Neuroradiology
DOI 10.1007/s00234-009-0614-8

INVITED REVIEW

Neuroimaging after coma

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Received: 7 September 2009 / Accepted: 7 October 2009

Abstract Following coma, some patients will recover wakefulness without signs of consciousness (only showing reflex movements, i.e., the vegetative state) or may show non-reflex movements but remain without functional communication (i.e., the minimally conscious state). Currently, there remains a high rate of misdiagnosis of the vegetative state (Schnakers et. al. BMC Neurol, 9:35, 8) and the clinical and electrophysiological markers of outcome from the vegetative and minimally conscious states remain unsatisfactory. This should incite clinicians to use multimodal assessment to detect objective signs of consciousness and validate para-clinical prognostic markers in these challenging patients. This review will focus on advanced magnetic resonance imaging (MRI) techniques such as magnetic resonance spectroscopy, diffusion tensor imaging, and functional MRI (fMRI studies in both "activation" and "resting state" conditions) that were recently introduced in the assessment of patients with chronic disorders of consciousness.

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Keywords Vegetative state · Diffusion tensor imaging · MR spectroscopy · Functional MRI · Consciousness

Introduction

Progress in emergency medicine and reanimation has increased the number of patients who survive severe acute brain damage [1]. The majority of these patients recover and transit through different clinical stages. Coma is characterized by the complete failure of the arousal system with no spontaneous eye opening, and results from a structural or metabolic lesion of the brainstem reticular system or from widespread bilateral cerebral damage. These patients will never open their eyes even when intensively stimulated [2]. Coma is usually a transient condition which will last no longer than a few days or weeks. Some patients may evolve to brain death (i.e., irreversible coma with absent brainstem function); others will progress to a vegetative state. Vegetative state is characterized by the complete absence of behavioral evidence for self or environmental awareness with the capacity for spontaneous or stimulus-induced arousal, evidenced by sleep–wake cycles [3]. It is mainly caused by diffuse axonal injury which interrupts the white matter connections between the cortex and thalamus or by diffuse cortical damage in case of cardiorespiratory arrest. Many patients in vegetative state regain consciousness in the first month after brain injury. However, if patients show no sign of awareness 1 year after a traumatic brain injury or three months after brain damage from lack of oxygen, the chances of recovery are considered close to zero, and the patient is considered in a permanent vegetative state [3]. Those who recover from vegetative state, typically progress through different stages before fully or partially (minimally conscious state)

Published online: 28 October 2009

recovering consciousness. Minimally conscious patients are unable to communicate their thoughts and feelings, but demonstrate inconsistent but reproducible behavioral evidence of awareness of self or environment [4]. Minimally conscious patients have to show at least one of the following behaviors: oriented response to noxious stimuli, sustained visual pursuit, command following, intelligible verbalization or emotional or motor behaviors that are contingent upon the presence of specific eliciting stimuli such as episodes of crying that are precipitated by family voices only. Like the vegetative state, the minimally conscious state may be chronic and sometimes permanent. However, at present, no time intervals for "permanent minimally conscious state" have been agreed upon. These patients have a distribution of brain damage similar to that of vegetative patients with less severe lesion. Patients who emerge from the minimally conscious state are characterized by the ability to use functional interactive communication or functional use of objects [4]. Finally, patients may awaken from their coma fully aware but unable to move or speak—their only way to communicate is via small eye movements (locked-in syndrome). The locked-in syndrome, characterized by quadriplegia and anarthria with general preservation of cognition and vertical eye movement, describes patients who are awake and conscious but have no means of producing speech, limb, or facial movements. It is caused by hemorrhage or an infarction of the pontine tegmentum and must be distinguished from disorders of consciousness [5].

An accurate and reliable evaluation of the level and content of consciousness in severely brain-damaged patients is of paramount importance for their appropriate management. The clinical evaluation of consciousness in non-communicative patients remains erroneous in 40% of cases [6–8]. Bedside evaluation of residual brain function in severely brain-damaged patients is difficult because motor responses may be very limited or inconsistent. In addition, consciousness is not an all-or-none phenomenon and its clinical assessment relies on inferences made from observed responses to external stimuli at the time of the examination (i.e., assessing command following). Neuroimaging techniques such as proton MR spectroscopy (MRS), diffusion tensor imaging (DTI), and functional MRI (fMRI) have improved the quantification of neuronal damage and offers the possibility of directly measuring the brain's activity, not only at rest or during passive stimulation, but also in response to commands [1, 9]. This review focuses on the clinical application of DTI, MRS, and fMRI in vegetative and minimally conscious state patients. These techniques have played a key role in the transition of clinical MRI from a discipline based on morphology to one that combines structure with function.

Imaging of consciousness disorders

A comprehensive exploration of patients with disorders of consciousness should assess all structures involved in arousal and awareness functions, namely, the ascending reticular activating system located in the postero-superior part of the brainstem (primary arousal structure) [2, 10] and a large set of supratentorial structures responsible of awareness, encompassing thalamus, basal forebrain, and fronto-parietal association cortices [11]. Brain imaging of patients with consciousness disorders is routinely performed on 1.5 or 3-T MR scanners. There are potential limitations to this exploration, including patient motion, uncontrolled intracranial pressure, risks associated with the transportation of the sedated and ventilated patient from intensive care unit to the MRI suite and brain edema. The timing of the MR examination also remains a subject of debate. Taking into account the time since traumatic brain injury (TBI) or stroke, there are four clinical phases to be distinguished: (1) an acute phase, which lasts 24 h after TBI; (2) an early subacute phase, from day 1 to 13; (3) a late subacute phase, from days 14 to 20, and (4) a chronic phase, which starts on day 21 [12]. When performed in the acute phase, the exploration may take into account reversible lesions such as edema but can miss secondary lesions due to intracranial hypertension or systemic disorders [13–15]. On the contrary, an examination performed late after the injury may only detect sequels such as non-specific global atrophy [16] and will have less impact on medical management or prognosis [17–20]. An early subacute examination with precise evaluation of the brain damage is critical for therapeutic decisions (i.e., to determine outcome, cognitive and behavioral deficits [21, 22]). The late subacute phase seems to be the best moment to assess disorders of consciousness, taking into account the physiopathology (subsiding brain edema) and the medical and ethical issues raised by the management of these patients [23, 24].

Conventional MR imaging The morphologic MRI acquisitions usually include non-contrast-enhanced sagittal T1, axial diffusion, axial fluid attenuated inversion recovery (FLAIR), axial T2-SE, coronal T2* sequences and a 3D T1-weighted volume acquisition. FLAIR and T2-SE sequences permit to detect brain edema, contusion, hematoma, herniation, subarachnoid hemorrhage, or hydrocephalus. T2* sequences are useful in detecting hemorrhagic diffuse axonal injuries (DAI) [25, 26]. The total number of lesions detected by FLAIR and T2* are shown to be inversely correlated with Glasgow Outcome Scale (GOS [27]) of traumatic coma patients [21, 28]; while the 3D T1 sequence provides an opportunity to evaluate the brain atrophy during the follow up of these patients [16]. A lot of studies performed on traumatic coma patients with conventional

MRI showed that lesions of the pons, midbrain, and basal ganglia were predictive of poor outcome especially when they are bilateral [29–39]. Despite their encouraging results, these studies fail to explain why some patients in vegetative state or with long-term marked cognitive impairments have no or minimal lesions on conventional MRI examination. This raises the question of the lack of specificity and insufficient sensitivity of conventional MR sequences which fail to reveal lesions such as ischemic axonal injuries. Therefore, it is clear that morphological MRI alone cannot be considered as a reliable tool to assess consciousness disorders severity or to predict their evolution.

Diffusion tensor imaging DTI is an extension of diffusion-weighted imaging which is based on the principle that water molecule movement is restricted by barriers to diffusion in the brain depending on tissue organization (Fig. 1). The diffusion of water protons is higher along fiber tracts than across them in the white matter, which allows for directional measurement of diffusion and, hence, measurement of structural integrity. DTI data can be used to compute the fractional anisotropy as well as to track fibers. The fractional anisotropy quantifies anisotropic diffusion in the brain, which is related to the density, integrity, and directionality of white matter tracts [40, 41]. DTI evaluates the architectural organization of white matter fibers and is a powerful technique for in vivo detection of diffuse axonal injury after brain trauma [42]. Advantages of DTI are numerous: (1) it can permit to evaluate brain trauma in sedated patient; (2) DTI measures are not influenced by sedatives or hypnotics unlike the clinical scores; (3) changes in fractional anisotropy may help to evaluate response to treatment even if the clinical scores are insufficient to assess the patient; (4) it may be an important surrogate marker.

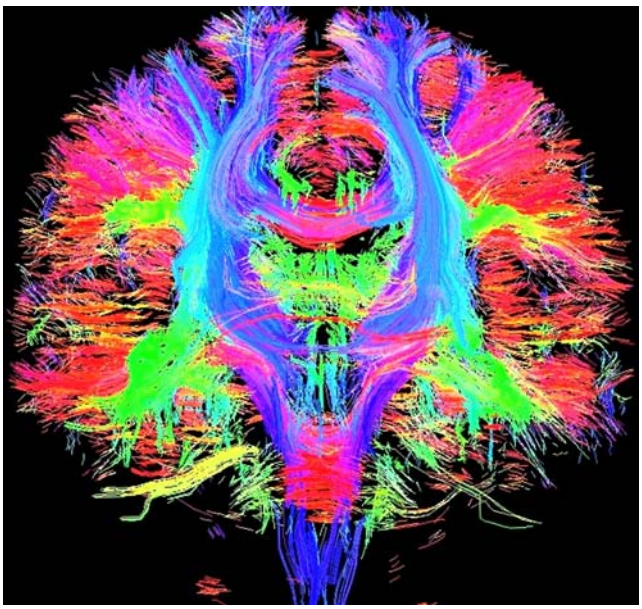

Fig. 1 Illustration of white matter tracts as visualized by diffusion tensor imaging in a healthy volunteers subject (*Blue*=*z*, *red*=*x*, *green*=*y* axes; TR/TE: 5700/90 ms, slices: 40, voxel size: 1.8×1.8×2.0 mm^3, FoV: 230×230 mm^2, bandwidth: 1,860 Hz/Px, diffusion weights: b=0, b=500, b=1,000)

The acquisition protocol, image processing, analysis, and interpretation of DTI are now routinely performed in clinical conditions essentially in the exploration of brain tumor. Studies on diffuse axonal injury [43, 44], as well as in other pathologies such as in patients with HIV [45] have shown that DTI may reveal damage in tissue appearing normal on conventional MRI sequences. In TBI patients, a significant negative correlation was reported between fractional anisotropy in the splenium of the corpus callosum and in the internal capsule and Glasgow Coma Scale (GCS [46]) score at discharge [13]. In a first study evaluating the combination of DTI and MRS as a tool for predicting long-term outcome of traumatic patients, Tollard et al. [24] observed that fractional anisotropy was significantly lower in patients who did not recover at all measurement sites, except in the posterior pons. They showed that 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 MRS values. Non-recovery of traumatic patients was also shown to be correlated with decreased fractional anisotropy in cerebral peduncle, posterior limb of the internal capsule, posterior corpus callosum, and inferior longitudinal fasciculus [47]. These studies confirm the relevance of the use of DTI as biomarker for consciousness recovery after a traumatic brain injury and support the possible use of this biomarker for early classification of patients. Furthermore, DTI recently revealed axonal regrowth in a patient who had been in a minimally conscious state but recovered verbal communication nearly two decades after a traumatic brain injury [48]. This demonstration of axonal regrowth after such a long time interval disproved the old dogma that neural plasticity is limited to the acute or subacute phase of cerebral injury.

Proton MR spectroscopy MRS is a noninvasive imaging method that provides useful metabolic information on brain damage that may not be visible on morphologic imaging. It has a better sensitivity than T2*sequences in the detection of ischemic or hemorrhagic diffuse axonal lesions in TBI [49]. Classically, the exploration of disorders of consciousness is performed at intermediate or long echo time (135–288 ms) and the main metabolites detected are choline (Cho), creatine (Cr), *N*-acetylaspartate (NAA), and lactate (La). Choline is a metabolic marker of membrane synthesis and catabolism. Its rate is slightly

higher in white than in gray matter and increases when there is an important membrane turnover due to cell proliferation or inflammatory process. Creatine is considered as a marker of the aerobic energy metabolism. It is used for calculating metabolite ratios such as NAA/Cr and Cho/Cr ratios. *N*-acetylaspartate is found in both gray and white matter in approximately equal quantities as a marker of neuronal density and viability produced in the mitochondria of the neurons and transported into the neuronal cytoplasm and the axons. In healthy subjects, there is an increase in NAA in gray matter from ventral to dorsal, and from the cerebral hemispheres to the spinal cord [50]. Several studies suggest NAA to be a brain osmolyte with possible reversible changes [51–53]. Finally, lactate is a marker of anaerobic glycolysis conditions which is at the limit of detectability in normal brain and may increase due to severe posttraumatic injury or brain hypoxia or ischemia.

To assess brain function in coma survivors, a comprehensive MRS protocol should include an axial chemical shift imaging at the level of the basal ganglia to include thalamus, insular cortex, and periventricular white matter in the field of exploration and a single-voxel 1H spectroscopy placed on the posterior two-thirds of the pons. Several investigations from the literature were promising in terms of the role of proton MRS as an accurate tool to predict patient outcome. A TBI case-control study revealed that the level of NAA/Cr ratio was correlated with recovery of patient whereas no clear link with other metabolite ratios such as Cho/Cr was observed [23]. Others showed that metabolic changes in TBI patients could be detected with MRS even in the days after the trauma [14]. Indeed, NAA was decreased and correlated with the initial GCS and the outcome at 3 months in these patients. The NAA/Cho ratio was shown to be able to disentangle patients who did not recover from those who regained consciousness [17]. Other studies have showed a significant correlation between NAA/Cr ratio and outcome of TBI patients in gray and white matter of occipito-parietal [15, 18], frontal [22], splenium of corpus callosum [19], and thalamic brain regions [20]. In addition, pons MRS recorded in the acute phase seems to allow to separate patients who recovered from patients with severe neurological impairment, death or in vegetative state [21]. Three MRS profiles of the pons could be drawn after a trauma: (1) normal profile with higher peak of NAA than Cho and Cr; (2) neuronal loss profile with a decreased NAA peak, nearly to the level of the Cr peak (the NAA/Cr ratio is 1.50 and NAA/(Cho+Cr+NAA)=0.40); (3) gliosis profile with increased Cho peak, no change in the Cr or NAA peak and Cho/Cr or NAA/Cr or Cho/(Cho+Cr+NAA)=0.40.

Finally, NAA/Cr ratio seems to be better than NAA/Cho for evaluating traumatic patients and its decrease appears to be a reliable index of unfavorable outcome [54]. Indeed, the NAA decreases within a few minutes after the traumatism and reaches its minimum within 48 h. Its level remains stable within the first month after the injury, supporting the validity of MRS assessments during the second or third week [55, 56]. Between 6 weeks and 1 year after the insult, the evolution of the NAA/Cr ratio is more heterogeneous, and NAA levels have been shown to decrease or increase. This possible variability in NAA levels is a potential limitation of this technique. In addition, the use of ratios may be problematic insofar that their common denominator is the Cr that is supposed to be stable in normal brain tissue and used to standardize other brain metabolites. However, to our knowledge, there is no evidence that Cr is invariable in TBI and it may be affected similarly to the metabolite of interest. Also, creatine MRS data can be reduced in hypermetabolic and raised in hypometabolic states [57, 58] which might bias recordings obtained in mild-traumatic-injured patients [59]. Whole brain NAA MRS and repetition of MRS examinations during the subacute phase might reduce the possible impact of NAA variability and hence improve MRS performance.

Functional magnetic resonance imaging fMRI now offers the possibility of directly measuring the brain's activity, not only at rest or during passive stimulation, but also in response to commands [9]. Several fMRI activation studies in vegetative state (see Table 1, [60–66]) have confirmed previous $H_2{}^{15}O$ positron emission tomography (PET) studies showing preserved activation of "lower level" primary sensory cortices which are disconnected from "higher order" associative cortical networks employing both auditory [67–70], somatosensory [67, 71], or visual [70, 72] stimulations. Schiff et al. [73] were the first to perform fMRI in minimally conscious patients. They demonstrated a residual capacity to activate large integrative networks in two minimally conscious patients. Similar studies in PET reported that minimally conscious patients showed a more widespread activation than did patients in a vegetative state, with a cortico-cortical functional connectivity more efficient in minimally conscious compared to vegetative patients [68]. Moreover, stimuli with emotional valence (cries and names) were showed to induce a much more widespread activation than did meaningless noise in the minimally conscious state [74]. Such context-dependent higher-order auditory processing shows that content does matter when talking to minimally conscious patients. Exceptionally, vegetative patients may also show higher atypical level cortical activation and this was proposed to be a surrogate marker of good prognosis [75].

However, in the absence of a full understanding of the neural correlates of consciousness, even a near-to-normal activation in response to passive sensory stimulation cannot

Table 1 Functional magnetic resonance imaging (fMRI) studies in chronic disorders of consciousness.

First author [reference]	Number of patients	Diagnosis	Etiology	Interval (mean±SD)	Stimulation	Main findings
Moritz [65]	1	VS	TBI	4 days	Tactile/visual/auditory	Near-normal primary sensory cortex activation (good recovery at 3 months post-fMRI)
Schiff [73]	2	MCS	TBI/NTBI	18–24 months	Tactile/auditory	Normal "lower" and "higher" level brain activity
Eickhoff [81]	1	Coma	TBI	35 months	Auditory/visual/tactile	Near-normal primary sensory cortex activation
Bekinschtein [60]	1	VS	TBI	2 months	Auditory	Limited primary auditory cortex activation (more widespread activation after recovery)
Staffen [66]	1	VS	Anoxic	11 months	Auditory	Differential mesiofrontal activation during own name compared to other name stimulation (no recovery)
Owen [76]	1	VS	TBI	5 months	Auditory active tasks	Near-normal activation during mental imagery tasks indicating preserved command following (recovered functional communication)
Di [63]	12	7VS/5MCS	TBI/NTBI	10±14 months	Auditory	Only the 2 VS patients showing atypical "high level" cortical activation recovered to MCS 3 months after fMRI
Coleman [62]	14	7VS/5MCS/2EMCS	TBI/NTBI	26±39 months	Auditory	No relationship between fMRI responses and diagnosis of VS vs MCS. Some VS patients retain near-normal speech-processing network activation
Fernández-Espejo [64]	7	3VS/4MCS	TBI	6±3 months	Auditory	No relationship between fMRI responses and diagnosis of VS vs MCS. 1VS with near-normal speech-processing network activation recovered 9 months later. 1MCS showed no activation
Coleman [61]	41	22VS/19MCS	TBI/NTBI	18±26 months	Auditory	All VS (7) showing near-normal speech-processing network activation recover to MCS 6-months post-fMRI
Zhu [82]	9	MCS	TBI/NTBI	1–2 months	Visual–emotional	Pictures of family members elicit near-normal activation (more than non-familiar pictures)
Boly [83]	2	1VS/1 BD	NTBI	18 months/2 days	Resting state	Residual default network integrity in VS (absent in BD)
Cauda [84]	3	VS	TBI/NTBI	20 months	Resting state	Residual default network integrity

BD brain death, *VS* vegetative state, *MCS* minimally conscious state, *EMC* emergence of minimally conscious state, *TBI* traumatic brain injury, *NTBI* non-traumatic brain injury

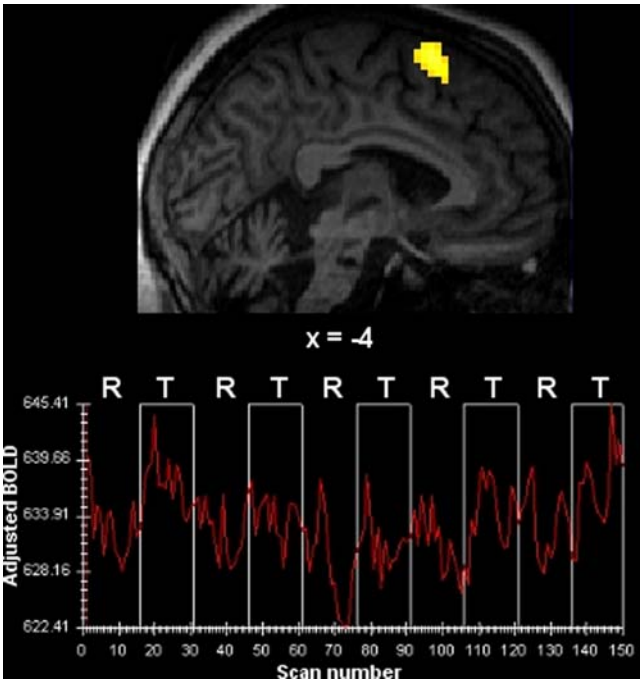

Fig. 2 Mental imagery ("play tennis") shows activation in pre-supplementary motor area in a 22-year-old locked-in syndrome patient. *T* play tennis, *R* rest (TR/TE: 2,000/30 ms, slices: 32, voxel size: 3.4×3.4×3 mm^3; Vanhaudenhuyse et al., unpublished data)

be considered as a proof of the presence of awareness in chronic disorders of consciousness patients. Instead, all that can be inferred is that a specific brain region is, to some degree, still able to process the relevant sensory stimuli. The question that arises is how can we disentangle automatic from conscious brain activation? The potential of fMRI, the best, so far, to unequivocally prove the presence of consciousness, was illustrated by the extraordinary case published by Owen et al. [76]. They reported fMRI results on a young woman in a vegetative state for 5 months following a severe TBI. When she was verbally requested to perform two ideational tasks consisting primarily to imagine playing tennis and then to imagine walking through her house, they observed fMRI activation in the same areas as the healthy controls (Fig. 2). They concluded that the patient was consciously aware of herself and her surroundings. Interestingly, she regained clinical signs of awareness 6 months later. This case illustrates that novel neuroimaging methods can now be used to detect signs of consciousness, not found during a thorough neurological examination, in non-communicative patients with brain damage. The results of this study should not be misinterpreted as evidence that all patients in a vegetative state may actually be conscious. Indeed, it should be noted

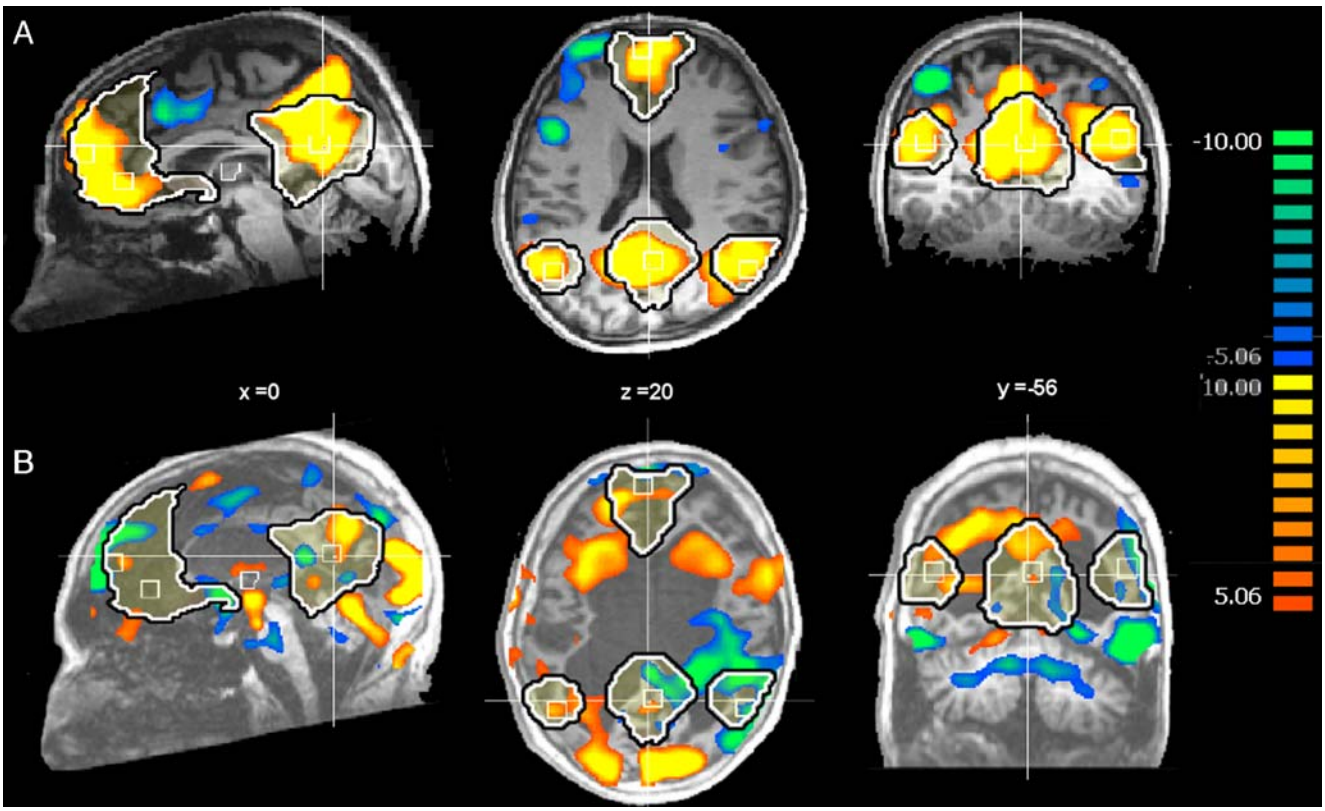

Fig. 3 Resting-state EPI acquisition in: **a** healthy volunteers illustrating the default mode network (*DMN*) in yellow encompassing mesiofrontal/anterior cingulate, precuneus/posterior cingulate and bilateral posterior parietal cortices. **b** A vegetative state patient 21 years post-anoxia, illustrating the absence of DMN connectivity (TR/TE: 2,000/30 ms, slices: 32, voxel size: 3.4×3.4×3 mm^3)

that some months after the study, the reported patient also showed behavioral signs of recovery. The most likely explanation of these results is that the patient was already beginning the transition to the minimally conscious state at the time of the experiment. This study also confirmed that fMRI could be a potentially good marker of prognosis. Active paradigm seems to provide a valuable additional diagnostic tool in cases of patients with atypical presentation, leading to persisting doubts in clinical diagnosis. Negative results, however, must be cautiously interpreted in case of patients with severely altered level of vigilance, which could present only transient activity in response to the presentation of instructions.

Resting-state fMRI acquisitions are also very easy to perform and could thus have a potentially broader and faster translation into clinical practice. Recent studies on spontaneous fluctuations in the functional MRI blood-oxygen-level-dependent (BOLD) signal recorded in "resting" awake healthy subjects showed the presence of coherent fluctuations among functionally defined neuroanatomical networks [77, 78]. The concept of "default mode network" (DMN) of brain function was proposed by Raichle et al. [79] to describe a number of brain regions encompassing the precuneus, posterior parietal lobe, and medial prefrontal cortex which are more active at rest than when we are involved in attention-demanding cognitive tasks (Fig. 3). The clinical interest of DMN MRI studies is that it allows the investigation of higher-order cognitive networks, without requiring patients' collaboration, particularly important in vegetative and minimally conscious patients. Recently, Boly et al. [80, 83] showed that some slow coherent BOLD fluctuations characteristic of the DMN in healthy subjects can be found in vegetative patients and not in brain death, and are thus unlikely to be uniquely due to ongoing modifications of conscious thoughts. While these results are very preliminary, this technique may be interesting to test the functional integrity of major brain structures and could be useful to distinguish unconscious–vegetative from conscious–minimally conscious patients. However, future studies are needed to give a full characterization of DMN connectivity in VS and MCS patients and its potential use in outcome prediction.

Conclusion

Assessing consciousness in coma survivors who remain unable to express (verbally or non-verbally) their thoughts and feelings is difficult by means of behavioral observation only. At present, MRI is the procedure of choice for the structural and functional imaging of the brain. While sequences such as DTI and MRS seems promising to reliably predict outcome in chronic disorders patients with severe TBI; passive, active, and resting-state functional neuroimaging paradigms are currently being validated to help in differentiating unconscious–vegetative from minimally conscious patients. These scientific progresses in neuroimaging, and its potential clinical translation, presents an opportunity to better meet the needs of these patients and provide families with better diagnostic and prognostic information. The major challenges of these acquisitions are patient selection, study design, and standardization of protocol (e.g., stimulus selection). Their susceptibility to movement artifacts and patients who are on life support systems or who have implanted MRI-incompatible material (pacemakers, prostheses, etc.) still remain problematic. Ongoing refinements for a wise use of these powerful tools and the information they produce can aid our understanding and management of chronic disorders of consciousness.

Acknowledgments This research was supported by the Fonds de la Recherche Scientifique (FRS), European Commission (DISCOS, Mindbridge, DECODER & CATIA), Concerted Research Action (ARC-06/11-340), McDonnell Foundation, Mind Science Foundation. The authors thank the technicians of the Department of Neuroradiology of the Centre Hospitalier Universitaire, Liege, for their active participation in the MRI studies in comatose patients.

Conflict of interest statement We declare that we have no conflict of interest.

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