HHS Public Access
Author manuscript
Curr Opin Neurol. Author manuscript; available in PMC 2022 March 22.

Published in final edited form as:
Curr Opin Neurol. 2020 December ; 33(6): 676–683. doi:10.1097/WCO.0000000000000873.

Magnetic Resonance Imaging in Disorders of Consciousness

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Abstract

Purpose of review: In the study of brain-injured patients with disorders of consciousness (DoC), structural and functional MRI seek to 1) provide insights into the neural correlates of consciousness, 2) identify neurophysiologic signatures of covert consciousness and 3) identify biomarkers for recovery of consciousness.

Recent Findings: Cortical volume, white matter volume and integrity, and structural connectivity across many grey and white matter regions have been shown to vary with level of awareness in brain-injured patients. Resting-state functional connectivity (rs-FC) within and between canonical cortical networks also correlates with DoC patients' level of awareness. Stimulus-based and motor-imagery fMRI paradigms have identified some behaviorally unresponsive DoC patients with cortical processing and activation patterns that mirror healthy controls. Emerging techniques like dynamic rs-FC have begun to identify temporal trends in brain-wide connectivity that may represent novel neural correlates of consciousness.

Summary: Structural and functional MRI will continue to advance our understanding of brain regions supporting human consciousness. Measures of regional and global white matter integrity and rs-FC in particular networks have shown significant improvement over clinical features in identifying acute and chronic DoC patients likely to recover awareness. As they are refined, functional MRI paradigms may additionally provide opportunities for interacting with behaviorally unresponsive patients.

Keywords

Disorders of consciousness; Resting-state functional MRI; Diffusion MRI; Coma; Brain Injury

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Conflicts of Interest:
Drs. Snider and Edlow report no conflicts of interest.

Introduction

The use of brain MRI in patients with disorders of consciousness (DoC) has three primary objectives. The first is to gain insight into the neural correlates of consciousness[1], the set of brain regions or networks that produce human consciousness. Investigations into the neural correlates of consciousness range from lesion mapping studies in patients with impaired consciousness[2] to resting-state functional connectivity studies in patients with chronic DoCs[3, 4].

The second objective is to identify neurophysiologic signatures of awareness in patients without behavioral signs of awareness (covert consciousness). Classic studies have used stimulus-based and task-based functional MRI (fMRI) paradigms to identify regional patterns of blood oxygen level-dependent (BOLD) signal change in behaviorally unresponsive patients that are similar to those seen in healthy control subjects[5, 6]. Identifying patients with covert consciousness is a crucial step towards meaningful therapeutics.

The final objective is the development of radiologic biomarkers of recovery potential for patients with both acute and chronic DoC. Loss of consciousness is common in critically ill patients and is not specific to any one underlying pathology[7]. Furthermore, in acutely injured patients, concurrent medical and surgical issues frequently prevent the complete suspension of sedation to allow for detailed, un-confounded behavioral characterization. Decisions about continuation of life-sustaining therapy may be required before a behavioral assessment can be performed. Accurate assessment of a patient’s burden of structural and functional injury in the immediate post-injury period will likely lead to improvement in current prognostic models and may have potential to identify patients amenable to targeted therapies[8–10]. It remains equally important to develop tools to identify patients with the potential to regain awareness in spite of an already prolonged DoC.

Neural Correlates of Consciousness

Stimulus based[1] and task-based[11] fMRI experiments in healthy subjects and resting state (rs)-fMRI studies in anesthetized subjects[12, 13] have sought to identify brain regions with neural mechanisms underlying conscious experience. There is still active debate about the interpretation of the collective results of these experiments[14, 15]. Patients with DoC represent a unique population in which to test the importance of a candidate network or region’s specific role in human consciousness. Experiments to this end compare a structural feature (e.g. lesion or atrophy) or functional property (e.g. BOLD signal correlation between two regions) between patients with DoC and controls, or among patients with DoC of increasing severity. Within brain-injured DoC patients, contrasts are generated according to behavioral subtype defined by Coma Recovery Scale-Revised (CRS-R) score[16, 17], seeking imaging features that systematically vary between groups with increasing awareness, or differ between groups with any (minimally conscious state [MCS]) as compared to no (coma, vegetative state [VS]) awareness. Rigorous comparison requires accounting for confounding sources of variance in the imaging feature (e.g. age, type of injury)[18] and behavioral score (e.g. presence of sedation, time since injury)[19–22].

Structural MRI

Lesion Mapping—Lesion mapping studies are most readily done with deep structural lesions, where focal lesions that produce unconsciousness are often in close proximity to lesions that do not impair consciousness. Lesion mapping studies of deep cerebral infarctions and hemorrhages have identified a region of rostral brainstem significantly associated with the presence of coma[2, 23, 24], confirming the importance of tegmental arousal nuclei identified from brainstem stimulation experiments in cats[25].

Clinical observations suggest that focal lesions in the cerebral hemispheres, while disruptive to certain aspects of cognition (e.g. hemianopsia, hemineglect, prosopagnosia) do not create a DoC[7]. Patients with a chronic DoC and cortical lesions have pathology that is often diffuse and less readily segmented on standard structural scans. Preliminary work using the novel technique of lesion-network mapping[26] in patients with cortical lesions and transient loss of consciousness has investigated the possible existence of distributed cortical networks important for arousal[27].

Volumetric Analysis—Morphometric or volumetric analyses, using a continuous measure at each voxel or surface vertex, can be undertaken with or without *a priori* hypotheses to identify regional associations with behavioral level of awareness (Figure). Complicating these analyses is that patients with a chronic DoC, other than those with brainstem lesions, almost uniformly have heterogenous and multifocal or diffuse brain structural abnormalities[3, 28, 29] that can create errors for standard registration and segmentation pipelines[28, 29].

Studies have avoided these limitations by restricting the search area to specific structures[30, 31], using region of interest (ROI)-based rather than voxel-based analyses[29], or by zeroing thickness and volume measurements in lesioned areas[32]. ROI-based volumetric analysis using a boosting classification tree procedure found that weighting and combining the degree of atrophy from a diverse set of regions was able to accurately classify 90–98% of DoC patients without (VS) as compared to with (MCS) awareness[29].

Structural connectivity—Diffusion MRI can be used in DoC patients to generate quantitative measurements of focal or global white matter integrity, or processed with tractography to measure differential connectivity between brain regions or networks (Figure). Level of awareness-dependent reductions in fractional anisotropy (FA) were identified in white matter tracts within the frequently-studied default mode network (DMN) and in pathways connecting the DMN to the thalamus in patients with DoC[33]. Whether the burden of white matter injury within the DMN exceeds the burden of diffuse white matter injury remains uncertain[33]. Tractography-based connectivity measurements in subcortical arousal pathways in patients with acute DoC after TBI were diminished compared to controls, but did not correlate with duration of unconsciousness[34]. Data-driven comparisons of thalamo-cortical connectivity patterns in DoC patients identified regional differences among DoC patients with varying levels of awareness, but which regions were identified depended on which behavioral subgroups were compared[35].

Structural connectivity matrices can also be generated from tractography measurements between pairs of brain regions defined according to standardized atlas segmentations. While diffuse abnormalities in these matrices were found between DoC patients and controls, they could not be used to reliably distinguish between DoC patients with different levels of awareness[36].

In summary, structural imaging approaches have identified diffuse abnormalities in cortical, subcortical and white matter volume and connectivity in patients with DoC as compared with healthy controls. Progress has been made towards finding focal abnormalities that systematically vary with level of awareness in DoC patients, but a consistent and definitive set of regions has not yet been identified.

Functional MRI

Stimulus-based—Stimulus-based auditory fMRI paradigms, first developed using regional cerebral blood flow measurements from $H_2{}^{15}O$-PET scans[37], identified that chronic VS patients lacked activation (e.g. BOLD signal increase) in auditory association areas, while retaining primary auditory cortex activation[38] (Figure). Subsequent experiments generalized this finding to other sensory modalities, identified it in VS patients who would go on to recover awareness, and generated the hypothesis that stimulus-induced, fMRI-based activation of higher-order sensory cortices may be a neural correlate of conscious awareness[39–41].

rs-fMRI—rs-fMRI offers the advantage of being a simpler undertaking, in that attention, auditory and visual function are not required. Resting state functional connectivity between any pair of brain regions or networks can be defined as the temporal correlation (Pearson R) between the averaged BOLD signal time course in each region or network (Figure). Alternatively, a statistical map of a particular region or network's brain-wide connectivity can be generated by correlating the BOLD signal in a seed ROI (or several averaged seeds that define a network) and every other voxel in the brain.

A landmark study in a cohort of 51 patients with DoC found that the intrinsic functional connectivity in six canonical[42] resting-state functional networks correlated with CRS-R score, and connectivity within the auditory network correctly classified almost all VS patients in an independent 22-patient dataset[4]. Separate work using a data-driven approach, without *a priori* network definitions, identified brain regions overlapping the nodes of the DMN and salience/executive control networks whose connectivity patterns varied across behavioral DoC groups and healthy controls[43]. However, the difference was driven primarily by comparisons between all DoC groups and controls rather than across DoC groups[43], a result also seen in an analysis of DMN connectivity in a different cohort[3]. Emerging from the latter study was the concept that negative functional correlations (i.e. anticorrelations) between the DMN and other resting-state networks systematically vary according to behavioral level of awareness, diminishing in MCS and inverting in VS patients[3]. Disordered connectivity between the DMN and other networks has subsequently been confirmed in VS patients using complementary method[43, 44].

Recent studies of acutely brain-injured patients have supported these observations, finding that DMN functional connectivity is reduced and anticorrelations are absent in behaviorally unaware as compared with aware patients[45]. Dynamic causal modeling has lent additional support to the model of progressively distorted DMN connectivity in patients with DoC of increasing severity[46].

Dynamic rs-fMRI—The time-varying BOLD signal measured in rs-fMRI lends itself to a variety of signal processing techniques for data analysis. Temporal correlations in the BOLD data, used to measure functional connectivity, may fluctuate during the acquisition period. Animal experiments have identified changes in functional connectivity affected by the administration of anesthesia, raising the intriguing possibility that the neural correlates of consciousness may reflect properties of brain network connectivity only evident when studied across time[47]. Without an analytic framework that accounts for these fluctuations, connectivity measurements derived from long blocks of rs-fMRI activity may miss relevant patterns.

Initial human work investigated temporal changes in spatial connectivity patterns of the posterior cingulate cortex, a central node of the DMN, finding that traditional DMN connectivity configuration occurred less frequently in patients with VS as compared to controls[44]. Recent experimental work using whole-brain, dynamic phase coherence-based connectivity matrices generated data-driven clusters of whole brain connectivity maps across time (Figure)[48]. The functional connectivity configuration most similar to the static, structural connectivity matrix was seen most frequently in VS patients, and its occurrence frequency varied across behavioral DoC diagnoses[48]. Individual heterogeneity and between-group overlap in the data raises the possibility that some patients with DoC have functional connectivity patterns that resemble those of healthy controls, if only for brief periods of time. Other work has begun to investigate transitions between functional connectivity states, finding that the number of between-state transitions was reasonably accurate at classifying a DoC patients' behavioral condition[49].

Structure vs Function

Few studies have rigorously compared the accuracy of features derived from structural versus functional MRI in classifying levels of awareness in DoC. Radiologist assessment of structural injury to DMN regions was found to be equivalent to DMN functional connectivity in classifying DoC patients' levels of awareness[50]. A separate study concluded that *whole-brain*, averaged volumetric analysis was inferior to rs-fMRI measures of DMN connectivity in classifying DoC patients' levels of awareness[3], but cortical volumes specifically within the DMN were not compared.

Covert Consciousness

Patients with no (VS) or minimal (MCS) signs of behavioral awareness may show brain responses to visual, auditory, or tactile stimulation that are similar to those of healthy controls[41, 51]. Given that the brain's passive response to a stimulus does not prove conscious awareness, subsequent task-based paradigms were developed to test for active, volitional responses to commands. In a patient in VS five months after traumatic brain injury (TBI), fMRI activation maps in response to instructions to imagine playing tennis or walking through her home appeared indistinguishable from healthy control subjects[5]. Given the complexity of the instructions and the specific regional activation, this result was interpreted as evidence of "covert consciousness" in a patient who by all other measures appeared unconscious.

Covert consciousness was subsequently assessed using the same motor imagery paradigm in a cohort of 54 subjects with chronic DoC[6]. Five of these patients showed significant activation[6] within prespecified brain ROIs defined from the previous study's activation maps[5]. A descriptive term for these patients was subsequently coined: "cognitive motor dissociation" or CMD[52]. One of these patients seemed to be able to use each cognitive motor imagery response to answer simple biographical questions. The authors correctly discerned "yes" or "no" answers based on semi-quantitative examination of the activation patterns in 5 of 6 questions[6]. In the following years, experiments using a similar fMRI paradigm have variably replicated this result[53, 54].

Evidence for CMD in acutely brain-injured patients has been investigated after severe TBI[55]. Four of 8 patients who did not have behavioral evidence of language function (VS or MCS-) showed brain activation in the relevant regions in response to motor imagery instructions[55]. However, only 50% of TBI patients *with* behavioral language function (MCS +) and 75% of healthy controls had a positive response[55], underscoring the high false negative rate for this emerging technique.

One hypothesis for the mechanism of CMD is that neural circuitry is intact for motor planning but disrupted for execution. A dynamic causal modeling fMRI study proposed that thalamus to supplementary motor area (SMA) connections are responsible for motor planning and excitatory coupling of the thalamus and primary motor cortex is responsible for motor execution[56]. Diffusion MRI subsequently demonstrated reduced thalamo-motor cortex fiber integrity but preserved thalamo-SMA integrity in a DoC (VS) patient with CMD[56].

In summary, there are patients without behavioral awareness who demonstrate stimulus and task-based fMRI activations that are similar to healthy control subjects[57]. The ability to use fMRI and other advanced neurodiagnostic paradigms to achieve reliable communication in DoC patients may be the ultimate standard by which their sensitivity is assessed, as there exists no gold standard for the detection of consciousness.

Predicting recovery in brain-injured patients

A final important goal of MRI in brain-injured patients is to develop imaging biomarkers of recovery potential. This work has incorporated hypothesis-based and data-driven approaches using structural and functional MRI across types of brain injury and recovery time scales.

Many of the same functional brain network properties identified from studies of neural correlates of consciousness, particularly the connectivity within the DMN and between the DMN and other networks, have emerged as relevant for identifying DoC patients who will recover awareness. Two studies of patients with DoC of variable duration after heterogenous brain injuries employed data-driven approaches to identify rs-fMRI features capable of classifying patients based on either 3-month[43] or 1-year[58] recovery of awareness (emergence from VS). In these studies, the spatial distribution of the DMN and executive control networks[58], connectivity strength within a central node of the DMN[43], and the magnitude of anticorrelation between DMN and the salience or executive control networks[43, 58] were all associated with recovery of awareness. In the larger study[58], the model incorporating these rs-fMRI features had classification accuracy approaching 90% in two validation datasets and was superior to a model with only clinical features.

Functional integrity of the DMN, and DMN-salience network anticorrelations, have also been studied to test their prognostic relevance in the immediate days to weeks after an acute brain injury. Intrinsic DMN connectivity differed between eight patients with favorable compared to nine with poor functional outcome at hospital discharge among patients unconscious after cardiac arrest[59]. DMN connectivity also tracked with level of consciousness[45] and near-term recovery of awareness[60] after TBI. Among 46 unconscious post-arrest patients, intrinsic connectivity within the DMN, and DMN-salience anti-correlation, were most significantly different between patients with favorable and unfavorable outcome, compared with measurements generated from four other functional networks[61].

There is emerging evidence that diffusion MRI can be used to prognosticate in patients with DoC after different types of acute brain injury. In patients who are unconscious after an acute TBI, regional white matter integrity, quantified as fractional anisotropy (FA) or mean diffusivity (MD), is a significant predictor of recovery[62]. A classifier built on diffusion parameter values at 20 white matter ROIs was superior at discriminating poor 6-month outcome (death or DoC) to a standard clinical TBI prognostication model[63] in both a training and validation dataset[62]. Furthermore, a threshold was identified beyond which no patient recovered beyond MCS[62].

Diffusion MRI has also shown promise in outcome prediction for post-cardiac arrest (hypoxic-ischemic) coma. Several recent studies have suggested that percentage of brain volume with apparent diffusion coefficient (ADC) less than a threshold value discriminates good from poor outcome better than does the neurological exam, with 100%[64, 65] or near 100%[66] specificity for poor outcome. Perhaps due to technical challenges with this technique, including time-dependent ADC signal changes[65] and variable definitions of the burden of signal abnormality (e.g. global average versus percent below threshold), other studies have found it to be less-predictive[67] or with false-positivity problems[68].

The largest study in hypoxic-ischemic coma used diffusion MRI in 150 patients across multiple centers to predict functional recovery at six months[67]. A machine learning derived whole white matter FA score discriminated between favorable and poor outcomes with better accuracy than clinical features, EEG, qualitative MRI abnormalities, or whole brain ADC, with 100% specificity for poor outcome. This result was robust to the exclusion of patients with withdrawal of life-sustaining therapy, and the identified FA threshold retained 100% specificity for poor-outcome in an independent, prospective replication cohort[67].

Structure vs Function

Whether structural or functional MRI features more readily predict outcome in DoC remains to be seen. Challenges in comparing across studies include different time-frames of enrollments (e.g. acute versus chronic), different analytic approaches in deriving the imaging features, and different outcome definitions (e.g. recovery of awareness versus good functional outcome). Outcome definition is particularly important given that recovery of consciousness, defined as emergence beyond VS, may occur despite profound disability. Several studies have compared the predictive utility of structural and functional MRI features following hypoxic-ischemic[61, 69] or both traumatic and hypoxic-ischemic[18] coma, but given small sample sizes, different modeling techniques, and different outcome definitions, it is difficult to arrive at a conclusion.

Thus far, in both traumatic and hypoxic-ischemic coma, multi-focal[62] and global[67] assessment of white matter integrity using diffusion parameters has been most rigorously shown to identify patients with a low likelihood of meaningful functional recovery at 6 months. While structural features may hold promise in identifying patients with insurmountable burdens of injury, confidently identifying those who will have a good outcome may be more challenging. fMRI is being actively studied in this context: intrinsic functional connectivity within the DMN as well as DMN anti-correlations with the salience network hold promise for prediction of recovery of awareness among patients with established brain injury[43, 58]. Furthermore, preserved intrinsic DMN functional connectivity was recently demonstrated in a patient with prolonged DoC and structural brain injury after COVID-19 who subsequently recovered consciousness[70].

Conclusions:

Applications of MRI in patients with DoC have rapidly expanded over the last 20 years, but much work remains to be done. Sophisticated mapping of brain injury patterns, network connectivity and functional network dynamics are highlighting differences between conscious and unconscious brains. In brain-injured patients, the observation that elements of cortical processing may mirror those of healthy controls has been a revelation – one that has reshaped diagnostic classification of these patients[9, 52] and launched many new lines of investigation[10]. Finally, the use of multiple MR modalities in different clinical contexts has already demonstrated a significant improvement compared to the use of clinical features alone in DoC neuroprognostication.

Many different techniques and analytic frameworks exist, and it is difficult to prioritize one over another. Over the next 20 years, it will be important to test preliminary findings identified with a particular technique/modality for replicability and performance in independent, prospective cohorts, to avoid confirmation bias and model overfitting. Ongoing, careful behavioral characterization of DoC patients as well as standardizing relevant outcome definitions will help to further refine the use of these powerful tools.

Financial Support and Sponsorship:

This work was supported by the NIH National Institute of Neurological Disorders and Stroke (R21NS109627, RF1NS115268), NIH Director's Office (DP2 HD101400), James S. McDonnell Foundation, and Tiny Blue Dot Foundation.

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Summary points

1. MRI in brain-injured patients with disorders of consciousness (DoC) yields insights into the neural correlates of consciousness and can identify patients with covert consciousness.
2. Structural MRI has demonstrated diffuse brain abnormalities in DoC patients, with multiple areas in which level of injury correlates with level of awareness.
3. Resting state fMRI in DoC patients has demonstrated that connectivity within multiple networks, including the default mode network, correlates with level of awareness.
4. Covertly conscious patients can be identified using task-based fMRI paradigms.
5. Focal and global fractional anisotropy, intrinsic default mode network (DMN) connectivity, and DMN anti-correlations are promising biomarkers for functional recovery after acute brain injury.

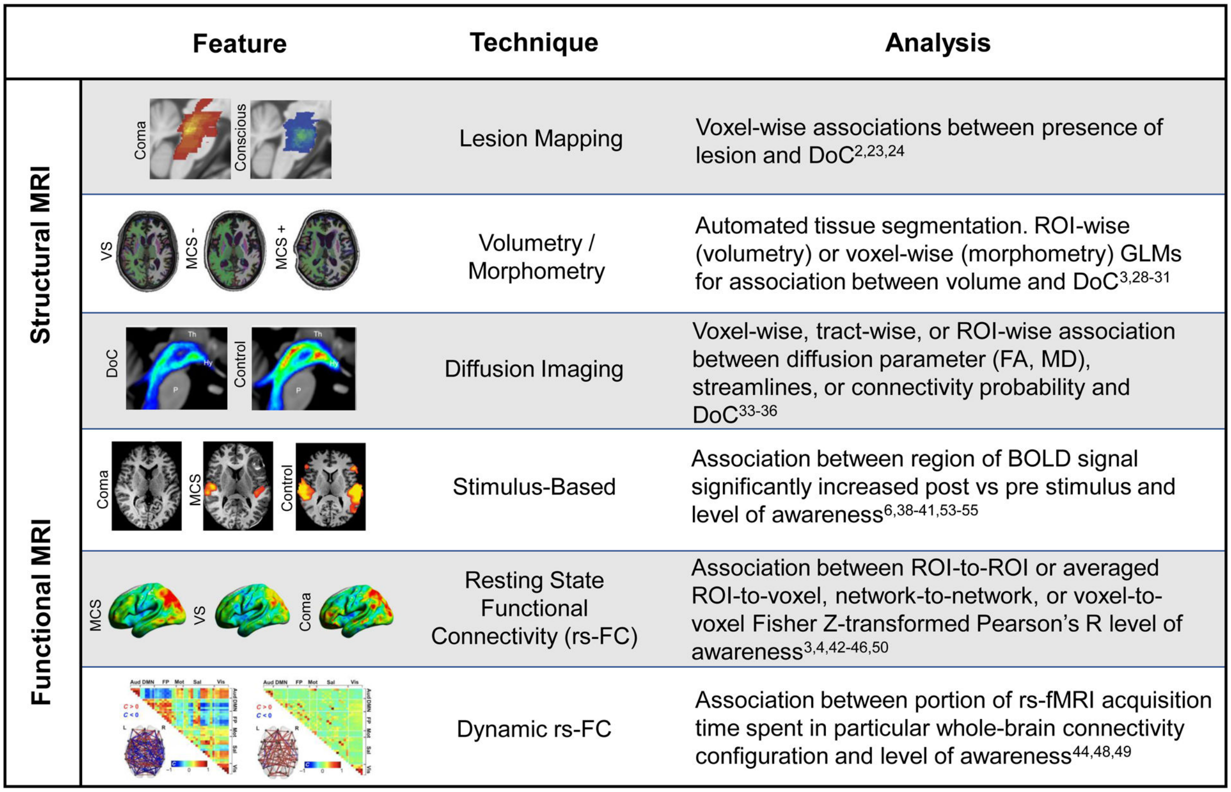

Figure. Structural and Functional MRI in DoC.

Schematic view of different MRI techniques used to investigate neural correlates of consciousness. The images in the *Feature* column are adapted from the following manuscripts: Lesion mapping adapted from Fischer et al. 2016[2], volumetry adapted from Annen et al. 2018[29], diffusion adapted from Snider et al. 2019[34], stimulus-based from Edlow et al. 2017[55], resting-state adapted from Wu et al. 2015[43], dynamic resting-state adapted from Demertzi et al. 2019[48].