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Applications of advanced MRI to disorders of consciousness

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Abstract

Disorders of consciousness (DoC) after severe brain injury present numerous challenges to clinicians, as the diagnosis, prognosis, and management are often uncertain. Magnetic resonance imaging (MRI) has long been used to evaluate brain structure in patients with DoC. More recently, advances in MRI technology have permitted more detailed investigations of the brain's structural integrity (via diffusion MRI) and function (via functional MRI). A growing literature has begun to show that these advanced forms of MRI may improve our understanding of DoC pathophysiology, facilitate the identification of patient consciousness, and improve the accuracy of clinical prognostication. Here we review the emerging evidence for the application of advanced MRI for patients with DoC.

Introduction

After severe brain injury, a subset of patients develop a disorder of consciousness (DoC), which presents several challenges to clinicians. In part because the pathophysiology of DoC remains poorly understood, it can be difficult to characterize a patient's current level of consciousness and capacity for future recovery. As such, the conventional clinical tools used to diagnose and prognosticate in DoC are limited, and management of these patients is susceptible to error[1-3]. The ramifications of such error can be profound – given that decisions about withdrawing life-sustaining treatment often hinge on these determinations of diagnosis and prognosis, an erroneous evaluation can lead to avoidable mortality or disability that the patient would consider unacceptably severe.

Conventional structural magnetic resonance imaging (MRI) sequences – those that are routinely acquired in current clinical practice, including T1, T2, diffusion-weighted, and susceptibility-weighted imaging – enable the visualization of brain lesions and have long aided the management of DoC. Across etiologies of brain injury – such as ischemic stroke, hypoxic-ischemic brain injury after cardiac arrest, and traumatic brain injury (TBI) – conventional MRI lends important insights into the degree of structural damage[4, 5]. However, conventional MRI has limitations. Some forms of neuronal injury – such as diffuse axonal injury or anoxia – may be too subtle to be detected with the resolution and sequences typical of conventional MRI. Moreover, conventional MRI only probes brain structure, and does not measure brain function.

Recent advances in MRI technology, and particularly innovations in the acquisition and analysis of MRI data, have permitted more detailed investigations of the

brain's structural integrity – via diffusion MRI (dMRI) – and function – via functional MRI (fMRI). Though not yet standard in routine clinical practice, emerging literature suggests that these forms of 'advanced MRI' can be used to understand and manage DoC in three primary ways (Figure 1)[6, 7]. First, advanced MRI may lend insight into the pathophysiology of DoC[8]. Second, advanced MRI may help identify evidence of conscious awareness in patients without behavioral signs of awareness[9]. And third, advanced MRI may help predict neurologic recovery and outcomes, which is crucial for effective neuroprognostication[10, 11]. Here we review studies that have suggested the potential utility of advanced MRI in the understanding and clinical management of DoC.

Pathophysiology of DoC

Advanced MRI has enabled the investigation of the pathophysiology of DoC in living patients, and the exploration of the neural underpinnings of consciousness more generally. These investigations build on insights from studies using animal experimentation and conventional MRI, which have demonstrated that lesions capable of producing coma often occur in the pontine and midbrain tegmentum[12-14]. However, many patients with DoC do not have overt brainstem injury[15-17], which suggests that the neurophysiology of consciousness involves structures outside the brainstem as well. Advanced MRI helps to explore these complexities.

fMRI measures a blood-oxygen-level-dependent (BOLD) signal across the brain. As neuronal activity in a region of the brain increases, so too does the BOLD signal; fMRI therefore offers a means of indirectly assessing regional patterns of brain activity. fMRI is chiefly used in two ways: to study the brain activity in response to a stimulus, or

to study the brain activity at rest (i.e., when the patient is not engaged in tasks or exposed to stimuli).

Stimulus-based fMRI revealed that, in response to an auditory stimulus, patients with DoC (specifically those in a vegetative state, who are thought to be awake but unaware) maintain activation of the primary auditory cortex, but lose the typical activation of the auditory association areas[18]. Some have theorized that the loss of conscious awareness in DoC may be characterized by dysfunction of higher-order sensory and association cortices[19-21].

Resting-state fMRI evaluates the coherence of activity across distributed brain regions in people at rest. Resting-state functional connectivity between brain regions is defined as the temporal correlation between fluctuations in the BOLD signal across brain regions[22]. Resting-state functional networks are collections of brain regions that are functionally connected. Though there are several such networks[23], the default mode network (DMN)[24, 25] has been most extensively studied in the context of DoC[26, 27]. The DMN becomes active in individuals not engaged in tasks, and includes the medial prefrontal cortex, posterior cingulate cortex, and inferior parietal lobule[24, 25].

A growing body of literature has implicated the DMN in consciousness and self-referential processes, and has found abnormalities of DMN connectivity associated with DoC[26, 27]. Among patients with DoC, higher levels of DMN connectivity correlate with higher levels of consciousness[28]. However, DMN connectivity alone is not sufficient for consciousness, as patients may remain unconscious despite intact DMN connectivity[29]. Rather, consciousness likely depends on multiple networks. For example, a recent study found that functional connectivity within many distributed brain networks was

associated with level of consciousness among patients with DoC, most significantly within the auditory network[30]. Other studies have indicated that alongside regions of the DMN, the salience network and executive control network – networks that become active when one is engaged in a cognitive task (i.e., "task-positive" networks)[31] – also correlate with levels of consciousness[32]. Negative functional correlations (i.e., anticorrelations) between the DMN and task-positive resting-state networks correlate with levels of consciousness as well, further suggesting that the interplay between networks may play an important role in sustaining consciousness[33-35].

Traditionally, the entire resting state fMRI acquisition is analyzed to yield a single estimate of functional connectivity for a given network. An emerging method of investigation examines changes in resting state functional connectivity patterns (i.e., brain states) over time during the acquisition period. Studies investigating changes in connectivity patterns over time have found that the traditional DMN connectivity configuration occurs less frequently in patients with DoC[36], and that the frequency of connectivity changes[37] and the number of transitions between states[38] correlate with a patient's level of consciousness.

In patients with DoC, advanced MRI offers not only the opportunity to study brain function, but also enables more detailed analyses of structural abnormalities. dMRI characterizes the movement of water molecules within tissue environments and is affected by changes in tissue composition and structure[39], facilitating insights into pathophysiological processes. In particular, it enables the three-dimensional reconstruction of major myelinated fiber bundles through tractography and evaluation of the white matter structural integrity with measurements of fractional anisotropy or mean

diffusivity. dMRI often shows diffuse axonal abnormalities in patients with DoC[40], including diminished network integration of the basal ganglia and thalamus[40], diminished structural connectivity between the thalamus and cortex[41], and diminished axonal integrity of the ascending arousal network[42]. Other network-specific investigations have shown patients with DoC to have reduced fractional anisotropy (lower structural integrity) of white matter tracts within the DMN, and of tracts connecting the DMN to the thalamus[26]. Of note, dMRI has demonstrated different types of abnormalities in different etiologies of brain injury; for example, TBI appears to cause more white matter injury in the brainstem than hypoxic-ischemic injury[43].

High resolution, T1 weighted structural MRI, can also be used to precisely map regional abnormalities and cortical thickness and volume. In patents with DoC who do not have focal damage to the rostral-dorsal brainstem, studies have uniformly found multifocal or diffuse brain structural abnormalities[33, 44, 45].

A consensus grey/white matter signature of DoC does not yet exist. Though many abnormalities have been shown to reliably differentiate patients with DoC from controls, we do not yet have a validated set of regions or connections that can robustly stratify DoC patients by level of consciousness.

Cognitive Motor Dissociation

Advanced MRI, specifically task-based fMRI, can be used to detect evidence of conscious awareness in patients who may otherwise appear unconscious, a phenomenon termed “cognitive motor dissociation” (CMD) or “covert consciousness”[9]. A

seminal report in 2006 demonstrated that a patient who appeared unconscious after TBI was able to willfully modulate their brain activity in response to commands – when instructed to imagine playing tennis, she demonstrated activity in the supplementary motor area, and when instructed to imagine walking through her house, she demonstrated activity in regions associated with spatial perception[46]. In a cohort of 54 patients with chronic DoC, five showed similar modulation of brain activity in response to instructions, and one could reliably answer yes or no questions using this paradigm[47]. In a cohort of 16 patients with acute DoC following severe TBI, four demonstrated evidence of CMD on task-based fMRI[48]. However, only 50% of patients with behavioral evidence of conscious awareness and 75% of healthy controls were able to willfully modulate their brain activity[48], underscoring the high false negative rate for this paradigm.

CMD may be caused by the disruption of neural circuity necessary for motor execution, despite intact circuitry necessary for motor planning. dMRI has indeed shown reduced integrity of fibers connecting the thalamus and motor cortex (thought to be necessary for execution of motor functions), but preserved integrity of fibers connecting the thalamus and supplementary motor area (thought to be necessary for motor planning) in a patient with CMD[49]. This finding was replicated in a larger cohort, suggesting that conventional behavioral assessments may underestimate the true level of awareness in patients with DoC [50].

Given a growing literature highlighting the importance of detecting CMD, clinical organizations have begun to endorse the clinical application of advanced MRI for this purpose[51, 52]. If clinically considering advanced MRI for the detection of CMD, there are

several factors to take into account. Though many of these factors have been reviewed in depth elsewhere[53], we propose a simplified overview of these considerations in Figure 2. First, clinicians should ensure that they are selecting the appropriate patient population – patients who appear unconscious due to brain injury. Second, clinicians should pursue a detailed behavioral examination, such as with the Coma Recovery Scale Revised[54], which may reveal subtle signs of conscious awareness. Third, if the behavioral examination does not reveal evidence of conscious awareness, clinicians should evaluate whether the possibility of CMD is important enough to justify more advanced diagnostics. For example, if life-sustaining treatment will be continued regardless of whether CMD is present, detecting CMD may be less important. Determining whether patients should be spoken to as if conscious is an insufficient justification for pursuing advanced diagnostics; given that such technologies have imperfect sensitivity for CMD – advanced MRI may overlook some patients with intact conscious awareness[48] – we advocate for interacting with all patients as if they were conscious. While the detection of CMD may eventually be important for establishing new methods of communication (e.g., brain computer interfaces), such technologies are currently not widely available. Fourth, if the evaluation of CMD is deemed sufficiently important to pursue advanced MRI, the clinician should ensure that their institution is capable of acquiring, analyzing and interpreting advanced MRI. Fifth, the clinician should ensure that the patient (who may be critically ill) can safely travel to the MRI scanner and undergo an MRI scan. Sixth, given that task-based MRI requires that commands are delivered to the patient, the clinician should evaluate whether there are any factors that would prohibit the effective delivery of those commands (hearing loss,

heavy sedation). If these factors can be eliminated, and all of the earlier conditions are met, it would be reasonable for clinicians to pursue advanced MRI for the detection of CMD.

If advanced MRI is pursued clinically for the detection of CMD, there are several other factors to consider. Sedation should be minimized to the extent possible, while also ensuring that the patient remains safe, comfortable, and immobile (since movement can be particularly deleterious to fMRI signal)[55]. Because the brains of patients DoC often have large lesions or mechanical distortions, fMRI data analysis should use registration or segmentation methods robust to such abnormalities, and should visually inspect all data for quality control. When interpreting and communicating the results of the fMRI, clinicians should remain mindful of the imperfect sensitivity of this technique and be careful not to overinterpret the significance of a negative result. For example, patients with aphasia or inattention may show no evidence of CMD on advanced MRI, though they remain conscious. Moreover, patients may have fluctuant levels of consciousness, and so the inability to detect CMD at one time point does not exclude its presence at another.

Neuroprognostication

An important component of management for patients with DoC is predicting the likelihood of neurologic recovery, termed neuroprognostication. Accurate neuroprognostication is crucial, as a poor neurologic prognosis often becomes the impetus for withdrawing life-sustaining treatment, which most often leads to death[3, 56-58]. However, the conventional tools typically relied upon for neuroprognostication – e.g.,

the physical exam, conventional MRI and electroencephalography – have imperfect prognostic value[59]. As such, advanced MRI may supplement the prediction of neurologic recovery for patients with DoC, in terms of regaining both consciousness and function.

Stimulus-based fMRI has indicated that patients with DoC who demonstrate activity of sensory cortices in response to sensory stimuli may demonstrate more robust recovery in the following months[60-62]. Numerous studies have also investigated the prognostic value of resting-state functional connectivity in patients with DoC, across different mechanisms of brain injury[10, 29, 63-70]. While most studies have evaluated the prognostic value of DMN connectivity, others evaluated connectivity between the DMN and other networks[10], evaluated connectivity within other networks[10, 65, 71], or evaluated whole brain connectivity (i.e., matrices of connectivity between many regions across many networks)[65, 67]. Despite methodological differences, these studies have similarly shown that patients with more robust functional connectivity are more likely to demonstrate improvements in their level of consciousness and neurologic function over time. The sensitivity for predicting recovery ranged from 72-100%, and the specificity from 64-94%, though functional connectivity measures and definitions of recovery varied between studies[65, 67, 68]. Preliminary data suggest that functional connectivity may more accurately predict recovery than conventional biomarkers, such as clinical data, laboratory data, or conventional MRI[10, 65, 67, 68]. Of note, there are numerous extraneous factors that can reduce measured functional connectivity, such as patient movement in the scanner[72], sedation[73-77], and toxic-metabolic derangements[78]. Therefore, while intact functional connectivity may indicate an intact substrate for behavioral improvement,

diminished functional connectivity does not necessarily indicate an irreversibly injured neurological substrate. While most assessments evaluate for evidence of neural injury that may reflect a poor prognosis, fMRI instead most effectively evaluates for evidence of intact brain function that may reflect a favorable prognosis.

dMRI may also help prognosticate for patients with DoC. After TBI, white matter integrity measured by dMRI predicts the degree of functional recovery at one year, and outperforms the IMPACT score (a clinical prognostic model) for moderate-to-severe TBI[79, 80] Among patients with hypoxic-ischemic brain injury, whole brain white matter fractional anisotropy predicted 6-month outcomes more accurately than clinical data, electroencephalography, or conventional MRI[11]. The sensitivity of dMRI for predicting a poor neurologic outcome has ranged from 64-94%, and specificity from 85-100%[11, 80-83]. Larger studies evaluating different etiologies of DoC, and integrating advanced MRI with other prognostic biomarkers, will facilitate the clinical application of these technologies.

Given the research above indicating the prognostic value of advanced MRI, the clinical application of these technologies has recently been endorsed[52]. As with advanced MRI for CMD, there are several factors to consider if clinically pursuing advanced MRI for neuroprognostication, which are summarized in Figure 3. First, clinicians should ensure that the patient population is appropriate, as only certain brain injury etiologies – including traumatic brain injury, anoxic brain injury after cardiac arrest, and vascular injury – have been studied in the context of advanced MRI for neuroprognostication[10, 29, 63-70]. In contrast, while brain network dysfunction has been observed in other etiologies of disordered consciousness – such as toxic-metabolic encephalopathy[78] – advanced MRI has not yet been shown to have prognostic value in

these conditions. Second, clinicians should initially pursue conventional prognostic biomarkers, such as the physical exam, conventional brain imaging, and other conventional biomarkers relevant to the brain injury under evaluation; if conventional biomarkers reveal a clear prognosis, advanced techniques may not be necessary. Third, if conventional biomarkers do not reveal a clear prognosis, clinicians should evaluate whether the importance of a clear prognosis justifies advanced techniques; for example, if life-sustaining treatment will be continued regardless of the results, advanced MRI may not be worth pursuing. Fourth, the clinician should ensure that their institution is capable of acquiring, analyzing and interpreting advanced MRI. Fifth, the clinician should ensure that the patient (who may be critically ill) can safely travel to the MRI scanner and undergo an MRI scan. Sixth, if pursuing fMRI, the clinician should minimize any factors that could interfere with brain function and reduce functional connectivity, such as sedation and toxic-metabolic insults[73-78] (although of note, mild sedation may not significantly interfere with functional connectivity[84]). dMRI can be pursued regardless of these factors that impede brain function.

If advanced MRI is pursued clinically for neuroprognostication, there are several other factors to consider. Like with advanced MRI for CMD, sedation should be minimized while also ensuring that the patient remains safe, comfortable, and immobile; mechanical distortion of the brain should be considered when analyzing the results; and clinicians should remain careful not to overinterpret the significance of a negative result, as diminished functional/structural connectivity can be caused by extraneous factors such as movement artifact, and do not necessarily indicate a poor neurologic prognosis. In addition, for techniques such as resting-state fMRI and dMRI, a comparator dataset

(either from previous patients or healthy controls evaluated on the same MRI scanner) may be necessary to establish a range of normal values, and to help determine whether a given patient deviates from this range.

Future Directions

There remain several potential avenues for the application of advanced MRI to DoC. First, though both fMRI and dMRI have advantages, a multimodal approach that combines the two, and synthesizes them with other conventional tools, may lend even greater insights into DoC[27, 51, 52, 69, 85, 86]. Second, there is an opportunity to optimize how advanced MRI data are collected, as ongoing research explores techniques to improve resolution[87, 88], eliminate sources of physiologic noise[89-94], and minimize the effects of confounders[72-78]. Third, the most effective way of analyzing and interpreting the data acquired with advanced MRI remains an active topic of investigation. While many dMRI studies investigate the prognostic value of whole brain white matter integrity, a more targeted assessment of specific tracts may yield additional insights. And while many fMRI studies have evaluated connectivity of individual functional networks, more advanced statistical tools may help decipher the complexity of network function necessary for sustaining consciosuness[95, 96]. Finally, and perhaps most importantly, structural and/or functional connectomics may ultimately facilitate the development of new therapeutic strategies. For example, while prior research suggests that brain stimulation[97] may have a therapeutic effect in DoC, this effect may be optimized by targeting networks important for consciousness[98-100]. Similarly, while pharmacologic

stimulants have demonstrated modest efficacy in improving levels of consciousness[97], efficacy may be higher in patients with intact arousal circuitry[94].

Conclusions

Advanced MRI – including both functional imaging and diffusion imaging – has significant potential to improve our understanding of the pathophysiology of DoC, our detection of conscious awareness, and our ability to predict recovery. There remain limitations to MRI – not all institutions have the necessary equipment, not all patients can safely undergo an MRI, MRI scans are costly, advanced MRI requires specialized expertise for analysis and interpretation, and there is still much research to be done to validate the application of these technologies. Nonetheless, the compelling evidence to date has led several organizations, including the American Academy of Neurology, the American Congress of Rehabilitation Medicine, the National Institute on Disability, Independent Living, and Rehabilitation Research, and the European Academy of Neurology, to endorse the clinical use of advanced MRI for patients with DoC[51, 52].

The uncertainty that plagues DoC has profound ramifications, as evidence of consciousness may be overlooked, decisions about life-sustaining treatment may be based on erroneous prognostic predictions, and therapeutic options remain limited. Supplementing our management of these complex disorders with advanced MRI may improve the management of the patients who suffer from them.

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