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Multimodal Neuroimaging Approaches to Disorders of Consciousness

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Advances in neuroimaging techniques hold significant promise for improving understanding of disorders of consciousness arising from severe brain injuries. We review neuroimaging studies of the vegetative state (VS) and minimally conscious state (MCS), and findings in an unusual case of late emergence from MCS. Multimodal neuroimaging studies using positron emission tomography techniques, functional magnetic resonance imaging, and quantitative electroencephalography and magnetoencephalography quantify variations of residual cerebral activity across these patient populations. The results suggest models to distinguish the pathophysiologic basis of VS and MCS. Less clear are potential brain mechanisms underlying late recovery of communication in rare MCS patients. Diffusion tensor magnetic resonance imaging studies and recent experimental findings suggest that structural remodeling of the brain following severe injury may play a role in late functional recoveries. More generally, relatively long time courses of recovery following severe brain injury emphasize the need to develop markers for identifying patients who may harbor potential for further meaningful recovery. Introduction of neuroimaging into the clinical evaluation process will require developing frameworks for longitudinal assessments of cerebral function. Although limited in number, available studies already provide important insights into underlying brain mechanisms that may help guide development of such assessment strategies. **Key words:** *axonal regrowth*, *minimally conscious state*, *traumatic brain injury*, *vegetative state*

DISORDERS of consciousness following severe traumatic brain injury (TBI) present unique challenges. Often the history, physical examination, and structural imaging studies that form the foundation of such neurologic practice are of limited prognostic value. No clinical endpoint underscores the problem more clearly than the rare cases of patients who recover significant functions despite very severe TBI and extended periods of low-level bedside function. In all of the available well-documented cases, clinical features consistent with the minimally conscious state (MCS) have been presented within the first year following injury.[1] Such late recoveries from MCS are important because they reflect a clear and meaningful functional change in this patient population. The observations thus prompt a search for the neuronal basis of recovery of communication and goal-directed behavior in the severely brain-injured patient. As discussed below, the combined use of neuroimaging modalities offers some hope of disambiguating the basis of such late clinical changes and developing frameworks to "risk stratify" the likelihood of an individual patient recovering function over long periods. At present, however, several challenges will limit application of neuroimaging

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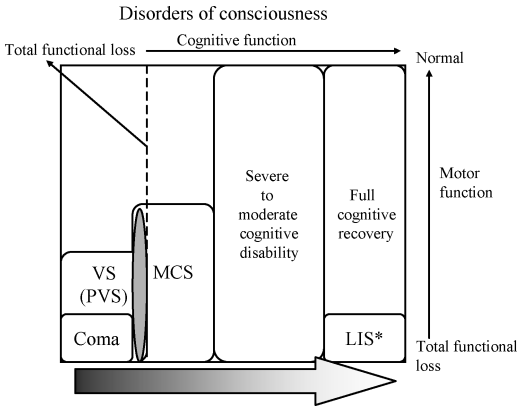

Figure 1. Conceptual scheme for global disorders of consciousness. Abbreviations: VS, vegetative state; PVS, persistent vegetative state; MCS, minimally conscious state; and LIS, locked-in state. Asterisk indicates that LIS is not a disorder of consciousness. (Reproduced from MIT Press with permission.)

techniques to assess level of awareness, prognosis, or guide rehabilitative efforts.[2–4]

The importance of developing neuroimaging capabilities is further underscored by current trends of more aggressive intensive care unit management, thus leading to reduced deaths and a possibly changing natural history of recovery for patients. As discussed below, time intervals for recovery may be long for some patients evolving to levels higher than the vegetative state (VS) following TBI. In addition, shortening of stays within the acute care hospital and rehabilitation facilities may limit a patient's access to skilled professionals able to detect cognitive changes in a patient with severe brain damage and motor dysfunction. Developing reliable functional imaging assessments to longitudinally evaluate patients over long time courses of functional recovery may help to mitigate risks of misdiagnosis and identify patients with the potential for further recovery.

NOSOLOGY AND PROGNOSTIC TIME COURSES FOR RECOVERY OF FUNCTION

Figure 1 provides the organization of disorders of consciousness with respect to the level of motor and cognitive functions. The large arrow with shading from black to white across the bottom of the diagram indicates the increasing difficulty of identifying patients who may recover significant cognitive function but not motor function within the middle gray zone of the arrow and to the right. On the far right bottom of the figure is the locked-in state (LIS), reflecting the endpoint of total preservation of cognitive function without motor capacity. Locked-in state is not a disorder of consciousness, and observations of patients in this condition provide several instructive points for consideration. Acute brain injuries producing LIS typically involve the ventral pontine regions and because of the proximity of brainstem arousal systems located more dorsally in the upper pons and midbrain, it is common for patients to experience an initial phase clinically consistent with coma. Recovery of inconsistent motor responses usually occurs within a few days of the injury similar to those observed in MCS patients.[5] Nonetheless, in most cases, the risk of LIS should be possible to anticipate on the basis of the initial clinical findings and structural imaging studies. Despite this context, in a survey of 44 LIS patients, the mean time of diagnosis was 2.5 months, and in more than one half of the patient's experiences a family member and not a physician first recognized the condition.[6] Thus, the clinical examinations of patients with severe motor impairment can be expected to present significant limitations in the setting of coexisting mild or moderate cognitive impairment.

At the other extreme on the lower left of the figure is brain death, an unequivocal diagnostic category with no attached prognosis.[7] The condition reflects neuronal death throughout the brain and brainstem. Brain imaging in brain death should confirm a complete loss of blood flow to the organ and no measured metabolic activity. Moving to the right across the bottom of the figure, coma and the VS are conditions characterized by unresponsiveness. Comatose patients show no variations in state and typically eyes remain closed with no response to the most vigorous stimulation.

In VS, patients recover a crude sleep-wake cycling reflected by irregular periods of eye opening and eye closure usually without identifiable electroencephalographic features of either sleep or normal wakefulness (see reference 8 for review). Prognosis of VS following TBI worsens considerably over time, however, even patients remaining in VS at 6 months following TBI patients have a 16% probability of recovery of consciousness, with rare recovery of independent function at this late time point.[9] Patients remaining in VS at 1 year following TBI are considered to transition into a permanent VS.[10]

Abutting VS on Figure 1 is a gray zone indicating a group of patients with atypical clinical features who nonetheless fulfill the VS criteria of showing no response to external stimulation or evidence of intentional behaviors[11,12] (see discussion below). Patients enter into the MCS once they demonstrate at bedside, unequivocal but inconsistent evidence of awareness of self or the environment.[1] Clinical features across the spectrum of MCS are quite broad.[13] Some patients may show little variation from the VS patients within the gray zone other than a reliable, if infrequent, demonstration of contingent responses to environmental stimuli. Most MCS patients show wide fluctuations in their demonstration of behaviors that may include verbal and gestural communications. Accordingly, the upper boundary of the figure determining a patient's emergence from MCS indicates reliable communication. At present, no data support establishing a predictive time frame for emergence from MCS following severe brain injuries. Moreover, recent studies of functional outcome after 5 years from injury demonstrate a lack of correlation of time in MCS and ultimate level of recovery.[14] As an endpoint, some carefully studied MCS patients have shown significant changes in their capacity to communicate, arising more than 5 years after the initial injuries.[15,16] To date, such very late functional recoveries have invariably been associated with TBI.

The variable time course of cognitive recovery and increasing likelihood of worsening motor disability over time following severe TBI suggest that some patients may recover integrative brain function past the point of professional involvement in their care when they are burdened by significant immobility. When motor function is severely impaired, recognition of intermediate states between MCS and LIS will present a difficult challenge. The cohort of patients recovering to the level of MCS within the first year of injury may be at the most risk based on the strong likelihood that many could continue to recover significant function.[14,17] After 3 months, or even soon after the end of acute inpatient management, it is unclear how many of these patients are carefully followed. Thus, the problem of conflating different disorders of consciousness should be a source of serious concern. For example, Wilson and colleagues[18] have detailed the experiences of a well-studied patient "Kate" (who has participated as a coauthor) during her slow recovery from encephalitis after initially remaining in VS for 6 months.[19] Notably, Kate reported being treated as mentally disabled for more than a year on the basis of her inability to organize an understandable motor output before skilled evaluators demonstrated her normal IQ through formal testing and provided her with appropriate communication devices. Some locked-in patients have given similar accounts of being treated as severely cognitively impaired over long periods.[20]

ANATOMICAL AND PHYSIOLOGICAL DISTINCTIONS BETWEEN VS AND MCS

Although the findings distinguishing VS and MCS patients on the clinical examination may be subtle, anatomic studies suggest significant variation in the underlying structural pathology associated with the two conditions. Patients remaining in VS for at least 3 months after TBI show a characteristic pathology of severe damage to the thalamus, a finding consistent with postanoxic VS pathology as well.[21] Most VS patients with TBI have suffered grade 2 or 3 diffuse axonal injury (DAI), and damage to the thalamus arises indirectly

as a result of transneuronal degeneration. The pathology demonstrates a wide disconnection of the corticothalamic system in VS and emphasizes the important role of the thalamus in providing the essential pass through for integration of cerebral networks.

Comparison of neuropathological findings in VS and MCS patients suggests that very different underlying anatomical substrates may be present in patients remaining in these states over relatively long periods. Jennett and colleagues[22] reviewed autopsy data from patients with severe disability, including a subgroup with clinical histories consistent with MCS. Roughly one half of the group of patients with severe disability demonstrated no evidence of thalamic injury or grade 2 or 3 DAI. No VS patient showed this pattern of injuries, however, 2 of the MCS patients did not evidence thalamic injury or significant DAI. These findings indicate a potential anatomical substrate for residual cerebral function in some patients with low-level clinical examinations consistent with MCS.

Measurements of resting brain metabolism have been used to place VS and other patients with severe disability on more equal footing. Several laboratories have identified strongly depressed cerebral metabolism in VS patients using fluoro-deoxyglucose positron emission tomography (FDG-PET).[11,23–27] Post-TBI, VS is associated with an overall reduction of global metabolic rate to ∼50% of normal metabolic rates or less in the "eyes-open" state. Similar levels of cerebral metabolism may be seen in pharmacologically induced coma.[2] FDG-PET measurements alone, however, provide only a limited benchmark to assess cerebral function following severe injuries. In a study of small number of VS patients using multimodal neuroimaging methods (FDG-PET, electroencephalography [EEG], magnetic resonance imaging [MRI], and magnetoencephalography [MEG]), regions' variations in cerebral metabolic rates were correlated in some patients with atypical behavioral fragments[11] (gray zone of Fig 1).

Figure 2 shows the combined results of FDG-PET measurements and MEG recordings from a patient who had remained in VS for 20 years but nonetheless rarely produced single understandable words unrelated to environmental stimulation.[28] Otherwise, the patient's examination was consistent with VS including a wakeful appearance without evidence of awareness or purposeful activity. In Figure 2A, regions of metabolic activity exceeding a threshold of 55% of normal metabolic rates are shaded gray. These small regions of preserved metabolism in the left cerebral hemisphere include Broca's area, temporal-parietal cortex including Heschl's gyrus and surrounding areas, and the left anterior basal ganglia (caudate nucleus, possibly putamen). Averaged MEG responses to repeated presentations of tones showed incompletely preserved patterns of spontaneous and evoked γ-band responses elicited from normal subject in response to the same stimuli (Figs 2C and D). The reconstruction of the sources of this time-varying magnetic field shows their origin in the left hemisphere in Heschl's gyrus, indicating the partial sparing of thalamocortical functional connectivity. In the aggregate, these findings support the inference that the patient's word emissions emanated from isolated thalamocortical-basal ganglia loops that support human language in intact brain. Other unusual behavioral fragments associated with isolated metabolic activity have been described in VS patients.[11]

The multimodal studies shown in Figure 2 can support observational inferences about the origin of behavioral variations but provide only limited insight into the function of distributed brain networks. To assess the functional connectivity of brain networks in VS and other conditions, functional PET and MRI techniques are necessary. In an important series of studies, Laureys and colleagues[26,27] examined a group of patients unequivocally fulfilling the diagnostic criteria for VS. Comparison of cortical activation patterns in response to simple auditory and somatosensory stimuli in the VS patients and normal controls showed a sharp reduction in the number of brain regions activated by the stimuli in

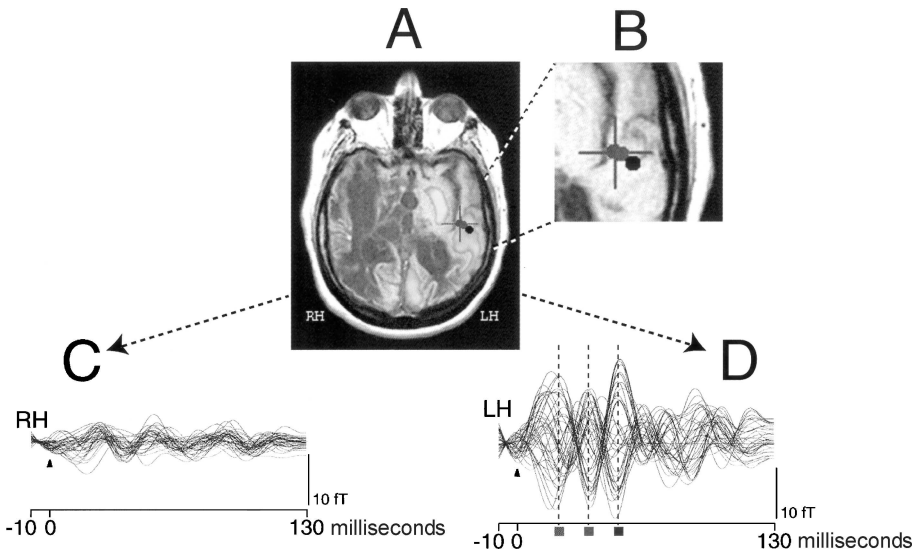

Figure 2. (A) Positron emission tomographic regions of interest demonstrating metabolism above a threshold of 5.5 mg 100 $g^{-1}mL^{-1}$ (regional cerebral metabolic rates for glucose [rCMRglc]) are displayed in yellow color coregistered magnetic resonance imaging and overlayed with locations of magnetoencephalographic (MEG) equivalent current dipoles having correlation of more than 97%. (B) MEG dipole locations. Crosshair and red dot correspond to dipole location of maximal response at a latency of 50 milliseconds. (C) MEG waveforms for right hemisphere γ-band (20–50 Hz filtered) mid-latency evoked activity in response to bilateral auditory stimulation. (D) MEG waveforms for left hemisphere γ-band (20–50 Hz filtered) mid-latency evoked activity in response to bilateral auditory stimulation. (Figure reproduced from Schiff et al,[28] MIT Press, with permission).

the VS group. Brain activations for the VS patients were restricted to the primary sensory cortices for both sensory stimuli and failed to activate the higher order cortical regions as observed in the control subjects. The results of these studies are consistent with a widespread functional disconnection across the corticothalamic system. The findings are also comparable to studies of EEG measured evoked potentials in VS patients. Although evoked potentials are typically present in VS patients following TBI, permanent VS is associated with the loss of the later components, reflecting the contribution of feedback from higher order cortical regions.[29] MEG measurements of evoked potentials in VS patients similarly identify the loss or abnormality of the evoked magnetic field in response to simple sensory stimuli.[11] Taken together, multimodal neuroimaging data along with more traditional pathologic and electrophysiologic studies suggest that VS correlates with a widely disconnected and inactive cerebrum.

The recent formalization of diagnostic criteria for MCS[1] has led to a number of recent neuroimaging studies aimed at delineating brain function associated with this condition.[30–34] Boly et al[30,31] reported findings in 5 MCS patients using functional PET activation paradigms originally applied to study VS patients. Compared to the earlier finding in VS patients, the MCS patients and healthy control subject in this study showed activated auditory association regions in the superior temporal gyrus and showed strong correlation of these auditory cortical responses with activity within the frontal cortex. Consistent with these studies, Schiff et al[34] studied 2 MCS patients using functional MRI (fMRI) activation paradigms and FDG-PET. This study compared fMRI responses during passive presentations of language and somatosensory stimuli.

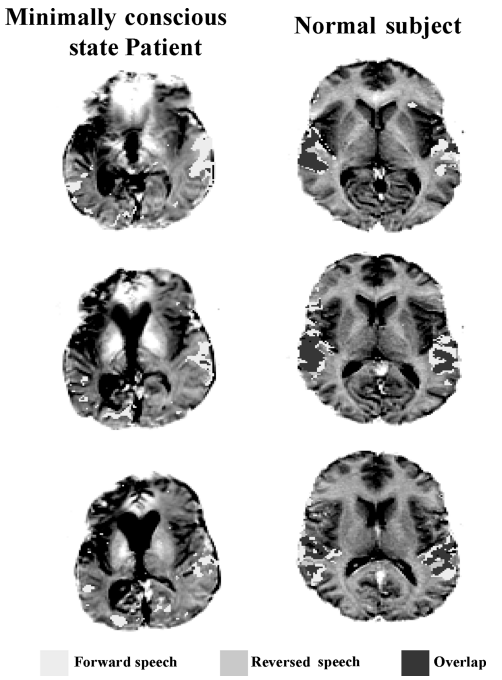

Figure 3. Images show functional magnetic resonance imaging activation patterns of BOLD signal in response to passive language presentations for a single patient in the minimally conscious state and a normal control subject. Forward narratives (light gray), time-reversed narratives (medium gray), overlap (dark gray); see text for further explanation.

As depicted in Figure 3, the MCS patients showed activated large-scale networks in response to narratives that were prerecorded by a familiar relative and presented as normal speech or played as time-reversed stimuli; overlapping response to both forward and time-reversed stimuli is also shown. The presentations of normal speech generated robust activity in several language-related areas in both patients. Regions of activation for an MCS patient and a normal subject are shown in the figure, and include the inferior and medial frontal gyri and superior and middle temporal gyri. Of note, the patient showed additional activations within the primary and secondary visual areas including the calcarine sulcus, inferior and middle occipital gyri, precuneus, cuneus, and inferior parietal lobule. For both MCS patients studied, the large-scale network activations arose only during forward speech, and not for reversed speech, whereas the normal control typically showed similar activation patterns for both stimuli (on average actually producing more activation for the time-reversed narratives). Schiff et al[34] proposed that the lack of activation seen for the time-reversed narratives reflects a loss of the anticipatory, goal-directed intentional activities that characterize the normal awake conscious state.[35] In support of this model, FDG-PET measurements during wakefulness in both patients demonstrated low-level functions consistent with those seen in VS patients, averaging ~50% of normal metabolic rates. The forward narrative may contain a variety of salient features (personal relevance, known speakers, emotional cues, etc) that can engage the language network. Similarly, the time-reversed narratives may simply fail to overcome very low resting neuronal activity at baseline to activate the patient's latent large-scale network processing capacities. Studies of both Boly et al[30,31] and Schiff et al[34] indicate a preservation of large-scale networks in MCS patients and prompt further investigations of the underlying differences in brain function between MCS patients and normal subjects. Related findings in other MCS patients include neuroimaging and electrophysiological evidence for selective activation in response to the subject's own name[33] and amgydala activation in response to a subject's mother's name.[32]

The demonstration of recruitable large-scale networks in MCS patients and electrophysiological evidence of semantic processing most important establishes a continuity of functional correlations of cognition in this patient population and normal subjects. The findings thus focus attention on improving our measurements of the quality of network interactions in MCS patient's brain. The findings of these studies also provide potential insight into the later recovery of function in some MCS patients who may retain widely integrative cerebral functions.

LATE EMERGENCE FROM MCS POSSIBLE MECHANISMS

Sporadic reports of late recovery of communication and goal-directed behavior following stable behavioral levels consistent with MCS continue to appear in the scientific literature and the lay press.[36–38] Although few of these patients have been evaluated with brain imaging and reported in the scientific literature, most reported cases involve TBI or injuries to the upper brainstem and thalamus. We have recently longitudinally characterized brain structural connectivity and functional activation profiles in a 40-year-old man who fully recovered expressive and receptive language after remaining in MCS for 19 years following a severe TBI.[39–41] The patient's recovery was spontaneous, and has been sustained for more than 2 years with further gradual clinical improvements.

In this patient, structural brain imaging studies reveal extensive cerebral and subcortical atrophy, particularly affecting the brainstem and frontal lobes with marked volume loss throughout the brain and ventricular dilatation. Evaluation of the patient's white matter regions using quantitative and qualitative analyses of diffusion tensor imaging data revealed very severe DAI.[39,40] As a surrogate marker for the severity of the overall injury, the medial corpus callosum showed a reduction of one-third to two-thirds normal volume throughout the structure. Aggregate measures of diffusion and fractional anisotropy and strength of directionality also showed marked abnormality compared with normal subjects; the quantitative indices revealed comparable features with another patient studied with severe DAI.

In addition to severe reduction of brain connectivity demonstrated in the diffusion tensor imaging data, the patient showed unusual large regions of increased connectivity (as measured by fractional anisotropy) and directionality in posterior brain structures not seen in 20 normal subjects.[16] The large, bilateral regions of posterior white matter anisotropy reduced in directionality when measured in a second diffusion tensor imaging study 18 months later. In contrast, marked increases in anisotropy arose within the midline cerebellar white matter in the second study that correlated with evident clinical improvements in motor functions. Both findings correlated with relatively increased resting metabolism measured by PET in the subregions, demonstrating changes in fractional anisotropy. These findings suggest the possibility of a slow variable of structural change playing a role in the patient's recovery. Related observations in other severely brain-injured patients also suggest the possibility of structural remodeling. For example, 5- and 10-year follow-up reports have provided tracking a patient who remained in MCS for 2 years after a severe TBI and then emerged to the point of indicating reliable yes or no responses.[15] Further recovery was documented 7 to 10 years later including the patient's regaining of the capacity to initiate conversation, express spontaneous humor, and indicate clear preferences. Danielsen and colleagues[42] reported longitudinal magnetic resonance spectroscopy (^{1}H-MRS) studies obtained from a patient with severe DAI who remained in coma for 3 months and gradually recovered over 21 months to a near independent functional level. Characteristic regional reductions of *N*-acetylaspartate/choline ratios associated with severe DAI were identified in the white matter that showed normalization at 21 months. Most likely, such improvements occurring over long periods involve both functional and associated structural changes in the brain; increasing neuronal activity may support organization of large-scale networks supporting goal-directed behavior, perception, and communication. Functional changes could lead to eventual remodeling of brain structure through several mechanisms.[42,43]

If slow structural changes do arise in the setting of severe TBI, this mechanism is likely to play a role in the recovery from TBI. Moreover, slow mechanisms for recovery may help in explaining the long time courses necessary for outcome prediction even in VS patients

following TBI. Many possible patterns of reconnection in the sparsely connected networks of the cortex could arise,[42] and it is unknown how many possible novel interactions may allow for recovery of communication and goal-directed behavior.

Other pathophysiologic mechanisms that may play an important role in late recovery of function include a variety of ongoing dynamic alterations following structural brain injuries (see discussion in reference 12). Such processes may limit the expression and use of large-scale network function in MCS patients who do retain wide functional connectivity of brain regions.

NEXT STEPS AND LIMITATIONS

The observations reviewed above suggest that longitudinal reassessment of brain function will be needed for some patients with severe injuries. However, it is unclear which patients should be tracked longitudinally, exactly which measurements should be obtained, and at what time points following injury the measurements should be taken. At present, insufficient data exist to guide an answer to any of these questions. Although existing studies identify important clues to follow, such as the presence of recruitable large-scale networks, there are many limitations (see discussion in reference 2). On the one hand, failure to identify network responses does not rule out the possibility that the functional state of the patient during the measurement may limit eliciting an optimal activation pattern. In fact, the variations of network response observed in Figure 3 demonstrate that very different results may be obtained from nearly physically identical stimuli within the same ambient brain state. Alternatively, identification of integrative cerebral network activation patterns does not yet suggest changes in prognosis or direction for therapy. Although frameworks for longitudinal assessments of cerebral function in severely brain-injured patients should be developed, the technologies are expensive and routine neuroimaging evaluations of patients will be impractical until guidelines that are adjusted on the basis of likelihood for further clinical evolution are developed.

Another limitation is the lack of reliable functional measurements to simultaneously assess both global brain state and selective network responses over diurnal or longer periods. Assessment of VS and MCS patients requires repeated examinations in different settings, times of day, and postures among other variables.[43] Thus, a single imaging study at one time may severely limit opportunity to assess functional capacities in these patients. Developing "fEEG" methods may allow wider diurnal sampling of brain states and network response to characterize recovery of communication systems over time. Such methods could be used to cross-validate imaging assessments that are sensitive to arousal state and within-state level of activation. In pilot studies, Goldfine et al[40] used quantitative EEG measures to assess responses of the patient studied following late emergence from MCS to the presentation of narrative auditory stimuli obtained from multiple presentations during resting wakeful states over several days. In this patient, parallel evaluation of brain network activations using the fMRI passive language paradigm shown in Figure 3 revealed a response consistent with that of normal subjects for both forward and time-reversed narratives (J. Hirsch, PhD, unpublished data, 2005). Spectral analysis of averaged EEG from single channels corresponding to regions over those generating a BOLD signal response in the temporal lobe varied across 3 conditions (forward narratives, time-reversed narratives, and baseline). A suppression of activity in the ~0–10 Hz frequency range and an increase in power in the ~30–50 Hz frequency range occurred during presentation of passive "forward" language stimuli compared with silent baseline period.[44] Further development of these methods may allow for correlation of fMRI evaluations against the frequency of resting brain state during the sampling and evaluation of potential interactions between state and selective network responses.

In the aggregate, though small in number, the available neuroimaging studies reviewed above provide insight into how some MCS patients may harbor residual cognitive capacities in the form of recruitable large-scale networks. Multimodal neuroimaging evaluations may help to address the complexity of severe brain injuries and allow patients to be compared on a more equal footing for considerations of prognosis and therapeutic avenues. Developing a systematic approach will present significant challenges and methodological requirements[2–4] including a need for diagnostic clarity,[45] careful comparison of etiologies of injury, time in the evolution of the course of the patient's illness and medication history. Perhaps, most important will be the need to create more rigorous paradigms to unambiguously assess the presence of volitional responses in the absence of overt behavior as suggested by Owen and colleagues.[3]

Finally, efforts to provide better diagnostic evaluations for the severely brain-injured patient population will lead to a rethinking of professional standards and ethical obligations. Fins[46,47] has argued that professional standards applied in other contexts are often not upheld for patients with disorders of consciousness. Efforts must be balanced to preserve self-determination through both informed consent and informal refusal of therapy based on accurate information. The hope of new neuroimaging opportunities lies in defining proportionate palliative or therapeutic goals for patients and families and providing information to aid in making informed medical decisions.

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