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Quarterly Medical Review - Disorders of consciousness

# The current and future contribution of neuroimaging to the understanding of disorders of consciousness

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ABSTRACT

Patients with disorders of consciousness (DoC) represent a group of severely brain-injured patients with varying capacities for consciousness in terms of both wakefulness and awareness. The current state-of-the-art for assessing these patients is through standardised behavioural examinations, but inaccuracies are commonplace. Neuroimaging and electrophysiological techniques have revealed vast insights into the relationships between neural alterations, andcognitive and behavioural features of consciousness in patients with DoC. This has led to the establishment of neuroimaging paradigms for the clinical assessment of DoC patients. Here, we review selected neuroimaging findings on the DoC population, outlining key findings of the dysfunction underlying DoC and presenting the current clinical utility of neuroimaging tools. We discuss that whilst individual brain areas play instrumental roles in generating and supporting consciousness, activation of these areas alone is not sufficient for conscious experience. Instead, for consciousness to arise, we need preserved thalamo-cortical circuits, in addition to sufficient connectivity between distinctly differentiated brain networks, underlined by connectivity both within, and between such brain networks. Finally, we present recent advances and future perspectives in computational methodologies applied to DoC, supporting the notion that progress in the science of DoC will be driven by a symbiosis of these data-driven analyses, and theory-driven research. Both perspectives will work in tandem to provide mechanistic insights contextualised within theoretical frameworks which ultimately inform the practice of clinical neurology.

## 1. Introduction

The term “consciousness” is problematic due to the several interpretations of the word; a single universally accepted definition is yet to be established. Several theory-driven conceptualisations have attempted to contextualise research findings within clinically useful dimensions. Accordingly, the current, most accepted clinical framework is based on a bi-dimensional continuum of wakefulness (i.e., physiological arousal) and awareness (i.e., the ability to consciously perceive information) [1]. The phenomenology of awareness can be split into two components: internal awareness (e.g., inner speech, stimulus-independent thoughts) and external awareness (e.g., stimulus-dependent thoughts, externally oriented attention) [2].

Severe brain damage can induce a transient state of complete absence of arousal and awareness lasting from one hour to several weeks, known as coma (Fig. 1) [1]. Subsequently, patients can recover reflexive or non-reflexive behaviours associated with various levels of consciousness and occupy one of several classified states collectively known as disorders of consciousness (DoC). The acute stage of DoC lasts up to 28 days after the injury, after this is considered the prolonged stage [3]. When patients display wakefulness (eye opening) but present reflex movements only, they suffer an unresponsive wakefulness syndrome (UWS), previously known as “vegetative state” [4]. Other patients show an increased level of awareness through reproducible non-reflex behaviours, hence evolving into a minimally conscious state (MCS) [5]. MCS can be divided into MCS+ and MCS- based on the presence or absence of a capacity for language comprehension respectively, with the former being able to follow simple commands, verbalise intelligibly or communicate intentionally [6,7]. Some patients eventually make an emergent recovery as defined by functional communication and/or object use [8], thereby classified as emergence from MCS. Locked-in syndrome is characterised by motor paralysis, in conjunction with preserved cognitive abilities [9]. Whilst it is not a DoC, it is often erroneously diagnosed as one.

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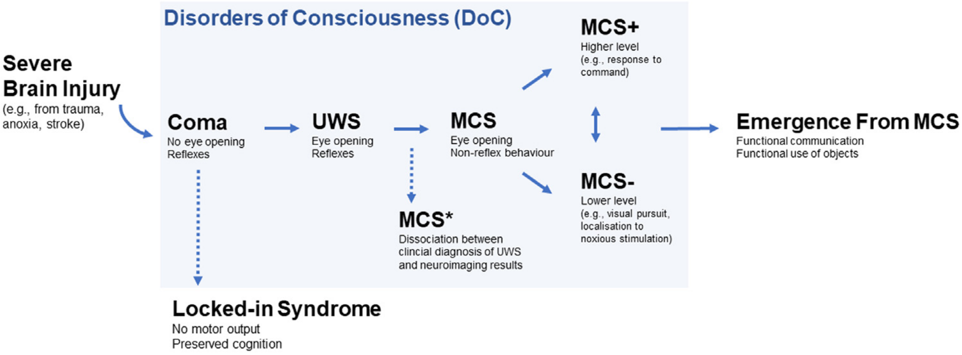

**Fig. 1.** Nosology of DoC and the associated levels of arousal and awareness. Following severe brain injury, some patients may develop a DoC, such as coma, unresponsive wakefulness syndrome (UWS) and minimally conscious state (MCS), further subcategorised into minimally conscious state plus (MCS+), and minimally conscious state minus (MCS-). The minimally conscious state star (MCS*) is characterised by a dissociation between behavioural and neuroimaging-based assessments. Locked-in syndrome and emergence from MCS are both not DoC since both states are underlined by functional communication, particularly in locked-in syndrome where cognition is entirely preserved yet apart from eye movements and some finger movements, all other motor output is eradicated.

Ethical considerations are prominent when distinguishing between conscious and unconscious patients. The clinical diagnosis influences both treatment and potential end-of-life decisions. Hence, it is of paramount importance to study DoC and improve diagnostic tools. Unfortunately, diagnosis based on clinical expertise without the use of standardised behavioural tests has been associated with up to a 40% misdiagnosis rate [10–12]. The state-of-the-art clinical diagnostic scale is the Coma Recovery Scale-Revised (CRS-R), shown in a comparison study to be the most reliable behavioural scale in DoC diagnosis [13]. Despite its proven utility, inconsistent scores due to circadian-driven fluctuations in arousal can contribute to misdiagnosis [14,15]. This emphasises the importance of repeated assessments to obtain the most accurate classification, yet the long duration of administration limits its clinical practicality [16]. Recently a shorter, simplified version of the CRS-R has been developed, the Simplified Evaluation of CONsciousness Disorders (SECONDs) [17,18]. This tool has the same sensitivity and specificity as the CRS-R and takes less than 10 min to perform.

Detecting consciousness is not always possible through behavioural measures alone; there is a developing clinical understanding concerning the presence of consciousness in patients who appear unresponsive at the bedside, yet have partially preserved consciousness as measured through neuroimaging assessment [19]. For instance, a cross-sectional study on 135 brain-injured patients showed that more than half of the patients behaviourally considered as occupying an UWS presented brain function more compatible with MCS, thus were reconsidered as MCS* [20]. Furthermore, some UWS or MCS patients can present cortical activations to commands analogous to the ones observed in healthy participants during active tasks, these patients are considered as possessing cognitive motor dissociation (CMD) [21], also known as covert cognition [19], and functional locked-in syndrome [7]. Additional terms have been proposed including higher-order cortex motor dissociation [22] (i.e., no evidence of language comprehension, but relatively preserved brain responses to passive stimulation), and the cortically mediated state [23] (i.e., a proposed MCS replacement which classifies based on weighting the evidence form functional brain imaging and behavioural assessment). Importantly MCS* encompasses all these classifications where there is a dissociation between behavioural diagnosis and neuroimaging results. MCS* patients also possess a greater likelihood of better functional recovery [11,24]. This makes identifying those patients that possess less apparent, residual consciousness paramount to ensure the most appropriate patient care and pain management. Neuroimaging techniques represent tools to investigate the activity in the brain underlying such dysfunction. They provide diagnostic and prognostic value, in addition to mechanistic insights into the generation of consciousness. Naturally, both European Academy of Neurology (EAN) and the American Academy of Neurology (AAN) guidelines recently acknowledged the power of neuroimaging, recommending for their use in diagnosis of DoC [25–27].

The heterogeneity of alterations of structure and function in DoC patients present a unique population to investigate the contribution of specific regions or networks in supporting human consciousness. Research to this end, compares structural (e.g., lesion) or functional (e.g., network connectivity) features between DoC patients and controls or across DoC patients with increasing severity, as indicated by standardised behavioural assessments. In this review, we will outline key neuroimaging findings that contribute to the understanding of the neural dysfunction underlying DoC and detail the current utility of neuroimaging and neurophysiological diagnostic techniques. Furthermore, we will outline recent advances in data-driven analyses and computational modelling-based simulations that show great potential in disseminating the mechanisms of consciousness, in addition to providing potentially valuable clinical neurology applications. We support the recent proposal outlined in a white paper as a part of the *Curing Coma Campaign* [28], that the advancement of the scientific understanding of DoC will be optimised by unifying data-driven and theory-driven research. This will allow the emergence of an integrated vantage point of knowledge that will facilitate a frictionless transition towards clinical applications, hence improving the lives of patients.

For a diagram of the clinical entities of DoC see Fig. 1. A summary of the main techniques and findings discussed here are presented in Fig. 2. Fig. 3 displays diagnostic differences through different modalities between UWS and MCS patients.

## 2. Brain structure

The most crucial technique for the study of the brain structure is magnetic resonance imaging (MRI). MRI is based on the detection of the magnetic properties of water. In structural MRI, the signal is derived from the differential water concertation within different brain tissues, producing high-resolution characterisations of grey and white matter density. Diffusion tensor imaging (DTI) is an MRI-based structural technique that allows the estimation of white matter connectivity via a three-dimensional visualisation of the diffusion of water molecules along white matter tracts.

Regarding the brain structures supporting consciousness, subcortical and brainstem regions contribute mostly to the maintenance of wakefulness. Particularly implicated are the structures of the ascending reticular arousal nuclei, a collection of brainstem (mesopontine tegmentum) and subcortical (hypothalamus, basal forebrain, thalamus) nuclei which are interconnected with one another and the cerebral cortex [29]. The role of the tegmental arousal nuclei in

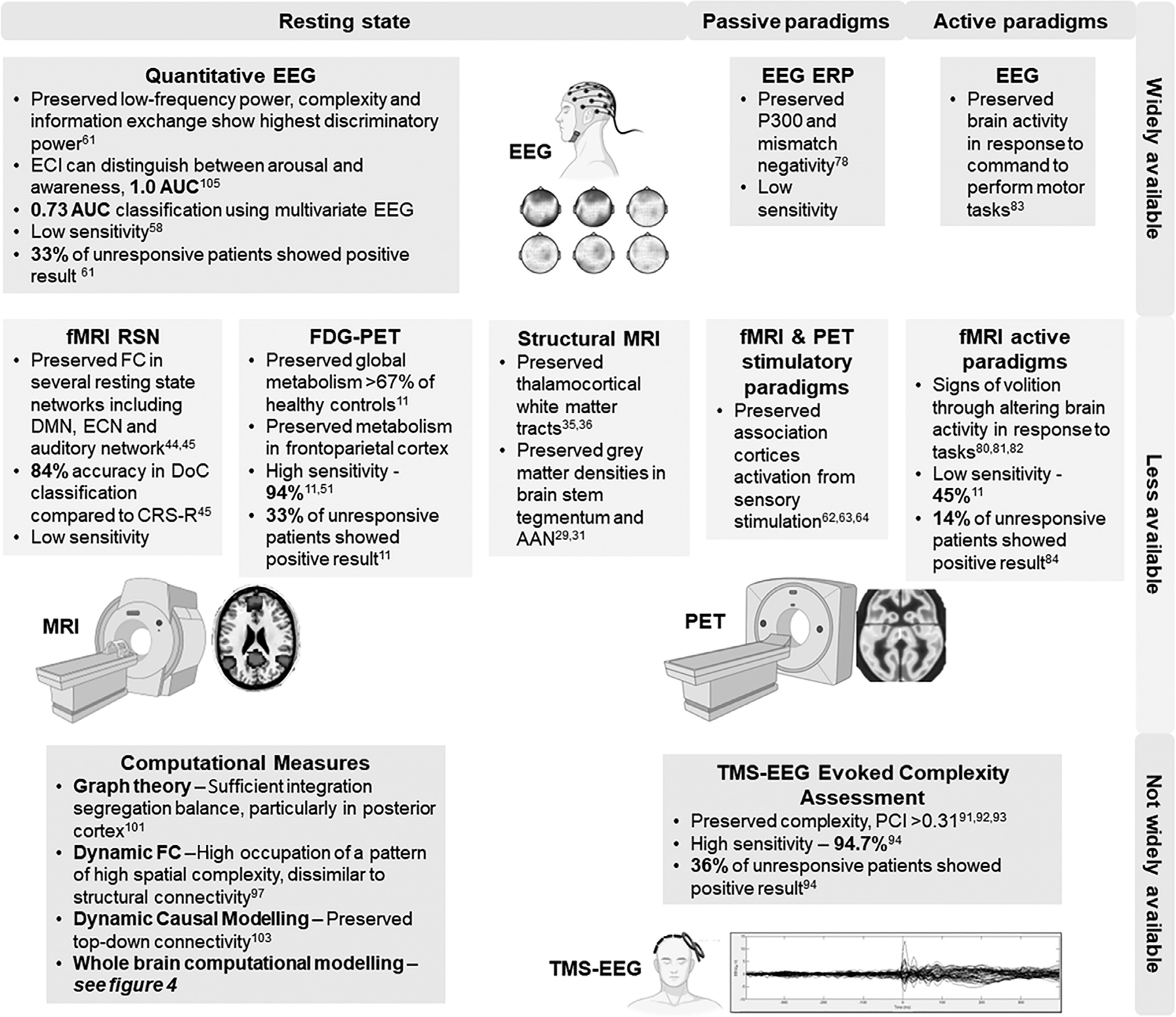

**Fig. 2.** The main neuroimaging modalities and results for the diagnosis of disorders of consciousness (DoC) ordered by resting state, passive paradigms, and active paradigms (left to right) and their availabilities in clinical practise (top to bottom). Top image represents firstly a schematic of an EEG cap and below are local-global EEG responses. Left images represent an MRI scanner and a typical BOLD response. Right images represent a PET scanner and an image of global metabolism. Bottom images represent a TMS coil and typical EEG recording following a perturbation. Exemplar neuroimaging responses are presented for healthy volunteers. Abbreviations: ECI: explainable consciousness indicator FC: functional connectivity, fMRI: functional magnetic resonance, FDG-PET: fluorodeoxyglucose positron emission tomography, EEG: electroencephalography, TMS: transcranial magnetic stimulation, AUC: area under the curve, PCI: perturbational complexity index, RSN: resting state networks, ERP: event-related potential, DMN: default mode network, ECN: executive control network, AAN: ascending arousal network.

maintaining wakefulness was initially exhibited by the seminal experiments in cats showing how the stimulation of these brainstem nuclei reliably eradicate arousal [30]. Subsequently, human lesion mapping studies have shown that lesions that extend to areas of the brainstem tegmentum are associated with decreased consciousness [29,31].

The thalamus is the major sensory relay station of the brain, receiving cortical inputs and connecting reciprocally with the overlying cortex. The thalamus plays a central role in the mesocircuit hypothesis [32]. This proposes that sensory information received by the thalamus drives excitation in both the striatum directly, and in the frontal cortex, which then drives striatal activity. Under optimal conditions the caudate nucleus of the dorsal striatum drives thalamic excitation, yet without the excitatory drive from the striatum, the thalamus becomes inhibited, this has been proposed to be a key circuit underlying the dysfunction in DoC [32]. Specific degeneration of the nuclei of the central thalamus has been shown to be preferentially damaged following severe brain injury with the degree of damage being associated with behavioural outcome [33,34]. Also, UWS and MCS patients can be distinguished based on integrity of thalamic nuclei white matter fibres revealed via DTI mean diffusivity [35]. A recent DTI tractography analysis showed reductions in thalamic projections reaching frontal, parietal, and sensorimotor cortices in UWS compared with MCS patients [36]. This study also showed that MCS- patients exhibited significantly less thalamo–premotor and thalamo–temporal connectivity than MCS+ patients, likely in part, underlying the language preservation in MCS+. Together, these findings highlight the role of thalamo–cortical connections in patients' behavioural capabilities and level of consciousness.

Brain structural differences between patient populations can also be assessed through brain volumetric analysis, whereby voxel-based (three-dimensional pixel) or region-wise quantification of brain volume are examined. This technique has allowed the identification of damage to the ventromedial prefrontal cortex and posterior cingulate cortex when comparing UWS and MCS [37]. However, issues with registration and segmentation can be

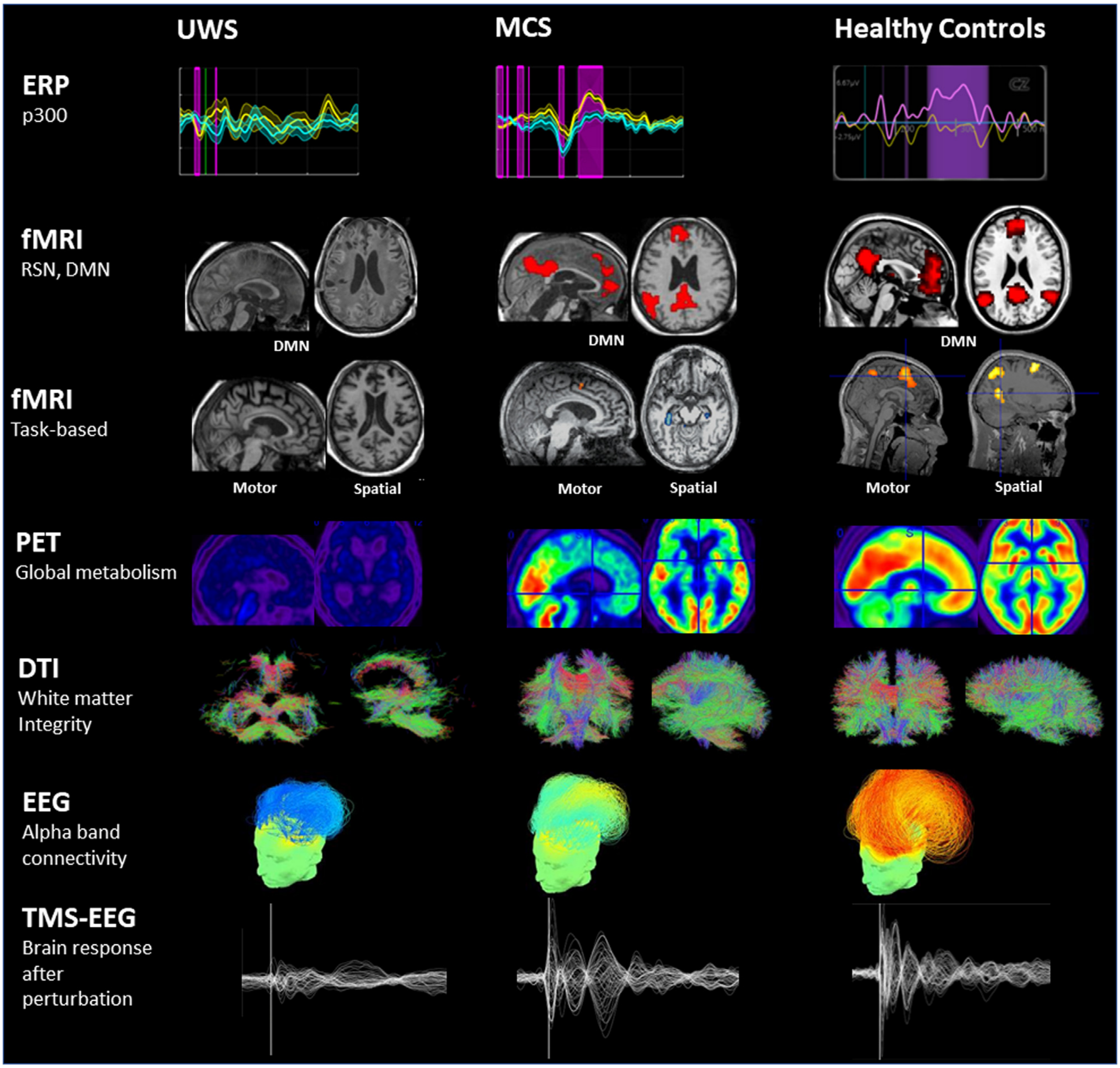

**Fig. 3.** Typical brain imaging and neurophysiological results in UWS, MCS and healthy controls. Results presented are from different patients. The P300 ERP is from an oddball paradigm. The MCS and healthy control patient examples show a difference between the amplitude of the response of the familiar stimulus (cyan) and the deviant (yellow), whilst the UWS patient example shows no difference, thus indicating a lack of conscious processing of the deviant. fMRI resting state network activity in the default mode network (DMN) is partly preserved in MCS compared to healthy controls, yet absent in the UWS example. Imagination, task-based fMRI paradigms in healthy controls for the motor task (left) showing activation in the supplementary motor area (left blue crosshair), and spatial navigation task (right) showing hippocampal and entorhinal cortex activation (right blue crosshair). Task-based paradigms in MCS patients show similar responses to healthy controls but responses in UWS patients show no activations. Global PET metabolism reductions in MCS and UWS compared to healthy controls, particularly in frontoparietal regions. DTI images show long-distance white matter fibre pathways. The control image shows intact complex connectivity of white matter fibres across cortical and subcortical areas. The MCS patient DTI image shows diffuse damage to peripheral fibres at frontal and parietal regions. The UWS patient DTI image shows major damage to cortical and subcortical areas (note that the image is incomplete at the frontal and peripheral level since the extensive damage meant segmentation difficulties were encountered). EEG alpha and delta band connectivity (taller connections with warmer colours represent stronger connectivity) from 256 electrodes recorded, showing the lowest connectivity in UWS and highest in MCS. The delta band connectivity images were adapted, with permission from [20]. TMS-EEG pattern in healthy controls shows a spatially complex pattern following the TMS perturbation (vertical line). The EEG responses following TMS of MCS patients is similar to healthy controls although it takes less time to return to baseline, while the response becomes stereotypical and even shorter in UWS patients. The TMS-EEG images were adapted, with permission from [112]. The task-based response in the MCS patient was taken with permission from [80]. All other images are original, unpublished materials.

encountered due to the heterogeneity of lesions associated with DoC. A 2018 study circumvented these difficulties by limiting analysis to regions of interest (ROI) defined in the single-subject space. Leveraging a data-driven analysis of atrophy from these diverse ROI achieved a classification rate of about 80% for distinguishing between UWS and MCS patients contrasted to the CRS-R based diagnosis, with the thalamus and caudate showing high relevance for classification [38].

## 3. Brain function

The assessment of brain function can be investigated through several means. Functional MRI (fMRI) derives its signal from the magnetic properties of the blood as a proxy for neural activity by calculating the blood-oxygen-level dependent (BOLD) signal time-series. It has high spatial resolution but low temporal resolution. Functional measures can also be obtained through positron emission tomography (PET). Here, an intravenous injection of a radioactive tracer allows a quantification of the cellular functions. A glucose tracer can facilitate the observation of brain metabolism during the uptake period, prior to the scan. Whereas the injection of a radioactive oxygen ligand is performed inside the scanner due to the short half-life, this allows the active visualisation of blood flow during the scan. Electroencephalography (EEG) is a non-invasive tool that measures the brain's electrical activity allowing the collection of fine temporal details of neural processing. These techniques can be applied in different types of protocols such as resting state assessments (no action required), passive paradigms (no action required but presence of external stimuli), and active tasks (participation required).

## 3.1. Resting state

There are several modalities that can be utilised in resting state conditions, during which the subject is not performing any task and the spontaneous activity of the brain is quantified. Resting state paradigms are easy to perform, making them ideal for clinical use.

### 3.1.1. fMRI

Resting state networks (RSNs) constitute of several brain regions whose activities are related to one another through low frequency fluctuations in the BOLD fMRI signal. This can be assessed through calculating the correlation between brain regions, this is known as functional connectivity (FC). Several RSNs are clinically relevant to consciousness [39]. The two most important functional networks for awareness are situated within the frontoparietal cortex. The first, showing increased activity during tasks [40], is the external awareness or executive control network (ECN), sub-served primarily by the dorsolateral prefrontal cortex bilaterally [40]. The second is the internal awareness network or the default mode network (DMN), which is distributed across the precuneus and posterior parietal cortex, inferior parietal, and medial prefrontal cortex. The DMN is active during task-free conditions and has been associated with self-referential thoughts and mind wandering [41,42]. Patients with DoC consistently display lower connectivity within these two networks compared to healthy controls [43]. Moreover, the baseline FC within the DMN can index the level of consciousness and distinguish between MCS and UWS patients with an accuracy of 84% [44,45]. Interestingly, all canonical RSNs (e.g., DMN, salience network, visual network, sensorimotor networks) can differentiate between UWS and MCS patients at the group level at a rate of at least 80%; the auditory cortex has the highest predictive power (91%) [45].

One important characteristic of the activity of the DMN and ECN is that they are anticorrelated and in healthy subjects they switch dominance every 20 s at rest [46]. In a study assessing resting state network FC in a cohort of 58 patients with severe brain injuries, anticorrelations between the DMN and the ECN were found in the 13 patients who had emerged from MCS, but not in UWS nor MCS patients [47]. Alterations in the anticorrelations between RSNs can be informative for recovery of consciousness following severe brain injury. For instance, separate investigations have confirmed that between network correlations between the DMN and other RSNs were absent in patients with acute DoC, whilst partially preserved in those that had recovered to a MCS [48,49].

### 3.1.2. Positron emission tomography

Fluorodeoxyglucose-PET (FDG-PET) techniques measure brain metabolism. Whole-brain energy metabolism correlates with level of consciousness, with a threshold of 42% that could represent the minimal energetic requirement for the presence of consciousness [50]. On average, global cerebral metabolic rate was found to be 38% and 56% of the normal rate in UWS and MCS patients respectively. Regions of the frontoparietal cortex show the largest difference in metabolic levels between UWS and MCS patients, at 42% and 60% of the normal level respectively [51]. Also, in this study, those with a global metabolic level of at least 45% were more likely to transition from UWS to MCS, compared with patients with global brain metabolism below this level. Furthermore, another study showed that 33% of CRS-R assigned UWS patients possessed frontoparietal metabolic activity consistent with MCS [11], and 69% of these patients subsequently recovered at the bedside. Hence, despite its limited accessibility, FDG-PET based assessment of consciousness is recognised as a powerful clinical diagnostic tool with the recent EAN and AAN guidelines affirming the high sensitivity (93%) and specificity of FDG-PET in differentiating UWS from MCS [26,27].

FDG-PET data also offer the possibility of regional analyses to investigate local metabolism in key brain areas. A recent study using a seed-based approach showed higher metabolic rates amongst MCS + compared to MCS- patients in the left middle temporal cortex, a key region for semantic language processing [52]. Metabolic decreases in the thalamus are also apparent in DoC patients [53], in addition to decreased metabolism in the DMN and ECN in UWS patients, whilst the ECN is relatively preserved in MCS patients (the DMN is primarily affected) [54].

### 3.1.3. Quantitative EEG

Quantitative EEG methods of detecting consciousness in DoC patients are ideal for clinical use due to the relative portability of EEG systems, and the ability to be rapidly employed in clinical practice. The quantitative analysis of the resting state EEG waveforms into neural oscillations at specific frequencies [delta (1–4 Hz lowest) to gamma (>30 Hz, highest)] is referred to as power spectrum analysis. Slow EEG oscillations occur more frequently in DoC patients. UWS patients possess decreased alpha power and increased delta power compared with MCS patients [55,56]. Specifically, the number of alpha rhythm spectral patterns has been shown to be reduced to 37% for MCS and 26% for UWS patients compared to healthy controls [57]. A 2019 study, using a network based EEG analysis, showed increased measures of local efficiency and high clustering in UWS patients as compared to MCS patients, consistent with more segregated networks which lack functional integration [57]. Recently, a data-driven study utilised machine-learning on extracted EEG features such as spectral density, permutation entropy and power spectral density from 268 DoC patients to robustly classify between UWS and MCS patients [58]. Another useful approach utilising EEG is the calculation of entropy or complexity of the signals. Generally, more entropic brain activity represents more complex stochastic relationships between the EEG signals, thus higher active information processing. A study examining the complexity of EEG signals over 3 electrodes on the forehead showed that MCS patients possessed higher resting state entropy compared to UWS patients in the acute stages [59]. Additionally, a recent randomised control trial of frontoparietal transcranial direct current stimulation (tDCS) in patients with severe brain injury, showed that tDCS treatment increased complexity of low frequency EEG bands, and that lower baseline complexity in those bands was associated with a greater CRS-R score improvement after treatment [60]. From the multitude of quantitative measures available, low-frequency power, EEG complexity, and information exchange, have been shown to have the highest discriminatory capacity for diagnosis, with a combination of these measures resulting in 33% of UWS patients being reclassified to MCS, with greater recovery in those classified as MCS via EEG (22% vs. 49%) [61].

## 3.2. Stimulation, task-based and event-related measures

### 3.2.1. Passive stimulation paradigms

Passive stimulation paradigms refer to the recording of brain activity while the patient is presented with sensory (e.g., verbal, auditory, noxious) stimulations, no action is required by the patient. In healthy controls, sensory processing engages the activation of primary sensory areas and high-order association cortices [62], although, UWS patients lack this accessory recruitment and only display activation of the primary cortices [63,64]. Similarly, early PET studies using 15 O-radiolabelled water showed that UWS patients typically activate only primary auditory cortices in response to simple auditory stimulations [62,65]. On the other hand, MCS patients displayed activation of higher-order areas including regions of the frontoparietal cortices [62]. More recent findings report that such extended patterns of activity are sometimes also present in UWS patients, albeit with a lower likelihood of appearance, hence highlighting the potential issues related to misdiagnoses present in a number of unresponsive patients [66]. These findings have also been extended to several other modalities including noxious and auditory stimulations. UWS patients with higher-order activations in response to an auditory stimulus, similar to the MCS group, were shown to have better functional outcome, later transitioning into MCS [67]. Interestingly, deactivation of medial regions of the DMN during a passive listening task is reduced in MCS patients and virtually absent in UWS patients. This is supported by a study showing that almost all DoC patients possessing a deactivation pattern in response to the stimulus also displayed activation in the left frontal regions during speech exposure [68]. This suggests that deactivation of the DMN during external stimuli reflects a shift in the attentional direction from introspective processes to external awareness. Similar findings have resulted from studies in which patients' favourite music is played with ECN FC being dependent on the subject's level of consciousness [69]. Passive movie watching tasks have also been used to detect consciousness [70]. Activity in frontal and parietal cortices representing executive demands during video watching were identified in a patient that had been unresponsive for 16 years.

EEG event-related potentials (ERP) measure the neural activity over specific electrodes in response to the presentation of a stimulus, e.g., a sound or an image. Several ERP components can be identified with varying valence polarity (positive – P, or negative – N) and latency time (milliseconds). The amplitude and latency of passive ERPs have been associated with symptom severity and outcome in UWS patients [71]. Notably, an early study by Kotchoubey et al. investigating a number of passive ERP components within 98 DoC patients showed differential responses in the N100, being delayed only in MCS patients, whilst it was preserved in UWS patients [72], although there was significant intragroup variability. That being said, the efficacy of short latency ERP components are questionable as a 2013 study showed delays in the N100 in UWS compared to MCS [73]. Oddball paradigms are characterised by a sequence of given stimuli interleaved randomly to deviant stimuli. In healthy subjects, these evoke a mismatch negativity in the processing of the repetitive stimuli compared to the deviant. The P300 is an ERP component that occurs around 300 ms after a deviant stimulus in an oddball paradigm. The P300 can be divided into an early P300a and P300b. The P300a is measured from frontal brain regions and is unrelated to consciousness [74], it has shown to be present in UWS and MCS patients [75,76]. Whilst the P300b is located in parietal brain regions and is related to cognitive processing and attention [77]. Yet, interestingly, the latency of the P300a has been shown to be modulated only in MCS patients following oddball paradigms comprising of differing levels of complexity (sine tones, subjects own name) which supports its utility in detecting consciousness [78]. Vibrotactile and auditory stimulations have been shown to evoke differential P300b responses within individual DoC patients [76]. This supports the use of multimodal paradigms to capture more information about the degree of residual consciousness and improve the overall diagnostic accuracy. Another promising, more recently developed ERP measure is generated after endogenous stimulation, namely the heartbeat-evoked response, which measures the brain's response to heartbeats. This was found to correlate better with FDG-PET-based diagnosis than behavioural diagnosis, supporting a potential role to probe covert consciousness [79].

### 3.2.2. *Active task-based paradigms*

In contrast to passive paradigms discussed so far, task-based paradigms can provide additional information towards the assessment of consciousness for those who are unresponsive at the bedside. Such assessments represent a higher-level of detection of consciousness since success indicates that the patient understood the request before generating a response. In task-based "mental imagery" paradigms, patients are for example, instructed to engage in a motor task ("imagine playing tennis") or a spatial navigation task ("imagine walking through the rooms of your house"). In a cohort of 54 subjects with chronic DoC, five patients were able to elicit reproducible and specific brain activation patterns comparable to healthy participants responses [80,81]. These brain responses to active paradigms have also been shown to predict recovery in patients with DoC [82], highlighting the prognostic benefit of using task-based fMRI paradigms in the clinic. Incredibly, one patient achieved communication with the experimenter by engaging in motor and spatial mental imagery paradigms to represent yes/no responses to questions respectively [80].

ERP paradigms can also be used to measure the brain's responses to commands. Often establishing command following to one or multiple commands, and hence detect covert consciousness, or even allowing communication. A study utilising a supervised machine learning algorithm to analyse the EEG responses following commands to perform motor tasks showed that 15% of acute patients could modulate their brain activity. This was linked to better functional outcomes for these patients at 12 months [83]. The presence of such measures is a reliable sign of consciousness as they act as a neuroimaging-based behavioural surrogate. However, the absence of a positive result does not necessarily indicate unconsciousness since such paradigms require that the patient has intact linguistic abilities, short-term memory, and executive functions for the duration of the task. A metanalysis found that only 14% of behaviourally unresponsive patients showed a positive response to task-based paradigms [84].

## 4. Structure & function relationship

### 4.1. *Multimodal studies*

Multimodal investigations can reveal information linking biomarkers from different modalities with a view towards providing a more unified understanding of the features of DoC. A multimodal study based on 56 patients with severe brain injury highlighted the importance of both functional and structural thalamic-posterior cortex connections. The authors showed that in addition to the reduced FC between the posterior cingulate/precuneus and the thalamus, the structural integrity of this pathway and others in the posterior DMN were correlated with the patients behavioural signs of awareness [85]. Further research shedding light on the relationships linking structural and functional diagnostic biomarkers can be seen in a study reporting significant anticorrelations between dorsal brainstem and clusters of cortical lesions, which were shown to be an independent predictor of loss of consciousness [86]. Following this, a cluster in the rostral brainstem was shown to be functionally connected to the ventral anterior insula and pregenual anterior cingulate cortex in healthy subjects; FC between these regions was significantly decreased in DoC patients [87]. These studies evidence the importance of the brainstem and its possible cortical functional connections that are important to the maintenance of wakefulness.

Multimodal paradigms using complementary data to overcome the shortcomings of individual modalities could also improve our ability to detect consciousness. For example, a 2020 multimodal study supported the establishment of auditory localisation as a clinically useful sign of consciousness. Authors showed that UWS patients who localised auditory stimuli had better neuroimaging profiles with increased fMRI FC between frontoparietal and visual areas, higher alpha band EEG connectivity, and higher levels of brain metabolism than those who could not localise auditory stimuli [88].

### 4.2. TMS-EEG

Leading theories of consciousness propose that the integration and differentiation of information in the brain permit complex neural activity patterns and underwrite the emergence of consciousness [89,90]. The entropic organisation and integrative capacity of brain networks can also be assessed through combining EEG with transcranial magnetic stimulation (TMS). By coupling these techniques, the brain's response to a magnetic stimulation can be quantified using effective connectivity, giving a measure known as the Perturbational Complexity Index (PCI) which pertains to the integrative capacity of the brain networks [91]. This measure has been shown to successfully distinguish between conscious and unconscious patients, and distinguish between states of consciousness altered by sleep and anaesthesia [92,93]. A 2016 study of 81 DoC patients yielded a 94.7% successful classification rate for MCS patients based on the PCI [94]. Interestingly, UWS patients with high PCI had higher chances of recovery, suggesting that they were already conscious at the time of examination. A recent multimodal study showed that PCI was correlated with the structural integrity of the globus pallidus [95], a striatal structure that has been previously implicated in arousal [96] and is highly connected to the thalamocortical system. Interestingly, no association between cortical thickness or thalamic integrity and PCI was found. Despite the high sensitivity of TMS-EEG techniques, it remains relatively unavailable in the clinic. Initiatives such as the Human Brain Project (HBP) innovation award exemplify the concerted efforts that exist to incentivise innovations to increase the accessibility of PCI by calculating it from low density EEG.

### 4.3. Computational approaches

Recent advances have reconsidered FC as possessing temporally dynamic properties that have direct relevance on function. These studies leverage novel analyses to reveal insights into the brain networks underlying DoC that would be hidden using basic FC analyses. A recent, seminal study in this domain used an unsupervised machine-learning algorithm to separate the time-averaged FC into clusters based on statistical intricacies within the BOLD signal [97]. This identified separate connectivity patters of temporal "sub-states" of activity. Interestingly, the FC cluster most resembling the structural connectivity, characterised by low spatial complexity, appeared more commonly in UWS patients than in both MCS patients and controls, in whom it appeared the least. This demonstrates that the neural activity underlying consciousness is underwritten by inflexible activity that follows structural priors. Whereas the pattern with a high spatial complexity, representing preserved long-range cortical connections possessed an antithetical probability of appearance, having the highest probability in healthy controls, then MCS patients, then UWS patients. The probability of the highly spatial complexity patterns appearing in DoC patients were not zero. This suggests that for brief periods of time, some DoC patients occupy FC patterns that resemble healthy controls. Relatedly, the number of state transitions between these FC sub-states has been shown to be a reasonably accurate metric to classify DoC patients [98].

Interactions between brain regions can also be considered to form networks via the computational framework of graph theory. Here, the networks underpinning pathological brain dysfunction can be investigated at a number of levels: from the connective properties of individual nodes, to the efficiency of information transfer in a small word organisation [99]. One study utilising graph theory revealed alterations in the thalamus of UWS patients but not in MCS patients. The network properties of the thalamus did not, however, show significant differences between UWS and MCS patients [100]. In a similar vein, another study identified specific patterns of dynamic functional connectivity that exhibited reduced functional diversity and compromised informational capacity associated with DoC [101]. This study also showed that posterior regions of DMN in DoC patients showed reduction in integration with the rest of the brain, supporting ideas establishing the posterior cortex regions as a critical locus of consciousness responsible for the integration widespread thalamocortical activity [102].

Measures of effective connectivity using Dynamic Causal Modelling (DCM), a hypothesis driven method, are used to identify directionality and strength of interaction in a priori defined limited set of brain regions. An early study using DCM on ERP data showed that UWS patients possessed an impairment of backward, top-down connectivity from the frontal to temporal regions compared to MCS patients [103]. Another study using DCM proposed a potential mechanism for the dissociation between motor and cognitive capacities apparent in covert consciousness (CMD, MCS*). They showed that a UWS patient with evidence of covert awareness from mental imagery tasks had an increase in the excitatory coupling between the thalamus and primary motor cortex (responsible for motor execution), whilst the connections between the supplementary motor cortex and thalamus involved in motor planning remained intact. This was supported by structural damage in the white matter fibres connecting the thalamus and the primary motor cortex bilaterally [104].

Many more of these complex, computationally driven measures will emerge. Yet, the current power of these measures is limited to research settings in which they probe for mechanistic insights of DoC. The prospect of these measures being implemented as a clinical standard is some time away, mainly due to inaccessibility of physical and intellectual resources, in addition to poor data quality. Nevertheless, future empirical findings that contribute to a better understanding of the clinical manifestations of DoC will be driven by a symbiosis of such data-driven methodological innovations, and theory-driven contextualisation. Both perspectives must work in tandem using unified terminology that can be readily compared to make the most efficient advances in the science of DoC and successful translation to the clinic. A recent 2022 study exemplifies this symbiosis through the development of a novel measure known as the "explainable consciousness indicator" (ECI) [105]. Through considering the bi-dimensional continuum of consciousness, the PCI reliably distinguishes between aware and unaware patients, but has no discriminatory capacity in arousal, therefore would be unable to distinguish between REM sleep and normal wakefulness. The ECI addresses these shortcomings, using deep layered machine learning algorithms applied to TMS-EEG data but also the EEG alone to disentangle between states of differential wakefulness and arousal. This could greatly expand accessibility if such valuable diagnostic information can be retrieved from EEG data alone, thus yielding exciting clinical neurology-based applications.

### 4.4. Whole brain computational models

Whole Brain computational Models (WBM) represent a set of powerful techniques that enable the investigation of the brain dynamics underlying unconsciousness. WBM also possess great clinical potential to support individualised diagnosis, prognosis, and the assessment of treatment efficacy. WBM involve the simulation of brain imaging data from semi-empirical models based on a mathematical model of the local neural dynamics coupled by the empirical structural connectivity. The definition of the local dynamics can originate from a number of theoretical principles such a Hopf oscillators, whereby each brain area is simulated by a populational firing rate that reflects a Hopf bifurcation, or a dynamic mean-field model obtained by mean field reduction of integrate and fire spiking neurons with excitatory and inhibitory populations [106]. The

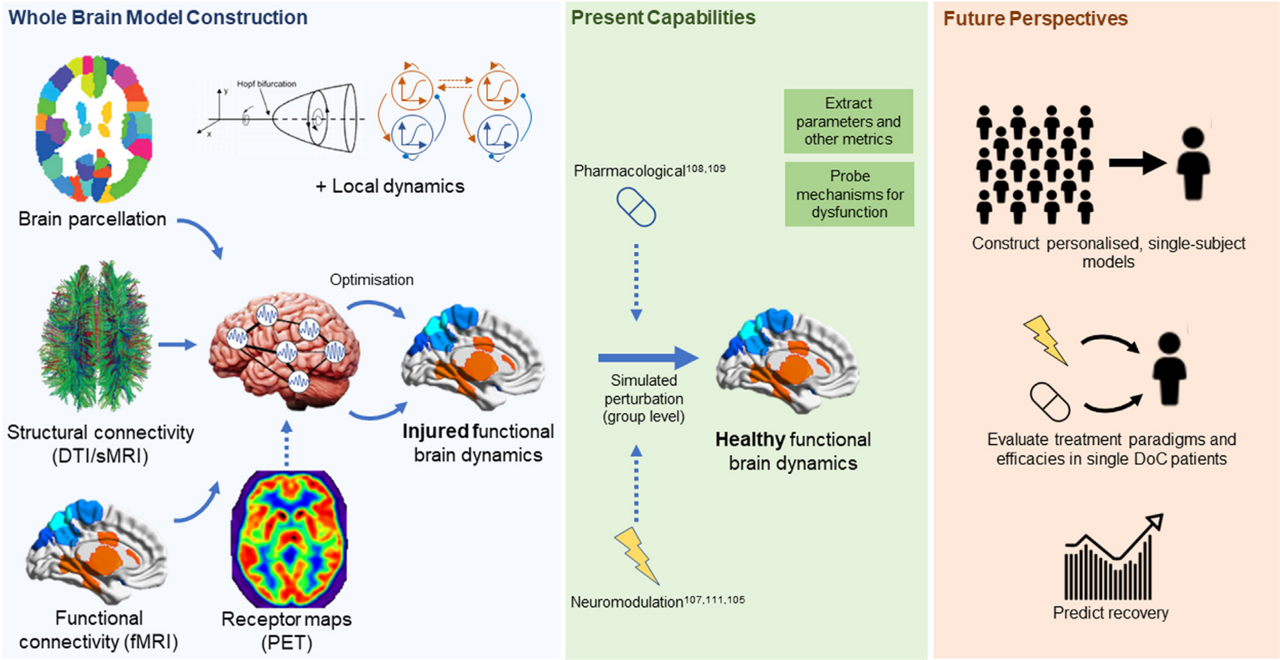

**Fig. 4.** Overview of computational whole brain modelling, its current uses, and future perspectives. **Left**, the brain is parcellated into a number of nodes, which are subsequently connected by the empirical structural connectivity from DTI. The empirical functional connectivity from resting state fMRI is used to optimise the model. A definition of the local dynamics can take several forms including supercritical Hopf bifurcations (left) or dynamic mean field (right). Neurotransmitter information from PET can also be added to the model, these can then be utilised in dynamic mean field models to simulate pharmacological perturbations. Lastly the model parameters are optimised to achieve the best fit between simulated and empirical dynamics. **Centre**, capabilities allow the simulation of pharmacological administration on healthy subjects, and the simulation of neuromodulatory-like perturbations on group-level patient models. The extracted parameters and other modelling metrics can be used to investigate the mechanisms of DoC. **Right,** in the future single subject models could be constructed on which different treatments could be simulated. Following this, it would be possible to calculate and compare treatment efficacy across individual patients.

interactions between such local dynamics and structural connectivity can simulate the spatiotemporal characteristics of empirical functional data in a number of modalities including fMRI and EEG. Importantly, the parameters of the model are optimised to minimise the distance between the simulated data and empirical data to obtain the most biologically realistic simulations. WBM can also be perturbed in several ways reflecting electrical stimulation or pharmacological application. In this way, simulated perturbations can be used to assess the efficacy of different treatments in patients based on the resultant global dynamics (following a simulated treatment perturbation) becoming more similar to dynamics of healthy brains, assessed through the characterisation of modelling-based biomarkers. A recent study exploring the infancy of these possibilities employed a data-driven approach in conjunction with simulated localised external perturbations of varying amplitude and frequencies reflecting a transcranial alternating current stimulation (tACS) within WBM [107]. They investigated likelihood of observing transitions between brain states as a result of these simulated perturbations, producing a map characterising the states of consciousness based on the dimensions of stability and level. The findings evidenced the relative stability of both MCS and UWS compared to propofol sedation and stages of sleep. All the simulated stimulations within UWS and MCS were unable to produce global dynamics resembling wakefulness, unlike sleep which showed potential of such a state transition. This presents a bleak initial prediction for treatments, although as WBM further develop, more accurate models will be created and other studies using other types of modelled perturbations might yield more promising results with a view towards transitioning DoC towards healthy waking consciousness. Considering the potential of modelling pharmacological perturbations, a 2018 study by Deco et al. [108] used the PET derived receptor density maps of serotonin-2A receptors input within WBM to simulate the effects of a pharmacological perturbation of lysergic acid diethylamide (LSD) on the global dynamics of brains of healthy subjects. The study showed that the modulation of global brain dynamics depends on the specific localised distribution of serotonin receptors and revealed non-linear interactions that drive the relationships between the anatomical connectivity and receptor modulation. The use of receptor density maps has also been applied to work relevant to DoC. In a study published in 2022, Luppi et al. [109], investigated the common possible mechanisms for loss of consciousness, the authors created two models to simulate propofol sedation and DoC by using gamma-aminobutyric acid (GABA) receptor density maps and the averaged injured structural connectome respectively. They reported that the dynamics simulated by these two models, generalised across each other, meaning that the model designed to simulate propofol sedation could accurately simulate DoC and vice versa. Integrating neuromodulatory actions into WBM could open exciting possibilities in the future for the evaluation of pharmacological treatments in DoC and other neurological disorders.

Unlike neuroimaging, computational models are ripe for the testing of mechanistic hypothesis since the model parameters are fully accessible to the researchers. In this way, using WBM could be viewed as having access to a digital scalpel, providing ethical ways of perturbing a system that would be experimentally challenging [110]. Therefore, WBM facilitate the investigation of the interplay between structural, functional, and dynamical brain properties via alterations of the model parameters to assess specific predictions of the mechanistic causes underlying the observed empirical spatiotemporal dynamics. A study using WBM constructed from local activity defined by Hopf bifurcations showed that the brain dynamics of DoC patients present more homogeneous dynamical behaviour across brain regions, especially in structural hubs which were more stable in conscious states compared to low conscious states [111]. This implicates the stability of hub regions in supporting the diverse patterns of local dynamics that underlie normal waking consciousness via a stability-regulated “anchoring” of the structural constraints [111].

The future possibilities for employing WBM are vast (Fig. 4). In addition to adding information about receptor densities, the biological realism of the model could be further improved through adding information based on local metabolism derived form FDG-PET values. Also, relating to personalised medicine, such models could be used to design and test different treatment options for individual patients. Utilising individual subject empirical data, models could be generated and subsequently tested to estimate the efficacy of different treatment options in addition to other metrics such as likelihood of treatment success or to locate optimal brain regions to be stimulated through neuromodulation. These model-based predictions could be subsequently verified using empirical observations, thus in return providing feedback to the model to improve its accuracy. Such a vision is not accessible in the immediate future, yet it remains within the scope of plans of future research.

## 5. Conclusion

Multimodal neuroimaging assessment has been recommended by both the American and European Academies of Neurology in the case that repeated behavioural assessments yield ambiguous results [26,27]. EEG-based techniques remain the most accessible, practical, and available technologies due to their portability and relative inexpensiveness. Resting-state quantitative EEG measures are more robust than passive stimulatory ERPs for diagnosis (moderate evidence, weak recommendation). FDG-PET has a high sensitivity and specificity (~94%) for diagnosis [50] and has been shown to provide the most accurate long-term prognosis in patients with subacute to chronic DoC [11]. Despite its relatively low sensitivity (~45%) due to the requirement of intact attentional and linguistic abilities [11], task-based fMRI and EEG techniques are referred to as “tests with potential clinical utility” in American guidelines, whilst European guidelines recommend for the use of task-based techniques for the assessment of patients without command following and “wherever feasible” [26,27]. Positive results on brain function quality assessments via fMRI and EEG resting state paradigms provide a robust prerequisite measure for minimal conscious awareness. However, the inferential power of these measures alone is weak as they only provide circumstantial evidence of MCS-like brain activity. TMS-EEG techniques are robust, highly sensitive (94.7%) measures for the detection residual consciousness [94], but the technique is yet to be widely implemented in the clinic. During multimodal assessment, the differential specificity and sensitivity of each modality means that conflicting results can arise, in this case the EAN recommends that patients are diagnosed according to the highest level of consciousness revealed by any of the assessments [27].

Neuroimaging is at the vanguard of empirical scientific discovery to inform clinical applications for DoC. Future research combing data-driven machine learning techniques with resting state measures, contextualised within theoretical frameworks such as the novel ECI measure hold promise to combine high inferential power with low ease of acquisition [105]. Additionally, the advent of WBM with increasingly biologically realistic features will present opportunities to investigate mechanistic hypotheses of consciousness and assess different treatment efficacies within individual DoC patients’ brains. The computational methodologies presented here represent tools that we must harness to facilitate innovations in methodologies and analyses; formulate predictions precise enough to develop a mechanistic understanding of DoC. However, as our technological capabilities widen and the premises underpinning novel findings becomes more convoluted, it remains ever pertinent to contextualise such findings within theoretical frameworks, thus circumventing the loss of applicable insight within a sea of data-driven methodology. In this way, driving forward the science of DoC can be represented by a “virtuous cycle” of empirical discovery, theoretical conceptualisation, and clinical implementation [28]. Each of these steps will scaffold upon one other informing diagnosis and prognosis, and ultimately improving the lives of DoC patients.

## Declaration of Competing Interest

The authors declare that they have no competing interest.

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