This was observed in 9 out of 24 patients (38%) with high [18F]FDG-PET metabolism and/or rich EEG activity vs. 0 out of 16 patients (0%) with low-level [18F]FDG-PET metabolism and EEG activity (Hermann et al., 2021). In spite of the encouraging evidence in DoC, the *US guidelines* do not recommend nor refute the use of [18F]FDG-PET for prognostication of prolonged DoC, due to the lack of studies available in (specifically) this subgroup of patients, at the time of guidelines redaction (Giacino et al., 2018). The *UK guidelines* acknowledge the predictive value of [18F]FDG-PET shown in previous studies (Stender et al., 2014) but do not recommend [18F]FDG-PET for prognostication of prolonged DoC, due to the still unclear prognostic utility over and above clinical assessment and not widespread availability in general clinical settings (Royal College of Physicians, 2020).

PET, blood flow – The prognostic utility of [15O]H2O-PET has been assessed in a descriptive review (Di et al., 2008) of eight studies including 32 patients with acute and prolonged UWS/VS (Boly et al., 2004; De Jong et al., 1997; Giacino et al., 2006; Laureys et al., 2002b, 2000b; Menon et al., 1998; Owen et al., 2005, 2002). Overall, these studies reported favorable outcomes in 2 out of 3 UWS/VS patients (67%) showing extensive activations at [15O]H2O-PET in the associative cortices during *passive-stimulation* protocols, as compared to 5 out of 21 UWS/VS patients (24%) with activations restricted to the primary sensory cortices or no activation. Still, prognostic use of [15O]H2O-PET is not addressed in any of the *guidelines*.

SPECT, blood flow – The prognostic utility of SPECT was examined by one study including 28 prolonged UWS/VS patients of traumatic onset (Nayak and Mahapatra, 2011). Normal blood flow at SPECT was associated with a favorable outcome (in terms of moderate disability or recovery) at 12-month follow-up in 7 out of 7 patients (100%), whereas a favorable outcome was found in 4 out 17 patients (24%) with blood flow defects (Nayak and Mahapatra, 2011). Based on this evidence, the *US guidelines* recommend to perform SPECT to assess blood flow 1-2 months post-injury in patients with prolonged UWS/VS and traumatic onset, to predict 12-months prognosis (Giacino et al., 2018). A normal SPECT scan is considered as a factor *possibly* associated with a better prognosis in traumatic prolonged UWS/VS by US guidelines. Prognostic use of SPECT is not addressed in *UK guidelines*.

MRI

Visual inspection - One MRI study (Goodwin, 1998) evaluated visual inspection of sMRI images in 80 prolonged UWS/VS patients of traumatic origin, showing that lack of recovery (change in diagnosis) at 12-month follow-up was strongly associated with lesions of the corpus callosum. A less strong effect was also reported for dorsolateral upper brainstem and corona radiata (Goodwin, 1998). Based on this study, *US guidelines* recommend to perform a structural MRI (conventional neuroradiological assessment) 6-8 week post-injury in patients

with prolonged UWS/VS and traumatic onset, assessing lesions to the corpus callosum, dorsolateral upper brainstem or corona radiata to predict 12-months prognosis (Giacino et al., 2018). These factors are considered *possibly* associated with a worse prognosis in traumatic prolonged UWS/VS by US guidelines. Of note, this study was performed before the formal introduction of the diagnostic category of MCS. The *UK guidelines* (Royal College of Physicians, 2020) also acknowledge that the structural pattern of brain injury, at sMRI, is a factor that affects the probability of recovery of consciousness (Giacino et al., 2018).

Assessment of white matter integrity - Previous studies have shown that both DWI-sMRI imaging holds potential for prognostication of DoC patients. A case study suggested that recovery from MCS is related to increased anisotropy in mid-line white matter, encompassing the precuneus (Voss et al., 2006). Multicentric studies have shown that DWI-derived indices like fractional anisotropy hold better performance than both structural and clinical assessments in predicting clinical outcomes (Glasgow Outcome Scale) at 12-month follow-up in both traumatic (105 subacute and prolonged UWS/VS patients; AUC 0.80-0.84) and non-traumatic (57 subacute UWS/VS patients; AUC 0.92-0.96) DoC patients (Galanaud et al., 2012; Luyt et al., 2012). More recently, a multicentric study involving 150 subacute non-traumatic unresponsive patients demonstrated further potential of DWI-base whole-brain fractional anisotropy index in predicting favorable outcomes (based on the Glasgow-Pittsburgh Cerebral Performance Categories) at 6-months follow-up (0.91-0.95) (Velly et al., 2018). Still, *US guidelines* do not discuss the prognostic utility of DWI-sMRI images for the assessment of white matter integrity. *UK guidelines* do not recommend DWI-sMRI for prognostication of prolonged DoC, due to still unclear prognostic utility over and above clinical assessment and not widespread availability in general clinical settings (Royal College of Physicians, 2020).

BOLD-fMRI - A few studies have been published pointing at prognostic utility of fMRI functional connectivity in the default-mode and other resting-state networks. One study in 32 acute and prolonged UWS/VS and coma patients showed that functional connectivity strength in posterior cingulate cortex/precuneus, medial prefrontal cortex and lateral parietal cortex predicted consciousness recovery at 3-months follow-up with 81.25% accuracy (Wu et al., 2015). Another study in 53 UWS/VS patients similarly reported that connectivity between posterior cingulate gyrus and left lateral parietal cortex allowed to predict consciousness recovery at the Glasgow Outcome Scale with an accuracy of 74% at 3-months follow-up (Qin et al., 2015a). Finally, a more recent study in 112 UWS/VS and MCS patients reported that functional connectivity between hubs of the default-mode, executive and sensory networks predicted consciousness recovery at the CRS-R even at a longer time interval, after 12-months follow-up, with an accuracy of around 88% in three datasets (Song et al., 2018). Still, *US guidelines* do not address the issue of the prognostic utility of *resting-state* BOLD-fMRI.

Evidence for the prognostic utility of *passive-stimulation* BOLD-fMRI traces back to the early 2000s, when a descriptive review, summarizing the findings of 6 studies (Bekinschtein et al., 2005; Boly et al., 2007; Coleman et al., 2007; Di et al., 2007; Moritz et al., 2001; Owen et al., 2006, 2005; Staffen et al., 2006) over 17 patients with acute or prolonged UWS/VS, reported favorable outcomes in 7 out of 8 UWS/VS patients (88%) showing extensive activations in the associative cortices during *passive-stimulation* protocols, as compared to 0 out of 9 UWS/VS patients (0%) with activations restricted to the primary sensory cortices or no activation (Di et al., 2008). More recently, one study (Wang et al., 2015) in 23 patients with traumatic

VS/UWS showed that 12 out the 13 patients (92%) with extensive activation in auditory association cortex had a positive outcome (progression to MCS) compared to only 4 out of the 10 patients (40%) with no or limited activation in the same areas. Based on this study, *US guidelines* recommend to perform *passive-stimulation* BOLD-fMRI (listening to a familiar voice speaking the patient's name) 1-60 months post-injury in patients with prolonged UWS/VS and traumatic onset, assessing the activation of the auditory association cortex, to predict 12-months prognosis (Giacino et al., 2018). Activation on *passive-stimulation* BOLD-fMRI is considered as a factor *probably* associated with a better prognosis in traumatic prolonged UWS/VS by *US guidelines* (Giacino et al., 2018). No recommendation supporting or refuting the utility of passive-stimulation BOLD-fMRI for prognostic in patients with non-traumatic UWS/VS or any-onset MCS is provided due to the more limited prognostic value observed with the paradigm described above in such clinical groups.

Limited evidence is available for the prognostic value of *active-task* BOLD-fMRI in prolonged DoC, with one study investigating the prognostic value of a mental imagery task in DoC patients. This study reported a progression to (at least) MCS in 5 out of 5 UWS/VS patients (100%) with brain activation during this task after at least 2 months of follow-up, compared to 0 out 5 UWS/VS patients (0%) without activation, indicating a *possible* predictive value of active-task BOLD-fMRI in UWS/VS patients (Vogel et al., 2013). The same study reported less clear results in MCS patients, with 6 out of 9 MCS patients (67%) with brain activation emerging from MCS, as compared to 1 out of 3 MCS patients (33%) without brain activation (Vogel et al., 2013). Based on this evidence, the *US guidelines* do not support nor refute the utility of *active-task* BOLD-fMRI for prognosis in prolonged MCS patients (Giacino et al., 2018). On top of this evidence, another study in 65 subacute and prolonged DoC patients reported an unsatisfactory accuracy of only 56% for mental imagery tasks at BOLD-fMRI in predicting outcome at 12 months follow-up, with 12 out of 19 responders (63%) to the mental imagery task as well as 22 out of 46 non-responders (48%) recovering consciousness at 12-month follow-up (Stender et al., 2014). More recently, an *active-task* BOLD-fMRI in 29 prolonged DoC patients, allowed to predict favorable outcomes in 3 out of 4 patients (75%) (2 UWS and 1 MCS) with brain activation during a simple hand-raising motor task; of the 25 patients with no task-related brain activity, only 9 (36%) showed recovery (progression from one diagnostic category to the next) at 3- to 12-months follow-up (Wang et al., 2019).

UK guidelines do not recommend BOLD-fMRI for prognostication of prolonged DoC, due to its scarce availability in general clinical settings and the unclear prognostic significance of covert consciousness findings (Royal College of Physicians, 2020).

Summary - Overall, evidence for the utility of neuroimaging in predicting the prognosis of DoC is increasing, as reflected by the recommendations of the most recent clinical guidelines. While use of structural (visual assessment of CT and sMRI), and functional (BOLD-fMRI and SPECT) imaging is being recommended for the prognosis of UWS/VS patients, evidence is also emerging for the utility of the quantitative evaluation of brain glucose metabolism (FDG-PET), brain atrophy and white matter integrity (sMRI) for prognostic purposes. The use of resting-state FDG-PET for the detection of covert consciousness in behaviorally unresponsive patients, in place of more complicated active-task paradigms, represents a point of particular interest. A summary of the extensive evidence provided in this paragraph is presented in Table 2.

Future perspectives and open questions

As neuroimaging tools start to show their efficacy in aiding clinical diagnosis and prognosis of DoC, several challenges remain open. A few key recommendations for future actions are highlighted in this section.

(i) *validation of neuroimaging measures, exploration of sources of variability and standardization of analytical pipelines*. Many studies, to date, have investigated the usefulness of neuroimaging measures in aiding diagnosis and prognosis of patients with DoC. Considering the amount of neuroimaging evidence currently available in DoC, systematic validation of potentially useful neuroimaging measures should now be prioritized, so as to ensure proper clinical translation in the near future. Validation of neuroimaging measures should pass through robust testing not only in DoC patients but also in control subjects, to establish the degree of occurrence of false negative and false positive findings - fundamental for interpretation of results in DoC (Physicians, 2020). Reference values for proposed measures of interest should be provided for control populations, accounting for and documenting the effect of major variables like gender and age on the results. Test-retest reproducibility and out-of-sample replicability should be tested as well, something that could be implemented more systematically once large multi-centric databases of neuroimaging data will become available. Particular attention should also be reserved for innovative approaches for diagnosis or prognosis, such as those entailing the use of advanced statistical approaches for combination of different markers of interest, either in terms of neuroimaging measures (Panda et al., 2022) or neuroimaging and neurophysiological ones (Hermann et al., 2020; see also chapter on *Advances in EEG in encephalopathy and coma*). Such approaches will more and more likely take advantage of artificial intelligence and deep learning (Lee et al., 2022), and might prove useful in terms of complementing traditional approaches based on human expertise.

As illustrated above, studies have reported somehow variable findings for what concerns the clinical utility of different neuroimaging markers, something reflected in the different recommendations provided by the different guidelines. Variability can at least partially be ascribed to technical factors, like the adoption of different analytical pipelines, across different studies (e.g., Morbelli et al., 2015). Analytical variability is not addressed in currently available systematic reviews/meta-analyses or diagnostic guidelines. Variability in markers of interest should therefore be explored in relation to the use of different hardware (e.g., scanners with different characteristics) and acquisition parameters, so as to define the limits of applicability of different markers in different contexts.

Future neuroimaging studies in DoC should follow standardized and robust analytical pipelines when available (e.g., fmriprep.org) and/or adopt multiverse approaches for identification of best analytical choices (Dafflon et al., 2022). Code used to produce the analytical pipelines should be shared on public repositories like github.com.

(ii) *proper reporting in diagnostic, prognostic and treatment studies in DoC, with results stratification for acute, subacute and prolonged patients*. Many potentially relevant, robust neuroimaging studies failed to meet criteria for inclusion into the systematic reviews that the US and European guidelines are based upon. The effect is stronger for US guidelines, due to more restrictive inclusion criteria. Each recommendation in US guidelines is currently based on an extremely limited, sometimes outdated, amount of neuroimaging studies (most

commonly 1-2 studies). Future diagnostic, prognostic and treatment studies should systematically report either predictive performance indices (AUC, accuracy, sensitivity, specificity, odds ratio etc.), confusion matrices, or individual patient information, with stratification in clinical groups, stage (acute, subacute or prolonged) and onset to facilitate inclusion into future efforts of systematic review. Neuroimaging group results could be shared on public repositories like neurovault.org (currently including 3,841 entries; none on consciousness-related results).

(iii) *prioritization of neuroimaging studies for prognosis of DoC*. The number of prognostic studies is extremely limited in the literature of DoC. Prognostic studies are most urgently needed to better characterize the clinical category of MCS*, whose prognostic significance requires further investigation (Giacino et al., 2018; Kondziella et al., 2020; Royal College of Physicians, 2020), and in the earliest phases of DoC, where reliable prognostic markers are most likely to impact decisions about continuation of life-sustaining therapies (Edlow et al., 2023).Expansion towards prognostic, as opposed to diagnostic, studies is particularly important to obtain more straightforward information on the utility of each neuroimaging marker of interest for DoC patients' management. Indeed, a major issue with diagnostic studies is the issue of circularity: in diagnostic studies, statistical accuracy can be strongly dependent on the type of data used for generating the "gold standard" diagnosis, which often (also) relies on the neuroimaging marker whose accuracy is being evaluated. Reliance on the neuroimaging marker of interest to generate the gold standard might inflate statistical accuracy; at the same time, *not* relying on the neuroimaging marker of interest to generate the gold standard might make the latter less reliable, deflating statistical accuracy. This conundrum is avoided in prognostic studies, where behavioral and/or neuroimaging markers that are independent of the marker of interest (i.e., acquired at a different time point), can be used as gold standard.
Still, some challenges exist for the implementation of prognostic studies in DoC:

1) *Sample size*. Large-scale studies in DoC are usually rare, due to the low prevalence of DoC, and especially of prolonged DoC. Large-scale multicenter studies that pool data of different centers are logistically challenging but are fortunately becoming more common (e.g., CENTER-TBI, center-tbi.eu).
2) *Longitudinal follow-up*. Available neuroimaging studies in DoC typically assess clinical outcomes only up to one-year follow-up; as evidence suggests that recovery of consciousness occurs after one year in a significant proportion of patients (Estraneo et al., 2010; Katz et al., 2009), future studies should focus on the systematic collection of clinical outcomes at longer follow-up times as well.
3) *Biased selection*. Prognostic studies in DoC might suffer from selection bias, with only less impaired patients being able to receive neuroimaging assessment. MRI testing might be precluded in DoC patients with non-MRI compatible metallic implants. Implementation of neuroimaging assessments in acute DoC might be particularly challenging (Edlow et al., 2023), as clinical instability observed in acute patients might complicate MRI or PET assessments outside of the intensive care unit.
4) *Biased intervention*. The reliability of functional neuroimaging assessments might be questionable in patients under sedation, when the latter is required during scanning either for clinical reasons and/or to reduce patient's movement. A significant effect of sedation has been proven on fMRI resting-state functional connectivity in DoC patients (Kirsch et al., 2017). Effects of sedation on [18F]FDG-PET exams are modest

if sedation can be avoided during the first 20-30 minutes post-injection (Guedj et al., 2022).

5) *Biased outcomes*. Death is unfortunately a common outcome in prognostic studies of DoC patients, with around 50% of UWS/VS and 25% of MCS patients dying at one-year follow-up (Thibaut et al., 2021). As patients' death can occur for either natural causes or medical complications but also for discontinuation of treatment, studies should carefully consider how to deal with such a negative outcome when estimating prognostic accuracy. Prognostic studies should consider the cause of death in their study design, to avoid estimating biased prognostic accuracy in the cases where death has occurred following an 'active' end-of-life decision, preventing measurement of the actual outcome in the natural history of the DoC.

(iv) prioritization of neuroimaging studies testing treatment options for DoC – In the context of DoC treatment, neuroimaging is used mainly for making personalized decisions on patient-tailored treatment options in acute DoC, i.e., serving a primary role in identifying the cause of altered consciousness, and directing the clinician to the appropriate treatment (Posner et al., 2019). In subacute and prolonged DoC patients, neuroimaging is used mainly for the quantification of the effects of candidate treatments for DoC on brain function and/or for patient stratification. A few uncontrolled observational studies and case reports employed measures like [18F]FDG-PET (Chatelle et al., 2014; Corazzol et al., 2017; Kim et al., 2009; Lemaire et al., 2018), sMRI (Raguž et al., 2021), BOLD (Rodriguez-Rojas et al., 2013) or ASL-fMRI (Khalili et al., 2020) to investigate pre- vs. post-treatment effects on brain structure and function. These studies have shown the usefulness of neuroimaging for helping elucidating the mechanisms of action of a given treatment (e.g., Rodriguez-Rojas et al., 2013 demonstrated the neural basis of the paradoxical effect of zolpidem in DoC), or for patient stratification and identification of responders vs. non-responders (e.g., Khalili et al., 2020 demonstrated that responders to zolpidem are those that presents perfusion defects at ASL-MRI). In spite of the proven potential, neuroimaging is still not routinely used as secondary outcome in current clinical trials, with only one out of 14 clinical trials (according to a recent systematic review (Thibaut et al., 2019)), including neuroimaging (BOLD-fMRI) as secondary outcome (Pape et al., 2015)(see also chapters on *Advances in pharmacology to improve DOC* and *Advances in nonpharmacologic therapies to improve DOC*). While the emergence of behavioral signs of consciousness represents the gold standard for the evaluation of treatment efficacy, the lack of neuroimaging assessments as a secondary outcome could be problematic in clinical trials for DoC, as behavior is not always an accurate indicator of the level of consciousness (see Box 1). Future clinical trials in DoC should therefore aim at incorporating neuroimaging as a secondary outcome.

Possible advantages of stratifying patients based on neuroimaging findings, whereby evidence of heterogeneous effects of treatment is available (e.g., Khalili et al., 2020), should also be explored. Stratification could help optimize future clinical trials in DoC by reducing the sample size required for finding an effect of interest. This strategy, already adopted in clinical trials for other neurologic conditions (Grill et al., 2013), might prove particularly beneficial in a rare condition like DoC, where achievement of large-sample size often proves challenging.

(v) *prioritization of neuroimaging studies in pediatric DoC populations*. Neuroimaging evidence in pediatric DoC is extremely limited (see Vitello et al., 2022 and Molteni et al., 2023 for recent reviews). Only one group study is available in a group of 13 patients with pediatric

DoC, reporting alterations in white matter using DWI sMRI (Molteni et al., 2017). Some case studies also exist, reporting alterations in brain glucose metabolism at [18F]FDG-PET (Imataka and Arisaka, 2014; Larsen et al., 1993), in brain perfusion at SPECT (Imataka and Arisaka, 2014), in brain structure at sMRI (Clark et al., 2017; Liem et al., 2020; Machado et al., 2007; Steppacher et al., 2016) and in BOLD-fMRI, using a passive-stimulation paradigm (Nicholas et al., 2014). Interpretation of neuroimaging findings in pediatric populations is particularly challenging both on a technical point of view, i.e., need of ad-hoc pre-processing procedures and reference populations, and interpretative point of view, i.e., brain damage should be interpreted not only in terms of loss of function as in adults, but also in terms of disruption of standard developmental trajectories (Ismail et al., 2022). Future studies, potentially taking advantage of multicenter collaborations, should be conducted to, first, develop adequate tools to analyze neuroimaging data in pediatric patients and, second, gather more diagnostic and prognostic data in these patients.

Conclusions

As evidence for the utility of neuroimaging assessments in diagnostic, prognostic and treatment evaluation/management is increasing, clinical guidelines are moving towards recommending neuroimaging assessments in patients with DoC (Giacino et al., 2018; Kondziella et al., 2020). Still, only a minor translation of neuroimaging assessments into clinical practices has been made (Goldfine and Schiff, 2011; Luppi et al., 2021). As limited infrastructure, resources and expertise for neuroimaging assessments hinders neuroimaging assessments in general clinical settings, the question stands as to which strategies should be adopted to grant DoC patients access to useful neuroimaging assessments, namely: (i) data should be acquired locally to be sent to specialized center for analysis (Edlow et al., 2021), (ii) patients should be transferred to specialized centers for neuroimaging examination and analysis (Edlow et al., 2021) or (iii) easy-to-use tools should be made available in general clinical settings for local analysis (e.g., Sala et al., 2022). The latter option, supported by the diffusion of open science practices, might avoid privacy issues with data sharing as well as logistic complications in transferring patients for long distances. In parallel, philosophers of ethics and clinicians have now the complicated task to interact with family stakeholders to develop, likewise, guidelines on disclosure of neuroimaging results to patients' families (a challenge tackled for example by the DoCMA project project-docma.eu or the Human Brain Project humanbrainproject.eu). These efforts will surely benefit from future studies focused on prognostication and prediction of treatment response (Edlow et al., 2021), including also patients falling within the crucial category of MCS* (Thibaut et al., 2021), to which neuroimaging can greatly contribute.

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Tables

Table 1. Recommendations for neuroimaging use in diagnosis of DoC patients.

Please see annexed document for tables

Table reports a summary of the main evidence available per neuroimaging marker. Whenever evidence relative to a given neuroimaging marker is provided by consensus guidelines, we report such evidence. Whenever the neuroimaging maker is not or only partially considered by consensus guidelines, we report main findings and statistics obtained from other systematic review and meta-analysis and/or selected studies of interest.

Recommendation by the clinical guidelines is symbolized by color green; red color indicates that clinical guidelines do not recommend the tool, based on evidence against its utility; orange color indicates that clinical guidelines do not recommend the tool, due to unclear utility over and above clinical assessment and non-widespread availability in general clinical settings; yellow color indicates the tool is not recommended nor refuted by the guidelines, due to insufficient available evidence in favor or against its utility; 'NA' indicate a tool not discussed by the clinical guidelines.

Abbreviations: ASL, arterial spin labelling; Acc, accuracy; AUC, area under the curve; BOLD, blood oxygenated-level dependent; CT, computed tomography; DWI, diffusion weighted imaging; FDG, fluorodeoxyglucose; fMRI, functional magnetic resonance imaging; H2O, water; HMPAO, hexamethylpropyleneamine oxime; IMP, ^{123}I-N-isopropyl-p-iodo-amphetamine; NA, not available; PET, positron emission tomography; Sens, sensitivity; Spec, specificity; SPECT, single-positron emission computed tomography; sMRI, structural MRI; 99mTc, technetium 99m.

Table 2. Recommendations for neuroimaging use in prognosis of DoC patients.

Please see annexed document for tables

Table reports a summary of the main evidence available per neuroimaging marker. Whenever evidence relative to a given neuroimaging marker is provided by consensus guidelines, we report such evidence. Whenever the neuroimaging maker is not or only partially considered by consensus guidelines, we report main findings and statistics obtained from other systematic review and meta-analysis and/or selected studies of interest.

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European guidelines are not included in the table, as they do not provide guidelines on prognostication of DoC.

Abbreviations: ASL, arterial spin labelling; Acc, accuracy; AUC, area under the curve; BOLD, blood oxygenated-level dependent; CT, computed tomography; DWI, diffusion weighted imaging; FDG, fluorodeoxyglucose; fMRI, functional magnetic resonance imaging; H2O, water; NA, not available; OR, odds ratio; PET, positron emission tomography; Sens, sensitivity; Spec, specificity; SPECT, single-positron emission computed tomography; sMRI, structural MRI; 99mTc-ECD, technetium 99m ethyl cysteinate dimer.

Illustrations Captions

Figure 1. Neurobiological targets of the neuroimaging tools used to assess DoC. *Main neurobiological targets for each neuroimaging tool most commonly employed for the assessment of DoC. Currently used neuroimaging tools rely on neurobiological targets located at blood vessels, astrocytes and/or neurons to infer brain molecular, functional or structural damage. Due to their intrinsic characteristics, some tools are most commonly used in acute DoC, while others are most commonly employed in prolonged DoC. Figure has been partially created with BioRender.com.*

Figure 1 should be around ½ page.

Figure 2. Schematic representation of an automatic pipeline for analysis of [18F]FDG-PET images acquired in patients with suspected DoC. *The pipeline takes in DICOM images, runs a series of pre-processing and processing steps, to finally provide maps, renders and quantitative results, for individual assessment of both global (top) and local (bottom) alterations in brain glucose metabolism. The pipeline, described* in Sala et al., 2022*, is available on GitHub (tinyurl.com/DOC-TOOLBOX).*

Figure 2 should be full page (horizontal layout).

Figure 3. Alterations of brain glucose metabolism in cases with prolonged DoC. *Figure shows alterations of brain glucose metabolism in a UWS/VS, MCS- and MCS+ patient; alterations in MCS* (not shown) are similar to what is observed in MSC cases. Alterations in prolonged DoC occur at two levels: global (top panel) and local (bottom panel). A widespread, global decrease in brain glucose metabolism is typically observed in prolonged DoC, with a 40-70% decrease compared to reference controls. Global decreases are studied using indexes such as the standardized uptake value (SUV), an accessible, absolute measure of glucose consumption (top panel). Localized decreases in glucose metabolism, whose severity exceeds that explained by the global glucose decrease, are typically observed in regions of the internal and external awareness networks, encompassing medial and lateral fronto-parietal areas. Local decreases are studied by computing statistical parametric maps (SPM), indicating the magnitude and localization of significant differences in relative glucose consumption, compared to a reference groups of controls (bottom panel). Abbreviations: ACC, anterior cingulate cortex; F, female; M, male; MCS, minimally conscious state; mo, months; p.i., post-injury; SPM, statistical parametric mapping; UWS, unresponsive wakefulness syndrome; VS, vegetative state; yo, years old.*

Figure 3 should be around 1/3 to ½ page.

***Figure 4. Alterations of brain connectivity in the default mode and auditory networks in cases with prolonged DoC**. Figure shows resting-state connectivity in controls, in a UWS/VS and in an MCS+ patient; resting-state connectivity in MCS* (not shown) is similar to what is observed in MCS cases. Alterations in prolonged DoC have been reported in several resting state networks. fMRI resting state network activity in the default mode and auditory networks is partially preserved in some patients with MCS, and generally absent in VS/UWS. Standard network topographies, as observed in a reference group of controls, are shown for reference. Resting-state network topographies are studied using different methods of analysis, such as seed-based analysis. Results should be carefully interpreted in case patient's sedation during scanning, as detailed in Kirsch et al., 2017. Abbreviations: F, female; M, male;*

MCS, minimally conscious state; mo, months; p.i., post-injury; UWS, unresponsive wakefulness syndrome; VS, vegetative state; yo, years old.

Figure 4 should be around 1/3 page.