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Advancing the science of consciousness: From ethics to clinical care

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A R T I C L E   I N F O

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A B S T R A C T

Significant advances in the scientific investigation of the neurobiology of consciousness have been slow to be translated into clinical settings, limited by a lack of generally agreed working definition (e.g., what is consciousness?) and methodology (e.g., how to identify reliable biomarkers/indicators of consciousness? How to improve sensitivity and specificity of the technological identification of consciousness?). In the present paper we aim at proposing potential strategies for reducing the gap between research, clinical practice, and patients' and their caregivers' needs regarding disorders of consciousness. By implementing a multidisciplinary (i.e., involving different disciplines) and multiperspective (i.e., involving different stakeholders) approach, the paper focuses on disorders of consciousness: it starts from the review of some of the most promising measures of consciousness from brain activity (i.e., electrophysiology and spectral measures, measures of functional connectivity, complexity-based measures). Next the paper introduces brain responses to illusions as a possible new *indicator of consciousness* (i.e., a feature that facilitates the attribution of consciousness), and illustrates a possible clinical operationalization of the indicators of consciousness through the case of virtual reality. Finally, the paper

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analyses a set of urgent ethical issues and describes a model for assessing and dealing with those issues, concluding by elaborating key recommendations for improving the clinical treatment of patients with disorders of consciousness through a better translation of research into clinics.

1. Introduction

Without consciousness there is no subjective experience. Although loss of consciousness during anaesthesia (Mashour, 2024) or sleep (Tononi et al., 2024) is reversible, loss of consciousness following brain damage (i.e., coma state) may result in a disorder of consciousness (DoC) (Schnakers and Laureys, 2024), a condition that may not be fully reversible. In the adult population of the United States alone, the incidence of DoCs is estimated at about 305,000 adults (MultiSocietyTaskForceonPVS, 1994), (Fins et al., 2007), (Schiff and Fins, 2007). Although actual estimates of DoCs incidence worldwide are missing, the condition is of increasing concern in the Western world, where misdiagnosis rate remains fairly alarming (Owen, 2020) and treatments scarce (Pisa et al., 2014; Wang et al., 2020; Young et al., 2021). The relatively poor certainty of many clinical diagnosis, prognosis, and treatment decisions for DoC reflect the ambiguities of a field of research still in its infancy.

Following traumatic or non-traumatic brain damage, the patient may enter in a state of coma, characterised by an unarousable unresponsiveness, that is by the absence of the two main clinical dimensions of consciousness (i.e., arousal/wakefulness, related to the level of consciousness, and awareness, related to the content of consciousness) (Laureys et al., 2004). This state can be transient, and the patient can enter different DoCs (Schnakers and Laureys, 2024). Clinicians currently rely on a classification of patients based on the differentiation between reflexive and volitional behaviours: if patients exhibit behaviours and not only simple reflexes (e.g., auditory startle), they are considered conscious, even if in some cases consciousness might be limited to specific modalities and/or function. Given the frequently observed physical disabilities - in terms of output for motor impairments and/or input for difficulties in processing sensory stimuli – these patients are expected to have difficulty in interacting with the external world. It is essential to use behavioural scales specifically designed to detect subtle differences in behaviour, as the Coma Recovery Scale-Revised (CRS-r) (Giacino et al., 2004) or more recently the Simplified Evaluation of Consciousness Disorders (SECONDS) (Aubinet et al., 2021; Sanz et al., 2021). Based on a structured behavioural assessment, the CRS-r differentiates three categories of patients with DoCs: unresponsive wakefulness syndrome/vegetative state (UWS/VS) patients – presenting only reflexive behaviours; minimally conscious state (MCS) patients, showing non-reflexive behaviours with language functions (MCS+) or without language functions (MCS-). Patients emergent from the minimally conscious state (EMCS) have regained accurate communication and/or functional use of objects and are not considered to be in a DoC. The diagnosis of MCS is based on the presence of specific behaviours, among which five are more prevalent: reproducible response to command, visual pursuit, visual fixation, localisation to noxious stimulation and automatic motor responses (Wannez et al., 2018). Recent work also suggests investigating other potential signs of consciousness that are not considered in these scales, such as resistance to eye opening or eye blinking rate - for a review see (Mat et al., 2022). Also, a number of low-tech diagnostic approaches are currently under development, with different levels of reliability, which make use of olfactory measures (Arzi et al., 2020), cardiac activity (Candia-Rivera et al., 2021; Raimondo et al., 2017), respiration (Liuzzi et al., 2023)[16], and eye blinking (Magliacano et al., 2021), among others.

The majority of MCS patients are measurably conscious, at least to some extent, while for others it is harder to get a definitive answer from behavioural assessment. In these patients with so-called covert consciousness neuroimaging techniques can help to identify residual brain activity associated with consciousness (Fischer et al., 2025). Together with behavioral assessment, there is now a fine-grained stratification of states, corresponding to response to behavioral, resting state, passive and active assessment tools (Meys et al., 2023). However, a considerable degree of uncertainty still remains as to how to interpret behavioural and neuroimaging data, including on how to classify patients showing evidence of covert consciousness (Schnakers et al., 2022). For example, some researchers proposed to use "cortically mediated" state (Hermann et al., 2021; Naccache, 2018) rather than MCS to classify these patients, arguing that behavioural evidence does not really indicate consciousness but only that behaviour is mediated by cortical activity. According to this argument, behavioural data should be integrated with instrumental (e.g., EEG or neuroimaging) data to get a more reliable diagnosis of possible residual consciousness. Yet even the interpretation of data deriving from instrumental assessment may be problematic because cortical activity might not necessarily reflect consciousness (Hermann et al., 2021): in fact, cortical activity can be necessary but not sufficient for conscious processing to occur (Fins et al., 2007). Therefore, according to some, only successful application of active paradigms that allows one to provide subjective report should be considered as proof for the presence of consciousness (Naccache, 2018). However, at present, both EU and US Guidelines on DoC (Giacino et al., 2018; Kondziella et al., 2020) recommend complementing the behavioural diagnosis with the use of neurophysiological measures, neuroimaging, and (non)invasive brain stimulation technologies. (for an illustration of a possible diagnostic approach based on behaviour, resting state neuroimaging and the electrophysiological response to passive stimulation, see Fig. 1. (Please note that the exact approach can differ per patient and center, depending on contra-indication and available techniques).

With these techniques, brain activity at rest or in response to a stimulus is usually recorded and subsequently analysed to estimate various characteristics deemed indicative of consciousness, e.g. the level of complexity of baseline brain activity and in response to stimuli (Boly et al., 2012; Dehaene et al., 2011).

The actual implementation of the recommendation to use these technologies faces significant challenges (Farisco et al., 2024). Also, although research continues to uncover neural processes and structures (i.e., mechanisms) related to consciousness, with a significant positive impact on the clinical care of patients with DoC (Sanz et al., 2023), at present a conclusive biological model of consciousness (and thus a related "consciousness meter" and an agreed-upon test for detecting and measuring consciousness) is still a distant achievement (Bayne et al., 2024). Indeed, not only is consciousness far from being completely understood, there is no consensus in the scientific community even on its meaning. At present, a multiplicity of theories support different definitions of consciousness and refer to diverse mechanisms of how consciousness operates in the brain (Evers et al., 2024). These theoretical disparities may have a negative impact on the clinical practice with DoC, where some of the most pressing questions for physicians and family are: "Is (s)he conscious? And if so, to what extent? What does (s)he need to be comfortable?". While we acknowledge this risk, we think that the need for an overarching shared definition of consciousness should not be overemphasised: for clinical care to be effective it is more important to agree on what criteria reliably indicate residual conscious abilities within a minimal shared conceptual framework, irrespective of how consciousness as such is defined. To illustrate, identifying cognitive capacities that require residual conscious abilities as their necessary condition is what matters for diagnostic purposes. In other words, a pragmatic approach should eventually prevail on theoretical interests at the clinical level.

In addition to these clinical challenges, advances made in (pre-) clinical, cognitive and computational branches of neuroscience are often fragmented. It requires interdisciplinary expertise to interpret and replicate, and are therefore usually not promptly translated into clinical settings, even if a multimodal and multispecies framework might promote clinical translation (van der Lande et al., 2024). Nonetheless, clinical and ethical problems related to patients with DoC cannot be dismissed while waiting for the research field to mature. On the contrary, they require the search for solutions that can at least improve the conditions of these patients in the immediate term, for instance promoting an interventional science of recovery after coma (Bayne et al., 2024). With this goal in mind, the present paper sets forth a highly interdisciplinary approach, combining a plurality of different perspectives. Medical doctors, philosophers, neuroscientists, biologists, physicists, ethicists, and patients' family associations propose a uniquely comprehensive view on brain measures that promise to improve actual diagnostic strategies for DoC and to facilitate the advancement and the clinical translation of basic research to more effectively address clinical and ethical issues related to DoC.

Adopting a markedly pragmatic approach, this article aims at improving the diagnosis and eventually the patient care by contributing to closing the current translational gap, reconciling basic research, clinical practice, patients' caregivers' involvement and ethical considerations in the clinical treatment of this population (See Fig. 2).

Just as a theoretical and precise definition of "being alive" is still debated, yet life-saving medical measures are undertaken, here we propose methods to improve the clinical treatment of patients with DoC while waiting for science to solve the conundrum of consciousness.

The article begins by reviewing some of the most promising neuroimaging and neurophysiological measures of consciousness and suggests new methods (multistable percepts, illusions, and virtual reality) to improve detection of residual consciousness for patients with DoC. In particular, we propose the use of *indicators of consciousness* for the diagnosis of DoC - a provisional list of indicators has been introduced in (Pennartz et al., 2019) and subsequently elaborated in relation to DoC in (Farisco et al., 2022). The indicators of consciousness (IoC) refer to particular capacities deduced from observations of brain mechanisms as well as behavioural and cognitive performance of DoC patients as compared to healthy, conscious people. IoC do not provide a definitive answer to the issue whether the subject is conscious or not, but they offer the ground for an informed inference about his residual conscious abilities. Also, the IoC may be used in a cumulative sense: the consistency among different indicators reinforces the likelihood that the patient is actually conscious. Indeed, the main advantage of IoC is that they refer to cognitive capacities that are considered to require conscious abilities while remaining agnostic to a specific model of consciousness,

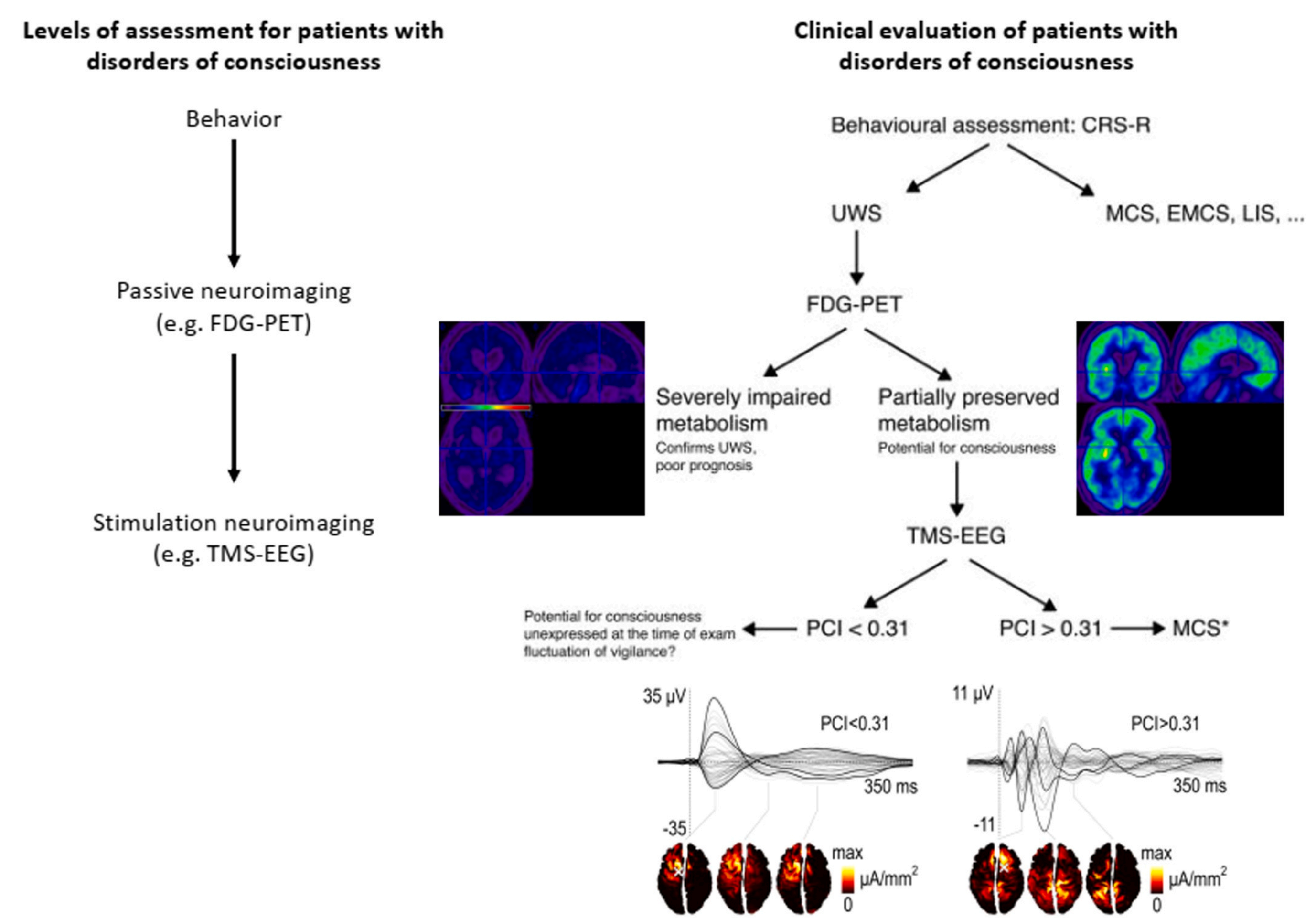

Fig. 1. Flowchart presenting the different levels of assessment of patients with disorders of consciousness, starting from behavior towards stimulation based paradigms.On the right side, an example of different clinical assessment tools are provided to come towards the best diagnosis in the current state of the art. The aim is to reduce the uncertainty regarding the diagnosis at every assesment level, and supplementary assessment is provided especially if uncertainty remains. Please note that other behavioral assessments (e.g. SECONDs) and neuroimaging tools might be used as well (e.g. resting state or task based fMR and EEG) to either supplement or replace the diagnostic tools presented here. Image modified from [18]. The FDG-PET data of the patient with partially preserved metabolism is available through EBRAINS (https://search.kg.ebrains.eu/instances/Dataset/68a61eab-7ba9-47cf-be78-b9addd64bb2f). The data is shared alongside code and healthy control data to assess reduced and preserved glucose metabolism in patients with disorders of consciousness to aid clinical diagnosis using FDG-PET.

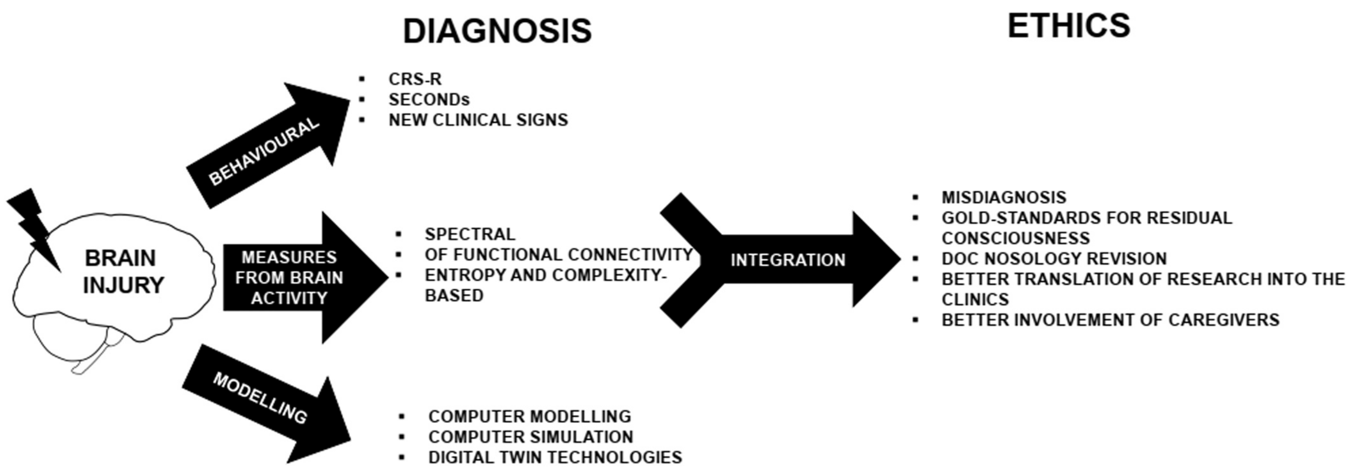

Fig. 2. The approach and main points of the paper.

providing an effective solution at a time when rigid consciousness thresholds cannot be established and an agreement among proponents of different theories is hard to achieve (Evers et al., 2024).

Against this background, the paper illustrates an ethical model - the distributed responsibility model (DRM) (Farisco and Salles, 2022) – which we here refine and within which we identify and analyse five particularly urgent ethical issues for people with DoC (Farisco, 2023): high misdiagnosis rate, the utility of metrics to be employed when gauging necessary and sufficient mechanisms for consciousness, the need to revise the nosology (classification) of DoC, the need for better involvement of caregivers in clinical treatment, and the importance of neurorehabilitative and neuropalliative care. Finally, we propose possible avenues and introduce recommendations to render the methods reviewed in the paper more accessible to the clinic.

The paper aims to provide a representative picture of the state-of-the-art and cutting-edge diagnostic techniques for non-specialised readers rather than a comprehensive and technically detailed review for the specialised scientific audience. The priority is to create a conceptual platform which makes it possible for people from different backgrounds to share knowledge on DoC, with the final aim to improve their diagnosis and clinical care. To this aim, in the following we report some illustrative diagnostic approaches presently used in the clinics or under development in research, and we elaborate a reflection on their potential clinical translation and positive impact on the diagnosis and care of affected patients. Therefore, the review of clinical and scientific data does not aim to be comprehensive but instrumental to reduce the gap between researchers, clinicians, patients, and their families. The multidisciplinary analysis developed below is an attempt to include multiple voices in the discussion (clinical, cognitive, and computational neuroscience, medicine, ethics, patients' associations).

2. Assessing consciousness from brain activity

The evaluation of the level of consciousness in patients that have suffered from brain injury is a difficult challenge, but it is also a very important task because clinical decision-making crucially depends on it. There are several reasons why this evaluation is problematic. Consciousness is arguably a graded and multidimensional phenomenon rather than an "on-off" process, and therefore, elaborating reliable assessments requires observing each case from different angles using a variety of tools and protocols.

Our view resonates with the notion of consciousness' dimensions that has been widely analysed by Bayne, Hohwy, and Owen (Bayne et al., 2016). Focusing on global states of consciousness (i.e., states of consciousness characterising the overall conscious condition of a subject) as distinguished from local states of consciousness (i.e., specific conscious contents or experiences), they argue that consciousness is manifested in multiple ways in different global states, and that the notion of levels should be replaced by that of dimensions of consciousness to properly describe its multifaceted nature. The central thesis is that global states of consciousness are not gradable along one dimension, but rather distinguished along different dimensions. The authors introduce two main families of consciousness' dimensions: content-related and functional. The first family includes gating of conscious content (e.g., low-level features vs. high-level features of an object). The second family includes cognitive and behavioural control (i.e., the availability of conscious contents for the control of thought and action). More specifically, Walter has recently proposed the following content-related dimensions: sensory richness, high-order object representation, semantic comprehension; and the following functional dimensions: executive functioning, memory consolidation, intentional agency, reasoning, attention control, vigilance, meta-awareness (Walter, 2021).

The question is open whether these dimensions actually target consciousness rather than cognition, whether there are additional. Seemingly unlimited dimensions of consciousness could be differentiated, including low-level perceptual, high-level cognitive dimensions (Birch et al., 2020) and self-consciousness related dimensions could be identified (Dung and Newen, 2023). However, it is unsure which dimensions are still to be identified and if relevant, how to identify them in healthy and injured subjects. In fact, the assessment of consciousness and its dimensions is particularly challenging in the case of patients with DoCs. Against this background, we here aim to expose the needs to establish and operationalise a broad framework that accounts for the multidimensionality of consciousness.

To date, the principal means of clinical diagnosis and prognosis in patients with DoC is their bedside behavioural assessment such as the response to sensory stimuli, pain or simple commands (Giacino et al., 2004; Wannez et al., 2018). Research is in progress to optimize the neurobehavioral assessment of DoC patients (Keech et al., 2025), and also to find new behavioural indicators of consciousness (Mat et al., 2022), but a shortcoming of these procedures is that they rely on the capacity of the patients to interact and communicate with the clinical staff (i.e., to perceive and process external stimuli, and to explicitly and reliably react to them). On the one hand, damage to sensory perception could impede a patient to recognise the cues from the clinicians while, on the other hand, the ability of a patient to communicate via language or to produce intentional responses could be deteriorated. As an alternative to the behavioural test, researchers are looking for methods to quantify the level of consciousness either from some organic measures like olfaction (Arzi et al., 2020), respiration (Liuzzi et al., 2023), cardiac activity (Candia-Rivera et al., 2021; Raimondo et al., 2017), and eye blinking (Magliacano et al., 2021), or from more high-tech approaches, like the spatio-temporal signals of brain activity as measured via EEG, Magnetoencephalography (MEG) or functional Magnetic Resonance Imaging (fMRI). (See Fig. 1. Find an interactive live figure at https://wiki.ebrains.eu/bin/view/Collabs/live-paper-ethics-and-clinical-care/ which illustrates some real clinical cases and the application of some diagnostic approaches).

The rationale behind the methods based on the analysis of brain signals is that one could quantify the cognitive effort of the patient without the need of externally observable behavioural responses. Two different stages should be distinguished within this diagnostic strategy: (i) quantifying the capacity to sustain consciousness by measuring the spontaneous or evoked brain activity (e.g., through fMRI, EEG, Stereo-electroencephalography (sEEG), MEG) in order to quantify the state of the network and (ii) quantifying the brain response in the context of trying to communicate with the patient (e.g., asking them to perform a particular mental action, like playing tennis).

2.1. Measures of consciousness from brain activity

Literature about the measures of consciousness from brain activity is rich. To provide a comprehensive overview, we start from a broad review of these measures to then identify some issues related to their clinical translation.

For the diagnosis of DoC patients, brain activity is typically recorded under two different paradigms. On the one hand, when a subject is not performing any particular task the paradigm is referred to as the *spontaneous* or *resting-state* brain activity. This represents the simplest condition under which brain activity can be monitored since it lacks the transient features commonly occurring after stimulus presentation or during cognitive processing. On the other hand, (un)consciousness is also studied by presenting external stimuli to the subject and investigating the evoked response signals, in either active or passive paradigms. In the following, we summarise the major findings to date by studying brain activity during conscious and non-conscious experiences, with a particular focus on patients with DoC. It shall be noted that the literature is vast and several contradictory results have been reported. The origin of those differences may lie in a variety of factors, e.g., (i) differing analysis methods, (ii) distinct acquisition parameters, or (iii) the fact that patient data tend to be very noisy with plenty of artefacts. Here, we restrict to summarise features that have been reported to a larger level of consensus across studies. Besides, our analysis does not aim to be all-inclusive but focuses on illustrative techniques and measures that may be translated into clinical practice. See (Bai et al., 2017; Kondziella et al., 2016; Kotchoubey and Pavlov, 2018; Nilsen et al., 2020; Rossi Sebastiano et al., 2021; Duszyk-Bogorodzka et al., 2022) for more extensive reviews and meta-analyses.

2.1.1. Spectral measures

A large part of the literature deals with the investigation of predominant rhythms of brain activity and their alteration during loss of consciousness. These focus preferentially on signals recorded via EEG as its fast temporal resolution allows to scan brain activity along broad ranges of frequencies. On the contrary, activity recorded with fMRI is usually constrained to the very slow frequency band of 0.01–0.1 Hz. One of the aims of spectral analyses is identifying the dominant frequencies in the recorded signals (by quantifying their power).

The EEG signals of conscious wakefulness in healthy subjects are characterised by the dominance of power in the alpha band (α: 8 – 12 Hz), especially in the temporal and the parietal regions. During unconscious states, however, a dominance of power in the lower frequencies has been consistently reported. The power spectra of patients with UWS is characterised by the absence of power in the α-band and the dominance of the delta (δ: 0 – 4 Hz) band (Babiloni et al., 2009; Lehembre et al., 2012; Sitt et al., 2014; Williams et al., 2013) across all channels. Patients with partial recovery of consciousness (classified as MCS) display an intermediate situation in which power in the α-band can be partially recovered (particularly in frontal and posterior regions), but with a significant dominance of power in the δ-band and some power in the θ-band (Bai et al., 2021; Naro et al., 2021). Accordingly, the level of power in the α-band at the posterior regions in patients with UWS has been proposed as a reliable predictor of their progression and of their chances for (partial) recovery (Babiloni et al., 2009; Bagnato et al., 2015; Bareham et al., 2018).

However, recent evidence has shown that the accuracy of the power of α-band to classify patients with DoC depends on the causes of loss of consciousness. The α-power seems to be useful to differentiate UWS and MCS patients with localised brain damage (Colombo et al., 2023) (e.g., due to traumatic injury or stroke) but the α-power is generally considered not predictive of the state of consciousness in patients who suffered from anoxia (i.e., suffering a severe lack of oxygenation to the brain, usually as a consequence of cardiac arrest).

For anesthesia and sleep, the discriminative capacity of consciousness by the power of the α-band alone has seen contradictory reports. The power of the α-band gradually decreases under isofluorane sedation (Hagihira, 2015) but its power is conserved (or even increased) under propofol anaesthesia or ether-derived compounds (Ching et al., 2010; Purdon et al., 2015; Scheinin et al., 2018; Vijayan et al., 2013). Non-REM sleep is characterised by a loss of power in the α-band and an increase in the δ-band. However, α-power can also be reduced despite consciousness being present, during disconnected consciousness, such as REM dreams (Baird et al., 2018; Benca et al., 1999; Esposito et al., 2004) and ketamine-induced dreams (Akeju et al., 2016; Vlisides et al., 2017). There seems to be a non-linear relation between alpha power, cortical glucose metabolism and level of consciousness, suggesting that alpha power knows an optimum that can be associated with consciousness (Annen et al., 2023). In summary, while large power of the α-band in the temporal and parietal regions is a characteristic hallmark of healthy, conscious awake state, its loss and the presence of power in lower frequencies seems to vary depending on the reason and the mechanism for loss of consciousness.

2.1.2. Measures of functional connectivity

Brain function relies on the co-activation of several structures into functional networks (Damoiseaux et al., 2006), with some of them related to the mechanisms of consciousness (Boly et al., 2008; Boveroux et al., 2010; Mason et al., 2007). Conceptually, functional connectivity refers to the co-activation, synchrony or statistical associations between the signals of activity measured at different locations of the brain. For EEG, functional connectivity can be calculated either between electrodes or between brain regions if the source localization is further performed. In fMRI scans, functional connectivity is usually calculated between voxels or between the brain regions delineated by a parcellation atlas. Mathematically, functional connectivity is usually calculated as the Pearson correlation, the coherence or the level of synchrony between the signals at two different locations or channels. This variety of choices can be confusing at first but reports are robust and all pointing in the same direction regardless of the measure or modality: loss of consciousness is characterised by a generalised decay in the structure of functional connectivity patterns over space and time.

For EEG recordings, changes in functional connectivity follow closely the observations found for the power spectrum of the signals. Normal wakefulness is characterised by a dominance of connectivity in the α-band within and between the temporal and the parietal regions. In patients with UWS, α-band connectivity is lost possibly due to the absence of power in the α-band, but a global increase of connectivity is observed at the δ-band. In MCS patients a partial restoration of fronto-posterior functional connections are found in the α-band but not as strong as in the normal awake state of healthy controls (Bai et al., 2021; Naro et al., 2021).

The brain is a complex network made of billions of neurons and trillions of synapses forming nested and recursive circuits. This vast network serves as the physical structure on which the neural information is transmitted and processed in a variety of spatio-temporal scales. It is often hypothesised that persistent spatio-temporal fluctuations in the brain's activity are a signature of a normally working awake brain because it reflects the transient interactions between distant neural circuits that switch their associations as information is processed, from sensory perception to multisensory integration. The generalised loss of functional connectivity has been recurrently reported in the transition from consciousness to unconsciousness due to anaesthesia both in animals and in humans (Alkire et al., 2008; Bettinardi et al., 2015; Bonhomme et al., 2016; Dasilva et al., 2021; Hahn et al., 2021; Sanders et al., 2018). Similar observations are found in both EEG and fMRI studies for patients with DoC where patients diagnosed as UWS are characterised by a severe loss of functional connectivity while patients in MCS display partially recovered levels of connectivity (Bareham et al., 2018; Laureys et al., 2000). Now, while the average level of functional connectivity could be regarded as an overall indication of consciousness, it is difficult to derive mechanistic understanding from them. Several reports have pointed that, more specifically, it is the level of functional connectivity over the frontoparietal axis which better correlates with loss of consciousness in several conditions (Sanders et al., 2018; White and Alkire, 2003) and also in patients with severe DoC (Laureys et al., 1999; Laureys et al., 2000). Analysis of time-resolved functional connectivity demonstrated that subcortical areas display spatial coordination with the fronto-temporoparietal resting-state network, and this increases in MCS compared to UWS patients (Panda et al., 2022). Patients in MCS display significant preservation of frontotemporal connectivity when assessed either via neuroimaging (Vanhaudenhuyse et al., 2010) or electrophysiology (Wu et al., 2011). During loss of consciousness this rich dynamical behaviour is expected to simplify, in the case of DoC patients due to brain injury, leading to e.g. the inability to process sensory information, the interrupted communication between brain regions or the ineffective binding or integration of multisensory information.

2.1.3. Variance and fluctuations of brain activity: entropy and complexity-based measures

Several measures have been proposed to capture and quantify the spatio-temporal fluctuations of the brain's activity and to relate these to cognitive functions or consciousness. Measures of entropy and complexity are encompassed within this category, although they are not the only useful metrics to quantify fluctuations. Given that the ecosystem of these measures is vast and rather confusing, a few clarifications should be made.

First, proper and intuitive definitions are required for transparency and adequate interpretability. On the one hand, it shall be reminded that Shannon entropy is, in practice, a metric of variance (e.g., a measure of randomness). The Shannon entropy of a system is largest when all the accessible states are equally likely, implying that the system is represented with largest variance or maximal randomness. Shannon entropy is minimal when the system is represented in a single state (e.g., the brain activity doesn't fluctuate). On the other hand, complexity is broadly defined as "*the non-trivial coexistence of order and disorder in a system*". The notion of complexity is in line with the idea that for conscious processing to happen, the brain should carry out, simultaneously, different types of information processes: from sensory perception to feature binding and multisensory integration. However, to add more confusion, not all measures coined as "complexity" quantify complexity, but some quantify randomness instead. Thus, they should be better framed as entropic measures. A notorious example of this is the Lempel-Ziv complexity (LZc). The origin of LZc lies in the realm of computer science and the problem of data compression. In the language of computer scientists, *complexity* refers to how difficult it is to compress a dataset. Periodic data is easy to compress due to its repetitive structure while random data is the most difficult to compress because of the lack of recurrent or predictable features. Hence, LZc is a measure of randomness, as it was expressed by the authors in their seminal paper (Lempel and Ziv, 1986): "*A new approach to the problem of evaluating the complexity ('randomness') of finite sequences is proposed.*"

Second, considered as measures of brain activity, the terms *entropy* or *complexity* alone are not fully informative. In the same manner in which *variance* could refer to the variance of an observable across subjects, the variance of an EEG signal over time or the variance of some property compared across brain regions. Hence, for an adequate interpretation, one should always keep in mind "*the entropy of what*" or "*the complexity of what*" is being quantified by a given measure before drawing conclusions.

Different notions and theories of consciousness assume the need of both local and distant brain regions to communicate in order to combine the specialised sensory processing by some brain regions with the binding, integrative and feedback control of others. This shall be reflected as fluctuations in the dynamical activity of the brain at various spatio-temporal levels. And the absence of such fluctuations should then be indicative of loss of consciousness. In fact, as empirical observations make evident, the metastability of whole brain dynamics (which measures the presence of brain-wide spatio-temporal fluctuations) and the spontaneous switching between functional resting-state networks are signatures of resting-state activity during normal wakefulness in healthy participants (Bertolero et al., 2015; Deco and Kringelbach, 2016; Ponce-Alvarez et al., 2015; Senden et al., 2017). These fluctuations are largely suppressed during loss of consciousness due either to sleep (Hahn et al., 2021), anesthesia (Hahn et al., 2021; López-González et al., 2021; Mashour, 2024) or DoC (López-González et al., 2021). Among the entropy-based measures, spectral entropy (measuring the variance of the frequency spectrum out of EEG signals) robustly showed correlation with CRS-r bedside assessment of patients with DoC, with its value reliably decreasing across healthy awake, MCS and UWS conditions (Gosseries et al., 2011; Piarulli et al., 2016; Sitt et al., 2014). Other entropic measures such as the Kolmogorov–Chaitin complexity and the permutation entropy have been indicated as capable of discriminating the MCS from the UWS (Sitt et al., 2014; Thul et al., 2016).

The decay of functional connectivity during loss of consciousness reflects the disruption of communication between brain regions. For example, the reduction of functional connectivity between brain regions during anesthesia is followed by a decrease in the complexity of the network (Dasilva et al., 2021; Luppi, 2024) evaluated as the richness of spatial correlations captured by functional connectivity (Zamora-López et al., 2016). Although the precise mechanisms for the loss of communication between brain regions may vary–different mechanisms are expected to underlie disrupted inter-areal communication in anaesthesia, non-REM sleep and DoC patients–it opens another door to probe states of consciousness by observing the spread of activity in the brain. Experiments have shown that during non-conscious processing, primary sensory cortical areas still activate normally in response to auditory or visual cues. However, under unconsciousness, this primary activity fails to propagate adequately, impeding the sensory information to be transferred and processed beyond the primary cortical areas (Ishizawa et al., 2016; Pavone et al., 2017).

A similar observation is found when applying external, yet direct cortical perturbations such as TMS. In normal awake states, the neural activity induced by the TMS pulse propagates throughout the brain, via the lateral cortical and the long-range white-matter fibers. But when TMS is applied to unconscious subjects (either focalised onto sensory or associative cortical regions), only the cortical region receiving the TMS pulse displays a neural response (Sarasso et al., 2014). This phenomenon (the disruption of the propagation of neural activity) is exploited by the Perturbational Complexity Index (PCI) to evaluate the level of consciousness. PCI employs EEG to quantify the (absence of) propagation of neural responses through the scalp that are elicited by a TMS pulse focalised at a given cortical region (Casali et al., 2013). In short, the quantification of PCI involves four steps: perturbing the brain via TMS; recording EEG cortical responses to the perturbation; extracting a binary matrix describing the spatio-temporal propagation of elicited responses; and compressing this matrix using Lempel-Ziv complexity (Casali et al., 2013). The less the pulse propagates, the more the matrix can be compressed and the lower is the PCI value reflecting the absence of responses by distant cortical areas to the TMS pulse. Larger values of PCI indicate a non-stereotypical way of activation, say, when the TMS input elicits brain-wide responses of cortical regions at different time-scales. A current strength of PCI is that, unlike most other measures for consciousness proposed in the literature, PCI has been systematically tested for several datasets and validated across a variety of brain states. These significant efforts have shown that PCI robustly discriminates between wakefulness and states of (un)consciousness both in sleep, anesthesia and DoC (Casali et al., 2013; Demertzi et al., 2019; Sarasso et al., 2014). Hence, PCI has been formally recommended in a number of international practice guidelines (Giacino et al., 2018; Kondziella et al., 2020) and expert reviews (Bai et al., 2021; Comanducci et al., 2020; Edlow et al., 2023) for the diagnosis and prognosis of DoC. The reader can find the concrete methodology and the software for PCI estimation via the EBRAINS research infrastructure (see Method1) together with a test dataset to validate its discriminatory power for a cohort of patients with DoC (see https://doi.org/10.25493/5TNA-R5P).

In summary, measures of the spatio-temporal fluctuations of the brain's activity form a promising category of indicators of consciousness. However, the clinical translation of these measures is still challenging for a variety of reasons including the costs of the technologies employed and the expertise needed to use them (Farisco et al., 2024). For clinicians to adopt these metrics still requires substantial efforts: the measures need to be clearly explained to the clinicians such that they can undoubtedly interpret their outcomes, which is a fundamental aspect for trusting new advances into the clinic.

Attempts to facilitate multimodal and/or multivariate diagnostic approaches in DoCs, which data indicate to improve also the prognostic accuracy (Rohaut et al., 2024), have been done recently, as recommended by both US and EU guidelines on DoCs ((Giacino et al., 2018; Kondziella et al., 2020)). To illustrate, they span from EEG, proposing a hierarchical pipeline of measures in increasing levels of implementation complexity (Comanducci et al., 2020) or combining different metrics (Chennu et al., 2017), to advanced imaging and electrophysiology, proposing a flowchart for deciding about its use (Monti and Schnakers, 2022), to the combination of EEG and fMRI, proposing a hierarchical approach for a multimodal prediction of residual consciousness (Amiri et al., 2023). Notwithstanding these valuable attempts, the challenge of translating research into the clinics is still open.

2.2. The challenge of translating research results into the clinics

Despite the intense research in this field, the implementation of the study of brain signals into the daily clinical practice is mostly restricted to hospital units involved in active research. We identify several factors that hamper the translation of these research efforts into the clinical practice:

(i) The literature of potential biomarkers of consciousness from brain activity forms a vast and very heterogeneous ecosystem that is complicated to permeate for non-experts. In a recent review Nilsen et al. [31] reported more than 250 proposed measures of consciousness in the literature, only for EEG, and only for papers published in the period between 2009 and 2018 (Nilsen et al., 2020).

(ii) Measures from brain activity are being defined for the different technologies used (EEG, MEG, fMRI and Local Field Potentials, LFPs) independently, making it difficult to discern redundant from original metrics. Besides, some metrics may take different names according to the recording modality and it is usually unclear whether the metric is specific for a given modality, or if it can be applied to others.

(iii) The proposed metrics are often both mathematically and conceptually challenging for the untrained personnel, making them difficult to apply in practice and especially to interpret their outcome. Without clear interpretability, clinicians cannot properly enclose the results coherently with those of other observations.

(iv) Systematic reviews and meta-analyses to explain and clarify the variety of metrics, to compare across them and to evaluate their reproducibility have been scarce.

(v) Many of those metrics have only been tested in particular scenarios. For example some have been tested on animal models and others in human data. Many of them have been only tested in either sedation, anaesthesia, sleep or in DoC patients. Also, the literature studies consciousness through different paradigms: resting-state, event-related potential to natural stimuli or the responses to artificial perturbations. Rarely a metric has been validated in all those cases which is essential to gain the confidence for the clinical community. There is also a lack of fully available standardised, validated methods that non experts can get reach of and use.

(vi) It is difficult to compare across proposed metrics of consciousness without a common, standard and accessible database that includes both DoC, sleep, and anaesthesia, in different modalities (EEG, MEG and fMRI) on which reliable comparisons can be performed. Without such a reference dataset, reports for each metric depend on the peculiarities of the specific dataset employed to report their outcome.

Against these translational challenges, we now explore the possibility of introducing new indicators of consciousness to be possibly translated in clinical measures of residual conscious activity.

3. Development of further indicators of consciousness: brain responses to illusions and complex stimuli

One of the most defining features of consciousness is intentionality: the capacity to have representations with various contents that are not direct, one-to-one reproductions of reality, but rather a contextualization of stimuli within mental schemata that determine the interpretation of physical reality (Olcese et al., 2018). Since intentionality is lost in states of un-awareness, this offers an opportunity to define future potential indicators of consciousness in DoC. Specifically, we propose that perceptual illusions, ambiguous, and multi-stable stimuli may be useful at gauging consciousness in clinics in the future since they rely on the (conscious) interpretation of a stimulus in various sensory modalities (Pennartz et al., 2019). This theoretical line of investigation leads us, first, to propose the use of illusions, ambiguous, and multistable stimuli in the context of diagnosis and state characterization of patients with DoC. The underlying rationale is based on intentionality as a key feature of conscious experience: if a subject shows evidence of encoding or responding to an illusion differently than to an unambiguous, monostable, non illusory stimulus (e.g., oscillating between different responses to the same ambiguous stimulus), then some high level interpretation consistent with intentionality is occurring in the brain (Pennartz, 2015), and this could be evidence for consciousness. Today, noninvasive neuroimaging makes it possible to detect neural activity in human subjects with increasing resolution (Kauppi et al., 2015; LaConte, 2011) that may be capable of detecting differences in the encoding of ambiguous and illusory stimuli (Hayashi et al., 2007; Kauppi et al., 2015; Kobayashi et al., 2007; Weilnhammer et al., 2017). As such, if the neural interpretation (i.e., the neural coding) of an ambiguous sensory stimulus (regardless of whether overt behaviour is observable) is detectable by neuroimaging, we may have a neural correlate of intentionality (i.e., of the capacity of top-down contextualization of incoming stimuli against a background of subjective expectations), which stands as an IoC with utility for detecting a new dimension of residual consciousness in patients with DoC. Obviously, an indication for consciousness of this kind can only be obtained if the sensory apparatus of the patient is sufficiently functioning (i.e., (s)he is able to perceive and process external stimuli). Thus, absence of evidence of this capacity in patients with DoC is not evidence of absence of residual intentionality and consciousness.

Empirical data on illusions suggests that a hierarchy of contextualization occurs in the visual system that can be detected with neuroimaging and analysis (Muckli et al., 2002; Muckli et al., 2002; Munk et al., 2002). Sensory input creates a feedforward stream of activity through the cascade of visual hierarchy that meets top-down cortical feedback reflecting expectation derived from internal models that creates a context for the sensory input. For illusory, multistable or ambiguous stimuli, cortical feedback influences the interpretation of the feedforward stream determining its perceptual interpretation, thus regulating the perception of illusions and determining the stability of one or another percept. In other words, an ambiguous, multistable, or illusory stimulus, induces identical neural activity as non-ambiguous stimuli in early processing stages of the brain –for example, in the subcortical and early sensory areas– but, in higher areas of processing –for example, association cortex– brain activity can detectably differ according to how a stimulus is interpreted. Similarly as in non-communicating patients with a DoC, visual perception can be tested in infants less than 6 years old, which suggests that feature binding is not present yet due to lacking recurrent processing (Tsurumi et al., 2023). Indeed, research has shown that the feedforward stream of sensory activity is contextualised and modified by top-down cortical feedback activity (e.g. (Singer, 2021). As an example, it was recently shown that increased activity in the human association cortex –V5 / hMT complex determines that a pair of asynchronously blinking dots is perceived as an apparent motion stimulus while diminished activity changes the perception to two independently blinking dots (Muckli et al., 2002). Moreover, feedback from human visual area V5/hMT to primary visual area V1 generates activity along the perceived apparent motion streak in V1, which indicates how the subject perceives the motion path in a motion quartet (vertically or horizontally, (Muckli et al., 2005). So in this example we would propose that reading out the apparent motion streak from brain activity in V1 functions as an IoC, as it disambiguates between possible interpretations of sensory input based on previous expectations and related internal models of the patient. Indeed, feedback from association cortex to primary sensory areas can amplify or suppress feedforward activity (Muckli et al., 2005).

We suggest a hierarchy of contextualising that can occur in the visual system and be investigated with brain reading. The hierarchy starts with (1) no contextualisation of sensory input as it may exist in anaesthesia, to (3) influencing bistable visual perception and to (5) vivid visual imagery as in a dream purely driven by top-down mechanism in absence of only minimal feedforward input.

Internal models play an increasingly strong role in the interpretation of the visual sensory input.

(1) Visual input creates feedforward stream of activity through the cascade of visual hierarchy

(2) Cortical feedback creates a visual spatial context for the upcoming visual input without creating an illusion

(3) Cortical feedback alternates the interpretation of the feedforward stream determining its perceptual interpretation. Cortical feedback determines bistable visual perception.

(4) Cortical feedback creates a visual illusion

(5) Cortical feedback creates visual imagery.

By using functional MRI and brain reading strategies we propose to be able to identify the ability to perceive illusions as an indicator of consciousness, i.e. as indicating the level of contextualisation (from point 2–4 above). This approach, which is informed by neuronal data and is theoretically justified by them, has not been tested in patients with DoC yet but has made its way to infant research, and in principle it is a candidate complement of already validated behavioural and instrumental diagnostic strategies.

4. Immersive virtual reality for assessment and rehabilitation in DoC

Against the background of the analysis above concerning different potential IoCs (i.e., biomarkers and illusions) in patients with DoC, we introduce here the use of virtual reality (VR) in the assessment and treatment of this condition. Numerous studies and clinical applications of VR already exist in the context of physical, cognitive, and neural rehabilitation (for reviews (Massetti et al., 2018, (Irazoki et al., 2020), (Georgiev et al., 2021), (Demeco et al., 2023), (Combalia et al., 2024). Even though the use of VR in DoC is far from established, its potential value in these patients is attracting increasing attention in applications that range from assessment to therapeutic interventions (Hyun et al., 2022; Liang et al., 2022; Maggio et al., 2020; Reale et al., 2023; Stasolla et al., 2022).

Immersive VR is a technology in which simulated, digital multisensory environments fully surround and envelop the user, offering a strong illusion of being in the rendered environment (Slater, 2009). In VR, users can interact with a virtual environment in ways that are not possible in the real world. These means of interaction are currently expanding, as recent head-mounted displays can integrate eye tracking, facial expression recognition and sensors for physiological monitoring that enhance the means of detection of stimulus-evoked responses and interactivity (Kim et al., 2021). Interaction in VR through brain signals that are analysed using machine learning has recently reached unprecedented success for speech recognition and avatar control (Metzger et al., 2023). Building on these breakthroughs, VR in DoC can now explore new avenues for assessment and rehabilitation.

As an assessment tool, VR integrated with physiological signals can serve clinicians to assess the patients' cognitive abilities and responsiveness in a highly controlled and standardised manner. For example, a recent study used eye tracking and VR to differentiate between UWS and MCS (Hyun et al., 2022), and reported advantages as a quantitative measurement system of visual function in patients with DoC, displaying higher sensitivity to detect visual startle, visual fixation, and visual pursuit than conventional clinical assessment. VR is multisensory, and thus illusions involving visual, audio, tactile and/or temperature stimulation can be set, either as mono- or multi-sensory modalities. These multisensory VR-induced experiences can include not only the environment, but also one's own body representation as well as social interactions with other avatars. Embodiment in a virtual body has a wide range of physiological, emotional, behavioural, and cognitive effects (Slater and Sanchez-Vives, 2016). In principle, the affordances provided by VR offer an opportunity to systematically investigate in patients with DoC their level of awareness of the environment, of themselves and of others, widely expanding the number and range of stimuli and interactions that can be provided in the real world. For example, an unexpected movement of their "own" virtual body has similarly been reported to trigger an EEG-measured brain response equivalent to the semantic violation (Padrao et al., 2016). Responses to human representations in VR (avatars) are also very similar to responses to real humans, including cognitive, emotional and behavioural responses (Bailenson et al., 2003) (Llobera et al., 2011), enhancing the type of meaningful stimuli that can be systematically used, such as social signals.

The therapeutic potential of immersive VR for DoC patients also remains largely unexplored, but the possibility to provide diverse and interactive experiences suggests that it can be useful for rehabilitation and treatment. Since the virtual world is processed in the same way as the real world through our sensory modalities, it is clear that DoC patients must be aware in order to exploit the capabilities offered by VR. If there is some level of awareness, VR can have a role in stimulation and engagement, interaction with safe and calming worlds, cognitive rehabilitation, induction of neuroplasticity or even as a means of communication. In patients who may have limited interactions with their environment, it can provide a rich, multisensory, engaging environment that encourages responsiveness and brain activity. In fact, VR is often already used in other conditions for cognitive rehabilitation (Georgiev et al., 2021; Irazoki et al., 2020), including virtual spatial navigation or gamified tasks, and it has begun to be used in DoC (Maggio et al., 2020), showing its usefulness in MCS specifically. Possible benefits could be derived from cognitive stimulation, interaction with virtual characters, or neurorehabilitation (Khan et al., 2023; Perez-Marcos et al., 2012).

Overall, immersive VR alone or in combination with other physiological measurements is a novel approach to assess, engage, stimulate, and potentially contribute to rehabilitate patients with DoC, providing a customizable and controlled environment that can adapt to individual needs and therapeutic goals.

The analysis above concerning the potential clinical relevance of specific IoCs (i.e., biomarkers and visual illusions) for assessing residual consciousness in DoC and their use in implementing diagnostic and therapeutic applications of VR with affected patients raises some ethical issues that we summarise in the following.

5. The relevance of the proposed indicators of consciousness to the clinical and ethical discussion about DoCs

Several ethical issues arise from both the clinical treatment and research on DoC (Lewis et al., 2023; Young et al., 2021), both chronic and transient. Issues are of two main kinds: fundamental/foundational (i.e., affecting basic ethical notions and rights, as well as the way we distinguish what is good and what is bad), and practical/applied (i.e., arising from different implications on how patients managed, diagnosed, and treated) (Farisco, 2023). Among the second kind of ethical issues, we highlight the following because they are particularly urgent and because the existing and proposed future IoCs described in this paper are relevant to better address them: misdiagnosis, the definition of gold-standards for detecting residual consciousness, the need to revise DoC nosology (classification), the need for a better translation of research into clinical practice, the need for a better involvement of patients' caregivers in clinical treatment, and the need for more effective neurorehabilitative and neuropalliative care.

5.1. Misdiagnosis

The high rate of misdiagnosis is specifically related to the difficulty in disentangling the different types of DoC. As highlighted above, to date, the diagnosis of residual consciousness in DoC patients is mainly formulated on the basis of behavioural tests, but there is abundant evidence that this kind of approach fails to detect possible covert forms of conscious activity. Notably, patients with DoC might be disconnected from the outside world both because of sensory and behavioural impairments. In fact, some studies using neuroimaging paradigms have revealed higher levels of consciousness in patients behaviourally classified as VS/UWS (Candia-Rivera et al., 2021; Thibaut et al., 2021). For this reason relevant international guidelines recommend the combined use of both behavioural and instrumental (e.g., functional MRI, MEG, and EEG) assessments(Giacino et al., 2018), (Kondziella et al., 2020). Importantly, the question of how to actually implement both behavioural and instrumental assessment approaches in the clinics is ethically relevant for the fundamental reason that it impacts the patients' best interest (i.e., receiving the best possible care)(Farisco and Salles, 2022), (Farisco et al., 2024).

Established and proposed IoCs discussed above as well as the possible clinical use of VR have the potential to improve the diagnosis of DoC, for instance making it possible to overcome the sensory and behavioural impairment of the patients focusing on the relevant brain responses. Therefore it is ethically recommendable to further refine IoCs and to work towards their clinical translation. Importantly, the biomarkers for consciousness considered above (i.e., spectral measures, measures of functional connectivity, complexity measures, neuronal signatures of illusions) may be most useful in conjunction, since they offer complementary information regarding the level and content of consciousness. It is also ethically important to take into account that the IoCs presented in this paper should be assumed as positive markers of consciousness: while their presence indicates the actual state of consciousness, their absence is insufficient to rule out that the patient is actually conscious (i.e., absence of evidence of consciousness is not evidence of absence of consciousness). For instance, the illusions paradigm assumes that the visual thalamo-cortical system of the patient is sufficiently intact to respond to visual stimuli. If the patient fails to respond to visual stimulation, he may still retain the ability to consciously process other kinds of stimuli, like auditory or tactile stimuli. Therefore, a precautionary interpretation of emerging results is recommended. This point emphasises the need that a virtuous cycle between basic research and clinical implementation could be amplified: clinicians anonymize and make patient data available to researchers, who construct tools with sufficient technology readiness for use in clinical settings. Feedback from clinical use of tools to researchers can ameliorate available tools in a cycle that more efficiently translates novel findings and refined metrics to the clinic.

5.2. Gold-standard

Another still open question concerns gold-standards for qualifying and quantifying the consciousness of patients with DoC (i.e., what should be reference parameters). In the clinical context, a "gold standard" is conceived as the condition with the highest validity, i.e. the highest correspondence with what is under scrutiny (Peterson, 2016), which in the case of DoC will likely continue to evolve with time. With respect to the diagnosis of DoC, the gold standard must be established in a benchmark population of subjects upon which the set of consciousness metrics is validated (Demertzi et al., 2017). If healthy, conscious neural activity is assumed as the reference point to calibrate the metric for consciousness, the problem of translating methods to patients with DoC arises. In other words, we might fail to detect residual consciousness in patients with DoC, because it might be too different from that assumed as the gold standard. Indeed, a variety of particular injuries to various brain systems may result in similar DoC phenotypes, indicating that a one-size-fits all gold standard may not be an achievable goal. Personalised approaches to the analysis and modelling of neural activity could rather achieve personalised gold standards for individual patients.

The IoCs introduced above do not assume that healthy consciousness is paradigmatic by default. In fact, they start from the need to account for the multidimensional and multilevel nature of consciousness, so that IoCs in principle accommodate the possibility that patients with DoC retain limited dimensions and lower levels of consciousness compared to healthy subjects.

5.3. Nosology

The need for a more reliable gold-standard connects also to the need for a better classification of DoC. In fact, the actual taxonomy has been criticised because dichotomic, binary distinctions are unable to account for the more graded condition characterising affected patients, whose consciousness is not disordered in exactly the same way for everyone with the same diagnosis (i.e., VS/UWS or MCS) (Fins and Bernat, 2018). Also, the possibility of changes in the diagnosis of a patient over time should be accommodated in relevant nosology, in order to avoid any form of therapeutic nihilism (Fins and Bernat, 2018). The IoCs discussed in this paper are inspired by the need for a more tailored diagnosis and characterization of residual consciousness in patients with DoCs.

To this aim it is necessary, among other things, to streamline and produce user-friendly software - to elaborate simplified, operational tools for clinicians using measures of consciousness available today and in the future - which are too numerous and subtle, as well as too mathematically and conceptually subtle for clinical professionals to personally implement. Namely, there is a need for tools which allow the use of various modalities to assess residual consciousness (e.g., EEG, MEG, and fMRI). It should be made clear for clinicians how to decide which modality to use in their assessments, how reliable are targeted biomarkers and the emerging results, and how to interpret conflicting results. Particularly, given the increasing importance of modelling and simulation in elucidating brain mechanisms of conscious processing, it is important that computational scientists actively promote the clinical translation of their tools within the main goals of their research. Analogously, the use of VR in clinical settings of patients with DoC should be further explored and translated into practice (Rousseaux et al., 2022).

5.4. Caregivers

Finally, caregivers' well-being and needs should be monitored, as at times they are overlooked by medical and paramedical communities. Logically, the primary objects of medical focus are the patients' care and recovery. However, the families are classically the patients' principal source of support and families' burden can negatively impact the patients' well-being and functional recovery (Brooks et al., 1986; Knight et al., 1998; Oddy et al., 1978). In fact, it has been recently shown that the caregivers' psychological well-being can be directly associated to a better level of care and to a better functional outcome of patients that, in turn, positively influences the caregivers' psychological well-being, thus leading to a virtuous cycle between medical personnel and patients' loved ones (Bivona et al., 2020). DoC patients' family members and caregivers experience high levels of distress and low quality of life (Gosseries et al., 2023). A number of common needs among caregivers have been shown in the last 40 years. In particular, honest and accurate communication of information regarding the patients' medical condition, treatment, and prognosis are reportedly the most important needs for patients' entourage in acute and post-acute states of brain injury (Gosseries et al., 2023; Knight et al., 1998; Kozloff, 1987; Lugo et al., 2017; Mathis, 1984; Serio et al., 1997). Further, kind and clear explanations, discussion of realistic expectations, emotional support, financial and legal counsellings, and advice about community resources are factors on which patients' families and support structures depend (Kozloff, 1987).

Importantly, families' burden (e.g., the presence of negative emotions, social isolation) has been strongly linked to patients' behavioural and psychological outcome more so than the physical severity of the injury (Brooks et al., 1986; Knight et al., 1998; Oddy et al., 1978). Recently, a study investigated the family caregivers' needs in the context of locked-in syndrome after brain injury (Lugo et al., 2017). Using the Family Needs Questionnaire (FNQ) (Kreutzer and Marwitz, 1989), the families answered that their five most important needs were (in order of importance): 1- medical information, 2- to be reassured that their loved ones received the best medical care, 3- to receive support from a professional if the patient is in need, 4- to receive information about the patients' journey after the hospital (i.e. rehabilitation centres, etc.), and 5- to receive honest answers about the patients' state. The need items that were globally not met were: 1- receiving help to prepare for the worst scenario, 2- receiving support for getting over the doubts and fears about the future, 3- having the possibility of external/institutional aide in case they had to be absent, 4- being told how long the patient's problems are expected to last, and 5- getting a break from their problems and responsibilities (Lugo et al., 2017).

For maximising the beneficial effects of clinical care of patients with DoCs, a better involvement of caregivers, who importantly mediate between the medical staff and the patients, is crucial. For this reason, it will be beneficial to create "family/patient-centred" care models in which caregivers' observations and feedback to medical professionals are met with open-minded consideration and counselling. In fact, in cases of altered states of consciousness, it has been reported that, compared to the medical staff, patients tend to show more conscious goal-oriented behaviours towards their loved ones (Benbassat et al., 1998). Hence, the assessment of consciousness level by untrained persons (e.g., family members and loved ones) using adequate scales such as the SECONDS might be an important step forward for improving behavioral diagnosis (Aubinet et al., 2021; Sanz et al., 2021). Moreover, family caregivers often have firsthand knowledge of patients' preferences before brain injury and can make important contributions to care decisions, particularly when patients are unable to communicate and/or to make decisions (Benbassat et al., 1998). However, family caregivers and other surrogates often feel uninformed and disenfranchised from clinical decision-making and day-to-day care of their loved ones (TheSUPPORTPrincipalInvestigators, 1995), (Heyland et al., 2002). With the goal of raising awareness on that issue, the Mind Care International Foundation (www.mindcare.foundation) and the Association for the Locked-In Syndrome (www.alis-asso.fr) work to create close support groups for patients' entourage as well as providing accessible medical and practical information for families and patients after brain injury.

5.5. Neurorehabilitative and neuropalliative care

Given the challenging clinical management and care of patients affected by DoC, neurorehabilitative and neuropalliative care play a significant role as potential effective strategies, at least for giving back patients a better quality of life. Neurorehabilitation in this population faces a number of difficulties and there are several factors impacting its effectiveness, including a possibly fluctuating residual capacity for conscious experience (Giacino et al., 2013), like related to sleep and circadian disturbances commonly observed in the DoC population (Van der Lande et al., 2022). The complex, multi-factorial character of neurorehabilitation in DoC makes it a highly multidisciplinary effort, which could and should involve experts from medicine, psychology, occupational therapy, physiotherapy, speech-language pathology, among others. Indeed, the discussion about the best possible neurorehabilitation approach in DoC is still open, and likely requires a personalized approach. However, there is a growing consensus on how to address some specific challenges, namely clinical assessment, complementary diagnostic tests, prognosis, and treatment (Noé et al., 2025). To illustrate, a remarkable nationwide study in the Netherlands is generating much-needed quantitative evidence on the effects of intensive neurorehabilitation, together with a comprehensive understanding of how DoC affects patients, families, and healthcare professionals, including their perspectives on recovery expectations, end-of-life decisions, and quality of dying (Sharma-Virk et al., 2021). These large-scale, systematic efforts, starting from the acute phase with rigorous monitoring of consciousness-related and quality-of-life indicators, are essential for building international, personalized guidelines that can meaningfully improve both short- and long-term care for individuals with DoC. Importantly, medical complications are highly prevalent among patients in MCS, yet advance medical decision-making is often hampered by medical instability, treatment disputes, and the emotional readiness of families, further underscoring the need for clear, specialized guidelines across all phases of care (Overbeek et al., 2025).

Also neuropalliative care (Creutzfeldt et al., 2018; Robinson and Holloway, 2017) is increasingly recognized as an important and promising approach for providing a better quality of life to patients with DoC, particularly in order to "ensure comprehensive care with symptom management, evaluation of beliefs, documentation of values, and care and treatment preferences to ensure a comfortable death, relief of suffering, and planning for expected decline" (Ramsburg et al., 2024). Convening a multidisciplinary panel of experts, the International Neuropalliative Care Society has recently identified three priority areas for the advancement of the field: patient- and care partner-centered symptoms and outcomes and tools to assess them; development of effective neuropalliative care; methods to support the capacity to foster, deliver, and measure goal-concordant care over time (Lau et al., 2025). A recent systematic review further underscores these needs by demonstrating that reconstructing treatment preferences for incapacitated DoC patients, an essential component of neuropalliative decision-making, relies on diverse and sometimes conflicting normative-epistemic approaches, ranging from correspondence with past statements to coherence with personal identity or communitarian considerations (Kok et al., 2025). Because patients' inferred preferences may shift as their clinical condition evolves, and because no standardized approach currently exists, preference reconstruction often becomes ethically complex and context-dependent, the review therefore highlights the importance of eliciting rich, nuanced input from surrogates while preserving trust, reinforcing the need for structured neuropalliative frameworks and guidance to support physicians, families, and care teams in navigating these highly consequential decisions.

The IoCs introduced above are highly relevant to the need to improve both neurorehabilitation and neuropalliative strategies in DoC. In fact, they are conceived to provide more reliable and measurable information about residual conscious capacities. Notably, neuroimaging-based IoCs can reveal covert consciousness as early as four days after injury in approximately 15 % of seemingly unconscious acute patients with severe acquired brain injury (Claassen et al., 2019). This finding has been replicated over time, with task-based neuroimaging paradigms consistently identifying covert consciousness in 15–20 % of patients in intensive care who appear unresponsive at the bedside (Edlow and Menon, 2024). Together, these studies suggest that insights derived from prolonged DoC may also be applicable to the acute stage (Frontera, 2012; Le Guennec et al., 2022), underscoring the importance of an integrated, longitudinal approach that includes early assessment after injury and regular follow-up evaluations in the prolonged phase. Such an approach is key to advance both neurorehabilitative and neuropalliative care in the direction of a more targeted clinical approach.

5.6. A model for assessing the ethical issues arising from DoC

Toward meeting ethical challenges summarised above and accelerating the identification and confrontation of other emerging ethical issues, an operational model that allows the translation of theoretical solutions and ethical recommendations into practice can be useful.

A "distributed responsibility model" (DRM) for the ethical analysis of DoC has been recently introduced (Farisco and Salles, 2022) (See Table 1), grounded on a modular understanding of responsibility: different parties share responsibility as professional and/or moral obligations, with specific responsibilities assigned to each.

We take DRM as a case study, which emerges as particularly promising because of its combination of wide scope of analysis and detailed identification of ethical issues and related responsibility. We are aware that this model is not perfect, and that it is not the only possible approach to identify and mitigate the ethical issues arising from DoCs, but we assume DRM as a promising starting point for further discussion.

According to DRM, researchers, medical staff, hospital managers, and family caregivers are all generally responsible to work for the benefit of patients, but their responsibility is differently specified in relation to their particular role (e.g., doing research, optimising healthcare procedures, taking care of clinic finances, and daily tasks to maintain and ameliorate the state of the patients). The goal of DRM is to provide a framework in order to identify with the best possible accuracy who is responsible for what. On the basis of this preliminary clarification it is then possible to a) identify relevant actions for assessing emerging issues, b) monitor the process and detect what possibly does not work, and c) eventually implement any correction needed. Of course, the responsibilities of each party are always intertwined, necessitating high fidelity of communication within the network of caregivers.

Table 1
Classes of issues emerging from DoC and respective levels of responsibility according to DRM.

Institutional responsibility		**Clinical responsibility**		**Inter-personal responsibility**	
Resources	Need for adequate financial resources	**Precautionary approach**	Caution in inferring evidence of absence of consciousness from the absence of evidence	**Medical decision-making**	Potential of multimodal assessment for giving back the patients their right to self-determination
	Needs for skilled practitioners		Acknowledging the limitation of both diagnosis and prognosis		Possible impact of multimodal assessment on surrogate decision-making
	Need for adequate infrastructures		Acknowledging the limitation of actual nosologic distinctions		Possible impact of multimodal assessment on the patients' best interest
Research and healthcare	Overcoming research/care dichotomization		Acknowledging the lack of strong statistical assessment of prognostic value of covert awareness detection		
	Facilitating reliable translation of aggregate statistical results into personalized medical procedures	**Multimodal assessment**	Improving the use of ancillary methods (e.g., functional Magnetic Resonance Imaging)		
	Clear regulation about the disclosure of individual information emerging from research to a patient's surrogate		Consider the impact of necessary therapeutic procedures and individual patient condition on the assessment of residual consciousness		
	Defining clear procedures for multimodal assessment of consciousness	**Communication**	Planning and implementing adequate communication protocols		
	Facilitating large studies on patients with DOCs		Acknowledging the risk of misinterpretation of results		
Nosology	Rethinking nosology of DOCs in the light of their dynamic character		Acknowledging the risk of bias		
	Facilitating the monitoring of consciousness recovery		Avoiding the risk of false hope about recovery		
	Facilitating the clinical operationalization of DOCs' nosology		Thinking about adequate procedures for handling possible disagreement		
Caregivers' counselling	Facilitating involvement of patients' caregivers				
	Making clinical assessment and related terminology consistent with patients' caregivers needs				
	Planning procedures and infrastructures in order to ensure that caregivers' decisions really reflect patients' values				

We identify the following three classes of issues and respective levels of responsibility:

– *Institutional issues*: ethically important topics arise at the level of the institutions and organisations responsible for research and primary care for patients with DoC. For instance: the need for adequate financial resources, the necessity for hospital staff to access constantly evolving research findings, the need for a clinical working environment that fosters kindness. Such issues have a macro-level relevance: the responsibility for identifying and assessing institutional issues is supported by political, direction, and management positions in the clinical environment (e.g., hospital administrative director, chairman of the board of directors, research leader, etc.). In other words, relevant decisions and actions at the institutional level are key for guaranteeing the highest level of patient care.
– *Clinical issues*: ethical considerations that arise at the level of clinician's practice, for instance, deciding the most effective tests for residual consciousness and how best to implement personalised approaches for patients with DoC. How should emerging data be interpreted? How should the patient's caregivers be involved in the clinical process? Such issues have broad relevance for clinician-patient relationships, involving medical professionals as well as patients' family caregivers and patient associations. Such clinical issues may eventually dissolve as a better understanding of consciousness and its measurement improve. For now, we promote a precautionary approach (i.e., the lack of evidence of consciousness is not evidence of the lack of consciousness) that is supported by multimodal assessment (i.e., the diagnosis of the patient's level of consciousness based behavioural and analysis of multi-modal neuroimaging data), improved comprehensive literature written for a lay audience, and direct communication between parties (i.e., families/caregivers should be involved as active agents in the clinical process).
– *Interpersonal issues*: ethical topics that arise at the specific level of decisions affecting the individual patient's right to self-determination, for instance, "how should the clinician guarantee the patient's right to informed consent"? are summarised as interpersonal issues. How to make decisions that respect the patient's best interest have relevance of a personalised kind; in other words, interpersonal issues apply to the individual clinician-patient relationship, which relies mainly on the clinical staff in collaboration with patients' caregivers. To illustrate, indicators of residual awareness might serve as the ground for exploring new strategies to empower patients to communicate and return their right to self-determination (e.g., through the implementation of BCI-based forms of communication). If residual, possibly covert consciousness is indicated, then clinical decisions potentially impacting the patient's best interest, like Life Saving Treatments (LST) or analgesia, can be consequently updated accordingly.

DRM does not provide analytical solutions to the ethical issues arising from DoC, but it defines a framework in order to facilitate the identification, assessment, and solution of ethical issues.

Last, we want to outline that even if we have developed a multidisciplinary and multi-perspective framework targeting the population of patients with chronic DoC, it is possible to extend the resulting model also to other contexts where information about residual conscious abilities is missing or challenging to get. For instance, acutely ill patients with metabolic and toxic encephalopathies in intensive care units may have covert forms of consciousness that are very hard to detect (Frontera, 2012; Le Guennec et al., 2022). The kind of approach that we argue for in this paper is potentially useful also in this case, even if specific relevance and implementation strategy need to be more specifically analyzed.

6. A responsibility model for the design of biomarkers in the research on consciousness

While DRM proposes a general framework to identify ethical responsibilities, we have highlighted before the difficulties of translating fundamental research into clinical practice. In order to facilitate this translation, we conclude by proposing a specific framework for maximising the impact of basic research, facilitating the development of reliable biomarkers, and accelerating their translation into clinical practice. While a large multidisciplinary effort is required to make advances, the medical teams caring for patients with disorders of consciousness play a crucial role in ensuring smooth advancements.

An explosion of literature proposing potential measures for consciousness evidences the race that has been opened for biomarkers in the last decade. However, considering consciousness as a graded and heterogeneous phenomenon, despite the potential value of biomarkers, it is unlikely that the clinical reality for DoC patients will be reduced to a single number. For a measure to become a biomarker with true clinical applicability it requires that the measure convincingly and transparently fulfils a number of conditions. We propose the following:

1) *Interpretability*: The quality of the interpretation of any measure starts with good quality data for the development thereof. Clinicians should put ample effort in sharing neuroimaging and neurophysiology data with the most complete metadata, so that metrics can be developed and validated before entering the clinical domain. The meaning of the metric and its outcomes must be clearly explained by researchers such that clinicians employing the biomarker can interpret the results without ambiguities. The added value of a measure (e.g., easier assessment/computation, higher accuracy) should be made clear by researchers to avoid the abundance in propositions of new measures. Ideally scientific associations should collectively pose clear standards for the clinical implementation and interpretation of a (set of) paraclinically derived markers of consciousness. Does the measure truly quantify what it claims? What are the extremal cases of the measure? Does the measure behave stable, regardless of geographical location and acquisition equipment? How shall the statistical significance of the values under different conditions be evaluated? Do healthy individuals vary significantly from the mean? Under what conditions? Do personalised considerations need to be made in order to best interpret results of the measurement?

2) *Accuracy and integration*: Much linked to the interpretation of a metric is the way it would be integrated in the clinical setting. Researchers should be responsible to define what a biomarker tells about the degree of consciousness and its multidimensional aspect, and with which level of accuracy. Depending on the quality of the metadata provided by the medical teams, researchers could quantify what (multidimensional) aspect of consciousness is being assessed and how well.

3) *Novelty and uniqueness*: When developing new measures, it is imperative to not waste resources. Researchers should be mindful to develop measures which can inform clinicians about aspects they could not know by other means – maybe already existing or cheaper methods? For the development of such measures, it would be most helpful to establish a continuous dialogue with the clinical experts so that researchers can help address the needs of healthcare professions and patients' families.

4) *Reliability and reproducibility*: Specifically in the case of classifiers it is important to address, how the biomarker compares to the classification power of other measures. To really address this properly, this would ideally also require large multicenter studies involving clinicians or the sharing of open-access datasets on e.g., EBRAINS https://search.kg.ebrains.eu/instances/10c4206f-8de4-44a0-b8ce-8d58484678f5. This would allow researchers to compare the effectiveness of different measures, and the same measures in different populations to ensure the most reliable interpretation possible. The scientific societies performing consciousness research would be responsible to, for instance, address the

following questions: Does the measure return the same results and with same accuracy across datasets? Is the measure equally valid and accurate across experimental protocols, e.g., DoC, anaesthesia, and sleep? Is the biomarker useful for any of the recording modalities –MEG, EEG, fMRI and LFPs– or is it only suitable for one of them? Has the measure been tested in both human data and in animal models?

5) *Difficulty to implement and interpret*: Difficulty for the implementation of these developments in daily clinical practice are likely to complicate the clinical implementation. On one hand, institutional steering boards could place this on the agenda. However, as resources are limited and the DoC population is small, it might be impossible for individual healthcare providers. Researchers could focus on the development of simple metrics, easily interpreted by clinicians. The implementation and the application of biomarkers which could be measured, calculated and interpreted by the clinical staff without ambiguities, after little training might be a promising avenue, it does not seem the most likely path for the future. (International) funding agencies could play a critical role by allocating resources to the development of online, multimodal, automated diagnostic pipelines. While a start had been made https://wiki.ebrains.eu/bin/view/Collabs/fdg-pet-analysis-for-doc/ the effort requires dedicated manpower to develop further.

6) *Cost*: This is fundamental for a biomarker to be incorporated by health systems and strongly depends on the recording modality (e.g., fMRI being more expensive than EEG, implanted electrodes being more expensive and invasive) and the training needed from the staff (markers that require dedicated or specialised research staff will be more difficult to be incorporated into health systems internationally). How realistic is it that health systems could incorporate the biomarker for generalised public use, or is its cost or specialised knowledge prohibitive, such that it will only be applicable in particular cases, e.g., research-oriented studies? Ultimately, it would be up to insurance companies to identify which assessments are covered (and alternatives in case of unavailability), and which not.

In summary, this section has provided an ethical frame to the need and use of indicators of consciousness, with a central role for the clinical teams involved with DoC patients. As we have discussed, this integrates a holistic approach ranging from the technical aspects and good practices for the definition of IoCs, to their effective operationalization in practice. This process is mediated by the DRM which identifies and assigns responsibilities to the different stakeholders involved. From clinicians to the institutions responsible for providing the best possible conditions for the treatment of disorders of consciousness to the relevant role played by the families and caregivers of the patients.

Thus, it is desirable to encourage administrations, journal editors, and funding bodies to loosen the pressure on researchers to deliver biomarkers, stratification techniques, and classifiers, and to promote instead the investigation of consciousness in its multidimensionality and individual variation across subjects. In this sense, not every measure employed to study consciousness needs to become a biomarker. Defining biomarkers for clinical practice should be taken seriously instead of becoming a "selling-point" for papers being accepted in scientific journals or for gaining points in grant proposals.

7. Conclusion

Brain damage can lead to coma and thus to a temporary or irreversible loss of consciousness. Patients surviving coma typically recover consciousness although some patients may only recover partially or remain in an irreversible state of loss of consciousness. Adequate assessment and treatment is still challenging for doctors, but is fundamental for the patients and their families. In this work, we have undertaken a multidisciplinary approach to describe the most pressing issues for DoC patients, with the goal of elaborating more faithful diagnoses with implications for prognosis and treatment of DoC patients, key for improving the well-being of both patients and their caregivers. First, current state of the art approaches to detect consciousness and diagnose DoC are presented, reviewing available biomarkers of consciousness and explaining their biological interpretations. Current biomarkers reviewed are *spatiotemporal and spectral patterns of neuronal activity* that are potential sources of information for detecting residual conscious activity in the absence of overt behavioural evidence. Next, *brain complexity-based measures* as operationalized in some clinical tools like PCI are reviewed as potential IoC. Next, we propose potential next generation biomarkers including the detection of neural activity related to intentionality and the modulation of neural activity by the presence of internal models indicative of conscious activity, for example, by detecting differential coding of illusory, multistable, and ambiguous stimuli. Further, we review the utility of immersive environments presented through VR for the delivery of complex stimuli that can be used in conjunction with readouts of neural activity as next generation tools for the detection of residual consciousness. Further, we report that VR is a promising modality for directly improving the quality of life for DoC patients, by returning a sense of bodily autonomy to them.

We particularly emphasised the need for closer collaboration between researchers doing analysis and modelling studies with clinicians to generate a virtuous cycle leading to better validation and interpretation of existing metrics and the design of better biomarkers of consciousness, built into user-friendly software, while improving data sharing and participation of researchers within clinical settings. Further, we proposed that better documentation should be prepared for families and caregivers to maximise their understanding of the condition of their loved ones, with family foundations dedicated to help translate personalised clinical findings into language that is accessible to patient entourages. The multi-disciplinary and multi-perspective approach illustrated in this paper, with the involvement of different disciplines and stakeholders, is an important premise to advance in the endeavour to eventually improve the prognosis and quality of life of patients with DoC and empower caregivers with the knowledge and capacity to most effectively participate in the clinical care of their loved ones.

Several ethical issues arise from the clinical treatment of DoC, like the need for better communication between stakeholders, including researchers, medical teams, primary caregivers, and family foundations. Further, the design of easily usable and interpretable biomarkers and communication technologies for DoC patients will be better accomplished with such communication between stakeholders. Also, it is desirable to encourage administrations, journal editors, and funding bodies to loosen the pressure on researchers to deliver biomarkers, stratification techniques, and classifiers, and to promote instead the investigation of consciousness in its multidimensionality and individual variation across subjects. One of the main risks to avoid is considering the introduction of new biomarkers naively, for instance as a "selling-point" for papers being accepted in scientific journals or for gaining points in grant proposals.

Finally, a model for operationalizing the ethical reflection, more specifically for identifying, prioritising, and advancing solving issues, is crucial. We have presented the DRM as a strategy for clearly assigning responsibilities and planning relevant actions. DRM does not aim to provide specific solutions to any particular issue, but rather to introduce an operational procedure (i.e., a framework for enabling particular decisions and actions), even if we also elaborated some recommendations on the basis of DRM as summarised in Fig. 3.

Further, we find that it is imperative to better involve the caregivers, not only for sharing information about the patient, but also *actively in all clinical stages*, from diagnosis and treatment decision-making to rehabilitation. In conclusion, indications about the ethical issues derive, in particular, from patients' and their caregivers' needs, as well as the importance of supporting medical teams with clear communication regarding novel findings emerging from scientific research and the return of clinical data collected in the process of assessing DoC patients to researchers will ameliorate the capacity of researchers to accelerate basic research and its translation to the clinic.

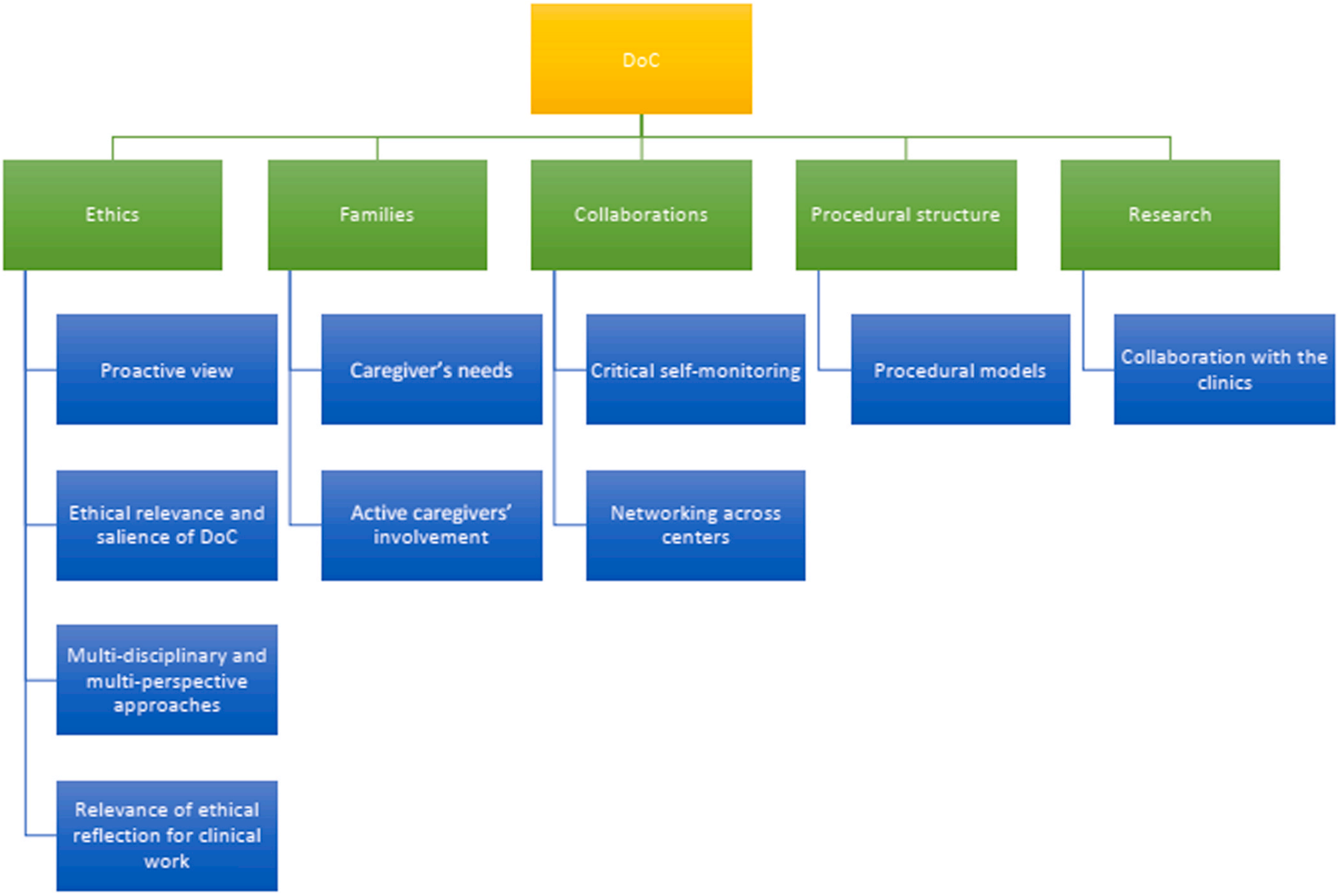

Fig. 3. Summary of recommendations reported in Supplementary Materials.

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Data availability

In adherence to principles of transparency and reproducibility, we have made the dataset, model, and Live Figure readily available to the scientific community. Researchers are encouraged to utilize these resources for validation, replication, and further exploration of the results discussed in the article.1.

Dataset: The dataset "Results for complexity measures and a read-out of the state of cortical circuits after injury" can be found at https://doi.org/10.25493/5TNA-R5P. Researchers may access and retrieve the dataset through this DOI link, which provides a permanent reference to the data.2.

Model: The computational models are accessible via https://wiki.ebrains.eu/bin/view/Collabs/showcase-3-tvb-brain-states-modelling. The model can directly be executed in the on-line EBRAINS Python Lab environment. Detailed comments and explanatory annotations are embedded within the notebook to guide users in executing the code and generating the figures as presented in this research.3.

Live Figure: To facilitate the reproduction of the figures presented herein, a Python Jupyter Notebook is provided. This notebook, containing the executable code for generating the figures, is accessible at the following location: https://wiki.ebrains.eu/bin/view/Collabs/live-paper-ethics-and-clinical-care/

When referencing the dataset, model, or code in subsequent research endeavors, we kindly request the following citation formats:•

Dataset: Nieus, T., Casarotto, S., Viganò, A., & Massimini, M. (2021). Results for complexity measures and a read-out of the state of cortical circuits after injury [Data set]. EBRAINS. https://doi.org/10.25493/5TNA-R5P•

Model: Goldman JS, Kusch L, Aquilue D, Yalçınkaya BH, Depannemaecker D, Ancourt K, Nghiem TE, Jirsa V, Destexhe A. A comprehensive neural simulation of slow-wave sleep and highly responsive wakefulness dynamics. Front Comput Neurosci. 2023 Jan 13;16:1058957. doi: 10.3389/fncom.2022.1058957. PMID: 36714530; PMCID: PMC9880280.•

Live Figure: Cite the current publication.

Please be aware that the dataset and code may undergo periodic updates or refinements. Refer to the provided links for access to the most up-to-date versions of these resources.

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