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REVIEW

Measuring consciousness in coma and related states

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Abstract

Consciousness is a prismatic and ambiguous concept that still eludes any universal definition. Severe acquired brain injuries resulting in a disorder of consciousness (DOC) provide a model from which insights into consciousness can be drawn. A number of recent studies highlight the difficulty in making a diagnosis in patients with DOC based only on behavioral assessments. Here we aim to provide an overview of how neuroimaging techniques can help assess patients with DOC. Such techniques are expected to facilitate a more accurate understanding of brain function in states of unconsciousness and to improve the evaluation of the patient's cognitive abilities by providing both diagnostic and prognostic indicators.

Key words: Disorders of consciousness; Neuroimaging; Magnetic resonance imaging; Transcranial magnetic stimulation/electroencephalography; Minimally conscious state; Vegetative state/unresponsive wakefulness syndrome

Core tip: In this review we show the main ways neuroimaging techniques contribute to both understanding the neural correlates of consciousness and detecting possible consciousness residual in severly traumatic brain injured patients. In particular, we make reference to the latest research in terms of both improving the diagnosis of patients with disorder of consciousness, and understanding the brain processes underlining consciousness, such as a broad and more complex than previously thought alteration of brain connectivity architecture.

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INTRODUCTION

Consciousness is a multifaceted and ambiguous concept, which is often the focus of passionate multi-disciplinant debates. Consciousness is thought to represent an emergent property of reciprocal connections between specialized areas of the grey matter within cortical and subcortical networks[1]. To date, there is no universal definition for consciousness covering all its essential characteristics[2], making everything particularly tricky and challenging when facing this specific topic and the related disorders.

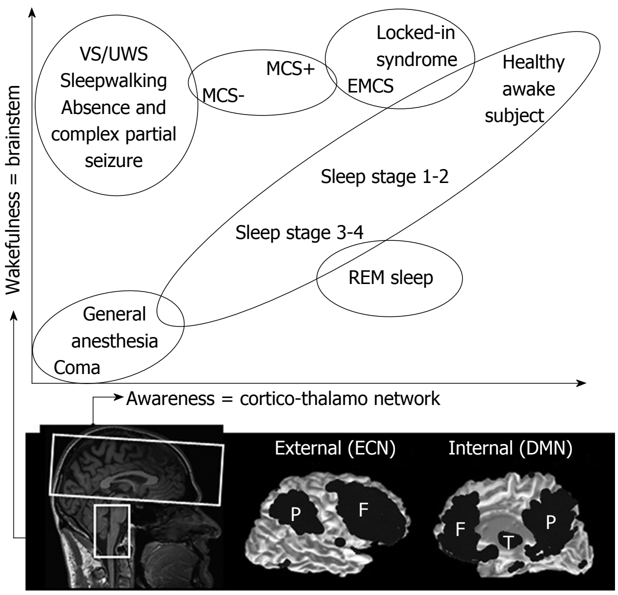

Figure 1 The two main components of consciousness: wakefulness and awareness. Correlation between wakefulness, related to the brainstem, and awareness, related to the cortico-thalamic network. In most pathological and physiological states, the two components are linearly correlated along the spectrum of consciousness. However, they are dissociated in some cases. Vegetative state/unresponsive wakefulness syndrome (VS/UWS); minimally conscious state (MCS); emergence of MCS, EMCS. Adapted from ref. [3,4]. EMCS: Emerge from minimally conscious state; ECN: Executive control network; DMN: Default mode network; REM: Rapid eyes movement.

We here adopt a perspective where consciousness is clinically defined as having two components: awareness and arousal[3]. Arousal, also called wakefulness, refers to the level of alertness (clinically determined by eye opening), whereas awareness refers to the content of consciousness (clinically determined by command following or non-reflex motor behaviour such as eye tracking or localized responses to pain)[3]. Arousal is anatomically related to structures in the brain and specifically in the brainstem and hypothalamus, whereas awareness has been shown to be related to a wide fronto-parietal network encompassing associative cortices and, more specifically, to the intrinsic connectivity of this network and the connectivity between the fronto-parietal associative cortices and the thalamus[4,5]. In physiological states, there is an intimate positive correlation between arousal and awareness. Sleep is the best way to describe the relationship between these two components: the less awake we become as we move towards deep sleep, the less aware we become of our surroundings and ourselves[3]. Based on this, subjects in pathological and pharmacological coma (*i.e.*, anesthesia) are not conscious because they cannot be awakened, even after noxious stimulation[3]. Similarly, under sedation (a drug-dose dependent impairment of consciousness) and in hypnotic state (a suggestion-dependent alteration of conscious experience), subjects report an altered state of awareness as they move towards lower levels of arousal[6-8]. Hence, arousal seems to be essential for awareness to emerge, *i.e.*, one needs to be awake in order to be aware. However, being awake is not sufficient in order to be aware.

There are, in fact, some exceptional cases in which these two components are dissociated. On the one hand, in the rapid eye movement stage of sleep, wakefulness is impaired while internal awareness is relatively spared. On the other hand, in vegetative state (VS), now also coined unresponsive wakefulness syndrome (UWS)[9], in minimally conscious state (MCS) and in some more transient states such as absence seizures, complex partial seizures or somnambulism, awareness is impaired while wakefulness is spared (Figure 1)[10-13]. The interest in understanding the neuropathology of such latter states, and in particular VS/UWS, is twofold. Firstly, VS/UWS patients offer a lesion approach to the study of human consciousness in terms of identifying the neural correlate of awareness[3]. These patients represent cases of awareness suppression but, unlike coma patients, exhibit intact wakefulness. Secondly, VS/UWS patients represent a clinical challenge, in terms of both diagnosis,and prognosis.

We aim to review here the knowledge of (un) consciousness obtained by studying disorders of consciousness (DOC) following brain injury (coma, VS/UWS, and MCS). We will focus mainly on structural and functional neuroimaging studies and we will pinpoint how developing such techniques could improve both scientific and clinical perspectives in DOC (Table 1).

We searched the MEDLINE database for English-language reports published between 2002 and April 2014 which used the terms "disorders of consciousness", "vegetative state", "minimally conscious state", "neuroimaging", "magnetic resonance imaging (MRI)", "positron emission tomography (PET)", "transcranial magnetic stimulation (TMS)" and "TMS/electroencephalography (TMS/EEG)". We reviewed the full text of all the original articles, reviews, early-release publications and associated citations retrieved, and relevant papers found in the authors' own files.

CLINICAL ENTITIES OF DISORDERS OF CONSCIOUSNESS

Disorders of consciousness are characterized by a prolonged impaired unconsciousness following an acquired severe brain injury. These conditions are more and more frequent in the clinical setting due to progress in emergency medicine and lifesaving technologies which have led to a better survival rate after severe brain damage[14].

Patients surviving severe brain damage may end up in a coma. This state may arise following structural or metabolic lesions to the brainstem reticular system or due to widespread bilateral cerebral damage[1]. Patients in coma show continuous absence of eye opening and any spontaneous or stimulus induced arousal or voluntary behavioural responses. Hence, they are neither awake nor aware. Coma is a time-limited condition (it usually does not last longer than a few weeks) leading either to brain death (*i.e.*, permanent loss of brainstem functions), a VS/UWS or the recovery of consciousness. Patients in a VS/UWS have recovered wakefulness (as evinced by

Table 1 Key points of the review

Novel neuroimaging techniques in patients with DOC give important key insights into both the understanding of consciousness and the differential diagnosis of clinical DOC entities, given that behavioural assessment alone can sometimes be incorrect and imprecise
Conventional MRI and DTI investigates the structural properties of the brain and the white matter integrity. These studies showed mainly a predictive rather than diagnostic value
PET activations show a critical role of a wide frontoparietal associative network for the emergence of consciousness
fMRI employing active paradigm detects covert awareness in approximately 17% of unresponsive patients at bedside. However, there is a high risk of false negative. fMRI employing passive paradigm shows also a prognostic value. fMRI during resting state shows a broad alteration of brain connectivity, implying both decreased and increased connectivity in patients with DOC
TMS-EEG shows a high diagnostic value even at single subject level

DOC: Disorders of consciousness; MRI: Magnetic resonance imaging; DTI: Diffusion tensor imaging; PET: Positron emission tomography; fMRI: Functional magnetic resonance imaging; TMS-EEG: Transcranial magnetic stimulation coupled with electroencephalography.

eye opening) but their motor responses are only reflexive and, therefore, do not indicate conscious awareness[15]. VS/UWS has been said to be permanent 12 mo after traumatic brain injury and 3 mo following non-traumatic brain damage, making chances of recovery very low[16]. However, this has recently been challenged[9]. It is now suggested that one substitute the term "permanent" with the association of the injury etiology (traumatic *vs* non traumatic) and the length of time since onset, as these factors appear to influence outcome. Non traumatic patients generally have the worst outcome. From VS/UWS, patients may progress into a MCS. This may either be the endpoint of their improvement or a provisional stage on the way to further recovery of consciousness[17]. MCS is a condition of severely altered consciousness characterized by minimal, inconstant yet definite behavioural signs of awareness of self and the surroundings. Based on the level of their purposeful behavioural signs, MCS patients were recently subcategorized as MCS plus (showing command following, intelligible verbalizations or non-functional communication) and MCS minus (showing visual pursuit, localization of noxious stimulation or contingent behaviour such as appropriate smiling or crying to emotional stimuli)[18]. Patients may emerge from MCS once they regain the ability to reliably communicate and/or use objects in a functional manner[17]. Although there is some evidence suggesting that patients in a MCS have better chances of recovery than patients in a VS/UWS, at present, we are not in a position to refer to possible temporal boundaries of irreversible MCS[19].

DOC must be differentiated from locked in syndrome (LIS). This is a rare state which usually follows a brain stem lesion with massive damage to the cortico-spinal and cortico-bulbar pathways, and classically results in loss of control of all voluntary muscles except for extrinsic eye muscles, making it possible for them only to communicate with small eyelid movements[20,21].

Differential diagnosis of the above mentioned clinical DOC entities raises important ethical and medical questions such as end-of-life decision and pain treatment[14,22,23]. Nowadays, the gold standard for assessing the level of consciousness is the clinical assessment of patients' behavioural responsiveness. Since responsiveness is only indirect proof of consciousness (lack of responsiveness does not necessarily imply lack of consciousness), reliance on these behavioural markers entails significant challenges and may lead to misdiagnoses. Clinical studies have shown that up to 40% of patients with a diagnosis of VS/UWS may in fact retain some level of awareness[24-26], and the main causes of misdiagnosis are associated with patient's disabilities, such as paralysis and aphasia, fluctuation in arousal level, difficulty differentiating between reflexive and involuntary movements and the non-use of standardized and sensitive clinical scales such as the Coma Recovery Scale-Revised (CRS-R)[27]. Furthermore, conventional brain structural imaging studies have shown highly variable and heterogeneous results in patients with DOC, suggesting that a specific brain region cannot be unequivocally related to awareness[28]. This knowledge has lead to the search for other non-clinical assessment techniques which can enable us to better understand brain function in these patients and to overcome the limits of behavioural assessment in the detection of possible retained consciousness in unresponsive patients.

NEUROIMAGING STUDIES IN DOC

Functional neuroimaging methods have made it possible to objectively study cognitive processing in the absence of behavioural reports. PET measures different aspects of metabolic function according to the type of administered radioactive tracer. Structural conventional MRI and diffusion tensor imaging (DTI) reveal the structural properties of the brain and the white matter integrity respectively. Functional MRI (fMRI) quantifies brain function derived from blood-oxygen-level dependent (BOLD) changes. TMS/EEG allows us to non-invasively stimulate a subset of cortical neurons and to measure the effects of this perturbation on the rest of the brain[29-33] (Table 2).

Below we will refer to the neuroimaging studies that have been most frequently adopted to infer covert cognitive abilities in behaviourally non responsive DOC patients.

PET

^{18}Fluorodesoxyglucose-PET (FDG-PET) studies were the first to demonstrate massive decrease in brain metabolism in patients with DOC. Using PET in resting state conditions, it was shown that patients in VS/UWS exhibit a decrease in brain metabolism of up to 40% of the normal value[3]. Nevertheless, recovery from the

Table 2 Main strength and limits of the different techniques

Technique	Strenght	Limits
PET	Relatively direct measure of brain activity	Ionizing, radioactive tracer, low spatial and temporal resolution expensive
MRI	No use of ionizing. Permits both high resolution study of structural brain (DTI) and fMRI employing active, passive and resting state paradigms	Indirect measure of brain activity (functional) Sensitive to movement and artifacts, impractical (application precluded in patients with contraindication), expensive
TMS-EEG	Practical (no important contraindications) gives information at single subject level	Sensitive to muscle artifacts

PET: Positron emission tomography; MRI: Magnetic resonance imaging; TMS-EEG: Transcranial magnetic stimulation coupled with electroencephalography; DTI: Diffusion tensor imaging; fMRI: Functional magnetic resonance imaging.

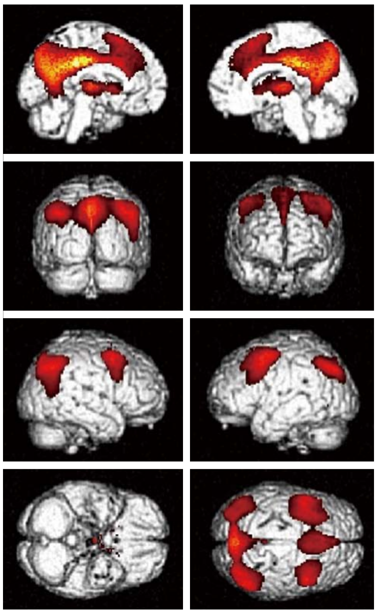

Figure 2 Brain areas where metabolism is impaired in vegetative state/unresponsive wakefulness syndrome patients compared to controls (areas in red), superimposed in a structural 3D image. $P < 0.05$, family wise error corrected.

VS/UWS does not coincide with the recovery of global metabolic levels. Instead it seems that some areas are more important to consciousness than others. In fact, patients suffering from DOC show decreased metabolism in a widespread network encompassing frontoparietal areas, such as in the lateral prefrontal and posterior parietal regions as well as midline anterior cingulate/mesiofrontal and posterior cingulate/precuneal associative cortices (Figure 2)[34,35]. Importantly, recovery from the VS/UWS parallels connectivity restoration in these areas (cortico-cortical) and between these regions and the thalamus (thalamo-cortical)[36].

FDG-PET cannot yet disentangle between VS/UWS and MCS at the single subject. However, it has shown to be highly sensitive in identifying patients in MCS[37] and displaying a correlation between metabolism in the above mentioned awareness network and the CRS-R score of the patients[38].

There is now growing evidence suggesting that this awareness network can be subdivided into two different networks: the intrinsic [default mode network (DMN)] and the extrinsic awareness network [executive control network (ECN)]. The extrinsic awareness network encompasses the lateral fronto-parietal brain regions and is related to sensory awareness or awareness of the environment. The intrinsic awareness network (most widely known as the DMN) encompasses mainly the medial prefrontal cortex and the precuneus and bilateral posterior parietal cortices and is related to internal awareness or self-related processes, such as mind-wandering and autobiographical thinking[39-41]. More recently, it has been demonstrated that patients in MCS retain metabolism in the lateral fronto-parietal areas whilst midline regions are highly dysfunctional[42]. As such, this data suggests that, at group level, patients in MCS display altered self-awareness besides their abilities to, at least to a certain extent, interact (but not communicate) with their surroundings. Furthermore, patients who are considered to be in MCS minus showed impairment of the left dominant hemisphere, possibly correlated to aphasia, consistent with their command-following impairment[18].

$^{15}H_2O$-PET studies using passive auditory and noxious stimulation[43,44], have furthermore highlighted a peculiar disconnection in VS/UWS patients between the primary sensory areas and these large-scale associative fronto-parietal cortices, which are thought to be essential for conscious perception[3]. In contrast, patients in MCS show a partial preservation of this large-scale associative fronto-parietal network[45]. Furthermore, PET studies employing nociceptive stimuli have highlighted an activation of the pain matrix in MCS patients similar to that observed in healthy controls, suggesting a possible perception of pain in this patient category. By contrast, activation in VS/UWS was limited to the primary sensory areas[46].

Structural MRI

MRI with conventional sequences (T1-TSE, T2-TSE, FLAIR) is the method of choice to detect brain edema, contusion, hematomas, herniation, hemorrhage, hydrocephalus, or hemorrhagic shearing lesion due to diffuse axonal injuries common in post-traumatic patients (T2* sequences). Nevertheless, in an emergency setting, the computed tomography scan is preferable in some cases due to its accessibility, speed of acquisition, and sensitivity to acute hemorrhagic lesions that require a surgical approach[38,47].

Some studies have highlighted the predictive value of the classical conventional sequences. For example, the number of lesions detected by FLAIR and T2* sequences has been shown to be inversely correlated with the Glasgow Coma Scale (GCS) of traumatic patients in a coma. The presence of lesions in the corpus callosum and the dorsal midbrain has been shown to be correlated with lack of recovery at group level in coma patients[47,48]. However, these methods have failed to explain why some patients in a VS/UWS and/or in a MCS have no or minimal brain lesions. This highlights the lack of specificity and sensitivity of conventional MRI in DOC, which alone cannot be considered a reliable tool for assessing this patient category.

Recently developed DTI techniques can reveal structural damage in tissue that appears normal in conventional-MRI.

These techniques have been able to predict scores on the GCS and successfully classify VS/UWS and MCS patients into their appropriate diagnostic categories with an accuracy of 95%[49]. Furthermore, recent multicentric studies have demonstrated that DTI is better at predicting outcome for both traumatic and anoxic patients at 1 year follow up from injury than structural and clinical assessment[50,51]. An other study evaluated the combination of DTI and MR-spectroscopy as a tool for predicting long-term outcome of traumatic patients[52], showing that a prediction of non-recovery after 1 year could be calculated with up to 86% sensitivity and 97% specificity when taking into account both DTI and MR-spectroscopy values.

With regards to diagnostic accuracy, a recent study used DTI to assess the neuropathology of patients in VS/UWS and MCS *in vivo* and to identify measurements that could potentially distinguish the patients in these two groups[49]. The MCS and VS/UWS patients appeared to differ significantly in subcortical white matter and thalamic regions (measured using diffusivity maps) but appeared not to differ in the brainstem. DTI results predicted scores on the GCS and successfully classified the patients into their appropriate diagnostic categories with an accuracy of 95%[49]. Furthermore, DTI proved to be helpful for characterizing etiologic differences in patients in VS/UWS, demonstrating that DTI abnormalities in the brainstem were confined to the traumatic brain injured group[53].

These studies suggest that DTI-MRI techniques can quantify white matter integrity and support the possible benefit of using these methods for an early classification of this patient population.

fMRI

In the last few years PET activation studies have been largely replaced by fMRI non-ionizing techniques. Activation studies using visual, auditory and somatosensory stimuli have revealed high level cortical activation encompassing the associative cortices in patients in MCS, similar to that observed in healthy controls[54,55]. In contrast, only low level cortical activation, limited to the primary sensory areas, was detected in VS/UWS. The minority of patients in VS/UWS with high level cortical activation often showed signs of recovery on the long term follow up[55,56]. Besides the prognostic value of this technique, active fMRI paradigms have recently been performed to detect covert awareness in patients who are behaviourally unresponsive by investigating signs which are independent from motor command following, and in some cases even establishing yes-no communication[57-59].

For instance, a recent fMRI study using mental imagery tasks (imagining playing tennis *vs* spatial navigation around one's house) showed that in a large cohort of 54 patients with DOC, 5 were able to willfully modulate their brain activity. Furthermore, one behaviourally VS/UWS patient was able to use this technique to correctly respond with yes (by imagining playing tennis) or no (by imagining visiting the rooms of his house) to autobiographical questions during the fMRI scanning[57]. Approximately 17% of patients diagnosed as in VS/UWS following behavioural assessment seem to be able to follow commands when the commands involve a change in blood oxygenation level dependent response, rather than overt motoric behaviour. Similarly, a further study using selective auditory attention showed that 3 patients (2 in MCS and 1 in VS/UWS) were able to convey their ability to follow commands, and the one in VS/UWS was even able to correctly communicate answers to several autobiographic binary questions[60].

Despite their potential diagnostic and prognostic value, active fMRI paradigm in terms of detecting covert awareness has remained mostly controversial. Indeed, without a comprehensive understanding of the neural correlates of awareness, the absence of cortical activation to external stimuli does not necessarily coincide with absence of awareness. Indeed, out of 31 MCS patients described in the study by Monti *et al*[57], only one was able to willfully modulate his brain activity. This could be due to the fact that patients may be asleep during the scan, or due to patients' disabilities, such as aphasia (patients cannot understand the task), *etc*[57].

In this context, the other fMRI paradigms commonly performed which partially overcome this latter limit are passive, measuring brain responses to external sensory stimulation (*e.g.*, auditory, somatosensory and visual) whilst the subject is not performing any mental task. An example is the brain activation elicited by the patient's own name spoken by a familiar voice. This is a salient auditory stimulus which has been preferred due to its attention-grabbing properties. For example, using the own-name paradigm, it was shown that 2 out of 7 patients in VS/UWS and all 4 patients in MCS not only showed activation in the primary auditory cortex, but also in higher order associative temporal areas, which are thought to be implicated in the conscious processing of the incoming stimuli[55]. Interestingly, these 2 patients in VS/UWS subsequently recovered to MCS. The absence of higher activation did not unequivocally coincide with the absence of awareness as sensory deficits, such as deafness, could have led to a false negative.

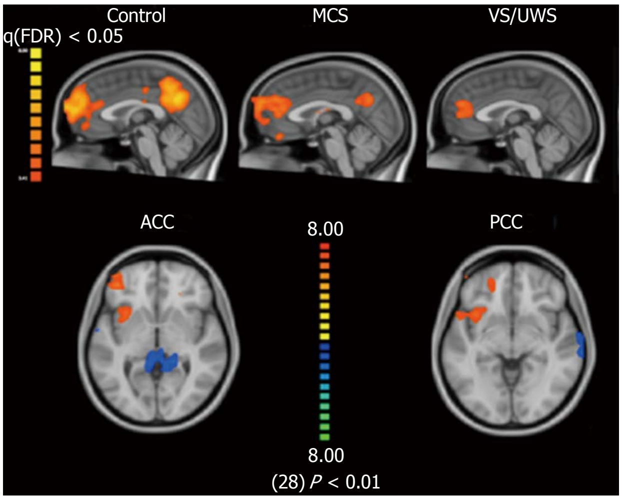

Figure 3 Default mode network in vegetative state/unresponsive wakefulness syndrome, minimally conscious state, healthy controls-sagittal view[68]. In vegetative state/unresponsive wakefulness syndrome (VS/UWS), the anterior cingulate cortex (ACC) and posterior cingulate cortex (PCC) are hypoconnected to the default mode network (in blue) and hyperconnected to the fronto-insular cortex (in red), axial view. Correlation from random effect (P < 0.01) and clustered corrected (P < 0.05) results based on general linear model maps with seed region of interest comparing VS/UWS to healthy controls[60]. MCS: Minimally conscious state.

Resting-state fMRI is a non invasive technique used to investigate the spontaneous temporal coherence in BOLD fluctuations related to the amount of synchronized neural activity (*i.e.*, functional connectivity) between distinct brain locations, in the absence of input or output tasks[61]. This technique has been increasingly used in the analysis of patients with DOC, mainly because it is not invasive and it surpasses the requirement for motor output or language comprehension. Among the several functional networks that have been detected so far[62], DMN has been the first to attract scientific attention. To date, resting state fMRI studies suggest that activity of this network is generally lower as a function of the level of consciousness. It has been demonstrated, for example, that the connectivity of this network is correlated to the level of consciousness, ranging from patients in VS/UWS (low connectivity) to patients in MCS and to healthy controls (higher connectivity)[63] (Figure 3). In addition, DMN connectivity could not be found in a brain dead patient, which highlights the neural origin of these MRI signals[64]. Recently, more networks at resting state have been investigated in DOC, such as the bilateral fronto-parietal or executive control networks, salience, sensorimotor, auditory, visual systems, and the cerebellar network. It was found that, besides DMN, the bilateral executive control networks and the auditory system were also significantly less identifiable (in terms of spatial and neural properties) in patients with DOC compared to healthy controls, and showed consciousness-level dependent decreases in functional connectivity across the spectrum of DOC[65].

Interestingly, it has been found that the resting brain is characterized by a switch between the dominance of the DMN (linked to "internal" or self-awareness) and the ECN (linked to "external" or environmental awareness[66,67]; when one shows activation, the other does not and vice-versa. More recently, it was found that such spontaneous anticorrelated patterns are closely related to mentation and behavioral status. This means that DMN activity is linked to behaviorally report of internal awareness whereas ECN activity is related to behavioural ratings for external awareness[39]. The decrease in anticorrelated pattern in disordered consciousness supports the functional relevance of anticorrelated patterns to the phenomenological complexity of consciousness[29].

Alongside the investigation of reduced connectivity is the presence of hyper-connectivity patterns, which might also be indicative of brain function. In fact, it has recently been demonstrated that, together with DMN hypoconnectivity, the subcortical limbic system (including the orbitofrontal cortex, insula and hypothalamus) exhibits paradoxically increased fMRI connectivity in patients with DOC when compared to healthy controls[68] (Figure 3). This could point to a more complex scenario of brain connectivity architecture in the emergence of consciousness, where hypoconnectivity may only represent a single aspect.

TMS-EEG

Unfortunately, fMRI-based techniques are impractical. The fact that a scanner is needed limits its use to hospital settings and precludes use in patients with pace makers, metal implants or those in a critical condition in intensive care units.

In this context, EEG recording associated with TMS is a promising way to assess cerebral connectivity and it may be especially useful for assessing the level of consciousness in patients with DOC as it does not require a scanner and it does not rely on the subject's ability to process sensory stimuli, to understand and follow instructions or to communicate. In addition, this technique permits consciousness assessment at single subject level, unlike the majority of fMRI and PET studies[33,69].

TMS-EEG can measure brain complexity by non-invasively stimulating a subset of cortical neurons (through TMS) and can immediately measure the effects of this perturbation on the rest of the brain (through high density EEG)[32,33].

Based on the level of consciousness, the perturbation will show either cortical interaction related to preservation or loss of information and/or integration. For example, in patients in VS/UWS, when stimulating a superficial region of the cerebral cortex, TMS either induced no response or triggered a simple, local EEG response, indicating a breakdown of effective connectivity (*i.e.*, of the influence that one brain region exerts on another[70,71], similar to that observed in deep sleep and anesthesia[33,72]). In contrast, for patients in MCS, TMS triggered complex EEG activations which sequentially involved distant cortical areas, similar to activations recorded in patients in LIS and healthy awake subjects. Recently, these TMS-EEG responses have been practically quantified by the perturbational complexity index (PCI)[32]. This index has demonstrated its potential as a unified measurement scale to grade the level of consciousness. The PCI, in fact, estimates the amount of information contained in the integrated response of the thalamo-cortical system to a direct TMS perturbation[32]. Empirically, it showed to provide a data-driven metric that can discriminate level of consciousness in single subjects under different conditions: below 0.31 for unconsciousness, above 0.51 for healthy consciousness and in the between for MCS.

CONCLUSION

In the last decade we have witnessed the development and the validation of standardized behavioural scales, together with neuroimaging and neurophysiological techniques to better understand the variable conditions of patients with DOC. The need to objectively measure phenomena associated with consciousness has promoted an increased use of these neuroimaging and neurophysiological tools in this patient population. Here we have reviewed the basic principles of how the main neuroimaging techniques (PET, structural MRI, fMRI and TMS-EEG), provide us with important insights into brain function in DOC patients. Since every single technique gives us specific and different information, we support the integration of structural and functional neuroimaging techniques, in order to have a broader and more holistic vision of both the disease and the single patient under our care. Furthermore, we expect that in the near future, with a wider use of standardized behavioural scales and the development of multimodal neuroimaging techniques, there will be a drop in diagnosis-error. Finally, the application of these methodologies at the single subject level, as clinical reality requires, is one of the next challenges.

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