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Functional Imaging of Severely Brain-Injured Patients

Progress, Challenges, and Limitations

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Despite the wide application of functional neuroimaging techniques to the study of neurological disorders, few reports have examined patterns of brain activity following severe injuries. In this review, we discuss recent functional brain imaging studies of patients in the vegetative state (VS) and pilot studies of patients meeting diagnostic criteria for the newly formulated minimally conscious state (MCS).[1] These neuroimaging studies support the clinical model of VS and provide neurophysiologic correlates of the condition. In addition, the studies suggest a foundation for the conceptual separation of VS and MCS on the basis of distinct physiological underpinnings. We consider the widely varying responses drawn by the definition of MCS[2,3] and argue for the relevance and importance of nosological distinctions, even within the lowest functional levels observed among patients who remain severely disabled. As further neuroimaging efforts are applied to study the outcomes of severe brain injuries, it is expected that fundamental questions will arise surrounding the underlying mechanisms of similar functional disabilities. Although it is possible that some MCS patients may harbor greater residual cognitive capacities, other MCS patients may never reach a level of reliable communication. Functional imaging studies in conjunction with other physiological and anatomical measurements will help develop an approach to these disorders based on differences in underlying mechanisms, eventually broadening the expertise of the neurologist.

NOSOLOGY

Vegetative state defines the limited recovery of a cyclical arousal pattern in an unresponsive patient characterized by an eyes-open, wakeful appearance alternating with an eyes-closed, sleep-like state.[4] A VS arises following a severe brain injury that initially produces a coma, and in all other respects VS is equivalent to coma in that patients demonstrate no evidence of awareness of themselves or their environment (**Table**). Coma typically resolves within 2 weeks and can be followed by a VS of indeterminate duration. A VS that lasts beyond 30 days is arbitrarily labeled a persistent vegetative state (PVS). A VS lasting more than 3 months after an anoxic injury or 1 year after a traumatic brain injury is considered permanent, with the chance of further recovery estimated to be less than 1 in 1000.[5] Vegetative states that are permanent usually result from widespread anoxic injuries or diffuse head trauma.[6] Quite rarely, despite overwhelming structural brain injury, PVS patients may exhibit fragmentary behaviors. These behaviors are not appropriate or specific to a given behavioral context, nor can they be reliably influenced to establish any evidence of interaction. Evidence that such fragments of behavior arise from isolated cerebral networks is discussed below. It must be emphasized, however, that careful and re-

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Table. Comparison of Global Disorders of Consciousness With the Locked-in State

	Unresponsive Patients		Minimally Responsive Patients	
	Coma	Vegetative State	Minimally Conscious State	Locked-in State
Cyclic arousal	Absent	Present	Present	Present
Command following	Absent	Absent	Inconsistently present	Present
Purposeful movements	Absent	Absent	Inconsistently present	Absent*
Functional communication†	Absent	Absent	Absent	Present
Cerebral metabolism, % normal	~ 50	40-50	NA	100

Abbreviation: NA, not available.
*Isolated if present.
†The criteria for functional communication are discussed in the "Nosology" section.

peated neurological examinations remain the foundation of this diagnosis. The mere identification of cerebral activation in a patient does not contravene the diagnosis, as will be discussed. By definition, the VS represents a total loss of cognitive function.

The recently defined MCS indicates a low level of functional recovery of contingent behaviors suggesting self- or environmental awareness.[1] For example, behavioral fragments exhibited by MCS patients may include basic verbalization or context-appropriate gestures or only sustained visual fixation or sound localization. Emergence from the MCS category is demonstrated by consistent functional communication with the patient. Achieving this milestone, however, requires more than the patient's ability to follow simple commands. A reliable communication system must be established with the patient, such as the use of printed cards with "yes" and "no" and a pointing method. Yet, it is not uncommon for a patient to accurately and repeatedly identify the cards presented by an examiner yet fail to reliably answer any questions using such signaling. Patients who cannot cross this threshold set the present upper boundary of the MCS diagnostic category (Table). The wide range of behavioral patterns of MCS patients invites further refinements of the concept of MCS, particularly if based on quantitative physiological criteria.

FUNCTIONAL BRAIN IMAGING TECHNIQUES AND STUDIES OF THE VEGETATIVE STATE

Several brain-imaging techniques are now available to probe the underlying mechanisms of neurological disorders. Functional magnetic resonance imaging and functional positron emission tomography studies correlate changes in blood oxygen level and regional cerebral blood flow, respectively, with neuronal activation. Brain metabolism can be quantified by fluorodeoxyglucose positron emission tomography imaging, and regional glucose metabolism is correlated with neuronal firing rates in cerebral structures.[7] Direct measurements of cerebral metabolism and neuronal activity indicate a rough equivalence of metabolic rate and the mean firing rate of local neuronal populations.[8] Similarly, functional magnetic resonance imaging signal activations are also correlated with neuronal local field potential activity in the normal brain.[9] In combination with traditional structural magnetic resonance imaging and electroencephalography (or magnetoencephalographic recordings obtained from measurements of the brain magnetic field), these techniques offer an integrative view of the damaged brain.

A fluorodeoxyglucose positron emission tomography study in the early 1980s showed overall cerebral metabolism to be reduced by 50% or more below normal levels in PVS patients, supporting the clinical inference that PVS patients remain unconscious.[10] In the same study, patients in the locked-in state maintained near-normal metabolic rates in most brain structures. Since that time, several laboratories have confirmed that in VS and PVS the brain shows a global resting metabolic rate of 40% to 50% of normal levels.[11-13]

In the late 1990s, investigative groups revisited the question of cerebral activity in VS. In a widely discussed case report, Menon et al[14] reported functional positron emission tomography findings from a 26-year-old woman 4 months after she experienced an acute encephalomyelitis; results of a neurological examination were consistent with the upper boundary of VS[5] or the lower boundary of MCS (with no evidence of responsiveness except preserved visual tracking).[1] Magnetic resonance imaging identified structural injuries of both brainstem and thalamic regions. The investigators used a functional positron emission tomography subtraction paradigm to assess brain activation in response to presentation of faces familiar to the patient and in response to scrambled images. The technique revealed selective activation of the right fusiform gyrus and extrastriate visual association areas without evidence of additional cortical activation. Menon and colleagues' patient gradually improved during several months to a near-complete cognitive recovery.[15] The investigators interpreted the positron emission tomographic activity measured at 4 months as indicating the recovery of minimal awareness.[16] This conclusion, however, is problematic because the selective identification of cerebral activity alone may not demonstrate the recovery of cognitive function or even the potential for such recovery.[17] The Menon case thus raises a critical issue for brain imaging studies in the severely brain injured: the limitation of any physiological measurements to correlate with awareness per se. It is the case that we cannot confirm awareness simply on the basis of imaging findings without some reliable communication from the patient. To maintain nosological clarity in such borderline cases, it would seem essential to diagnose the patient as having MCS if there is any reproducible evidence of awareness on examination and to diagnose the patient as having VS if not. The possibility that the finding of selective activation of a higher-order cortical region may be related to the subsequent recovery of the Menon patient warrants further studies with larger numbers of patients.

In studies of patients unequivocally meeting the clinical diagnosis of VS, Laureys et al[18,19] applied functional positron emission tomography subtraction paradigms to examine cortical activation patterns in response to simple auditory and somatosensory stimuli. In their studies, PVS patients did not activate higher-order cortical regions engaged by the same stimuli in normal control subjects. Brain activations in the PVS patients were restricted to the primary sensory cortices for both types of stimuli when compared with baseline resting conditions. Laureys and colleagues interpreted their findings to be consistent with widespread functional disconnection across cortical pathways that process sensory information beyond the primary sensory cortices. They also concluded that the residual cortical activity present in the PVS brain does not reflect cortical processing associated with awareness. These findings are consistent with other evidence of early sensory processing in PVS patients measured by evoked potentials.[6] Taken together with the findings of reduced cerebral metabolism in VS and PVS, these studies confirm and add important detail to the biological model of VS as an unconscious brain state.

The definition of PVS allows for some stereotyped responses to stimuli to be observed on examination, such as grimacing, crying, or occasionally vocalization, which are interpreted to arise primarily from brainstem circuits and limbic cortical regions. Quite rarely, fragments of behavior that may appear semipurposeful or inconsistently related to environmental stimuli may be identified in a patient who otherwise meets criteria for VS or PVS. Using fluorodeoxyglucose positron emission tomography, structural magnetic resonance imaging, and magnetoencephalography, we studied a series of PVS patients, including 3 patients with unusual fragments of behavior. Among these patients, we identified a 49-year-old woman, who had suffered successive hemorrhages from a vascular malformation of the right thalamus and basal ganglia and who infrequently expressed single words (typically epithets) in isolation of environmental stimulation, despite a 20-year period of PVS.[20] Magnetic resonance images showed loss of the right basal ganglia, loss of the right thalamus, and extensive injury to the left thalamus, along with an area of left cortical injury. Resting fluorodeoxyglucose positron emission tomography measurements of the patient's brain demonstrated a marked reduction in global cerebral metabolism of less than 50% of normal across most brain regions, with relatively small regions in the left hemisphere that expressed higher levels of metabolism. Magnetoencephalographic responses to bilateral auditory stimulation in this patient revealed an abnormal time-locked response in the gamma range (20-50 Hz) restricted to the left hemisphere that was localized by single-dipole analysis to primary auditory areas. These locations corresponded to the islands of higher resting brain metabolism observed by positron emission tomographic imaging. The incompletely preserved magnetoencephalographic patterns of evoked gamma-band responses provided clear evidence that some thalamocortical relay fibers remained spared and functionally active. The imaging and neurophysiological data together suggest that there was isolated sparing of left-sided thalamo-cortical-basal ganglia loops that normally support language function, including neuronal populations in Heschl gyrus, Broca area, and Wernicke area. This finding and similar observations in other PVS patients provide novel evidence that despite overwhelming brain injury producing behavioral unconsciousness, isolated cerebral networks may remain active.[21] The occasional generation of fragments of behavior may correlate with such isolated network activity and arise from the modular organization of brain systems.

APPROACHING THE MINIMALLY CONSCIOUS STATE: INITIAL IMAGING STUDIES AND PATHOLOGICAL SUBSTRATES

The recent Organization of Human Brain Mapping meeting in June 2003 included reports of 2 pilot studies of functional brain imaging of MCS patients. Laureys et al[22] reported the results of testing 5 patients who met the criteria for MCS; they used the same elementary auditory stimuli tested in the functional positron emission tomography paradigm used in PVS patients.[18] In their study, both MCS patients and healthy controls showed activation of auditory association regions in the superior temporal gyrus that did not activate in the PVS patients. In addition, they observed a stronger correlation of the auditory cortical responses with frontal cortical regions in both MCS patients and control subjects than in PVS patients. Our collaborators, Hirsch and colleagues, presented functional magnetic resonance imaging studies of 2 MCS patients, both of whom had suffered traumatic brain injuries and remained in an MCS for more than 18 months.[23] In these patients, passive sensory activation of language and somatosensory systems revealed intact network response across multiple regions of both hemispheres. Of note, a dissociation was observed in MCS patients compared with normal controls. Language networks activated by spoken narratives failed to produce similar responses when time reversed as those in the normal controls. For both patients studied, fluorodeoxyglucose positron emission tomography revealed marked reduction of resting metabolic rates to near VS levels. The low resting metabolic activity suggests that MCS patients may suffer a severe deficit of baseline or default self-monitoring brain activity, as proposed by Raichle et al[24] to account for high resting cerebral metabolic rates in the normal human brain. The dissociation of distributed network responses despite low resting cerebral metabolic rates also raises the question of whether MCS patients have any ongoing reflective self-awareness. Although much further work is necessary to begin to construct the biological basis of MCS, these initial findings suggest that functional imaging may provide useful correlates of the differences in MCS and PVS evident at the bedside. Given the limited present knowledge of mechanisms underlying varying levels of severe disability, such efforts appear to be critical to improve our understanding of diagnostic, prognostic, and ultimately therapeutic considerations in this patient population. Recent pathological studies comparing patients remaining in VS with other patients with severe disability following brain injuries provide evidence for this assertion. Jennett et al[25] reported 65 autopsies of patients with traumatic brain injury leading either to a VS (n=35) or a severe disability, including MCS patients (n=30). More than half of the severely disabled group demonstrated only focal brain injuries, without diffuse axonal injury or focal thalamic injuries (including 2 of the MCS cases). These findings suggest that significant variations in underlying residual brain function accompany these severe but less disabling brain injuries and raise important questions about mechanisms limiting recovery of cognitive function.

OTHER DEFINITIONAL AND ETHICAL CONSIDERATIONS

The separation of MCS patients from the category of severe disability is aimed at identifying patients who may harbor some substrate for further recovery despite limited behavioral evidence of awareness. Further investigation of the physiological correlates of MCS may eventually lead to markers for identifying neurological substrates to support additional recovery of cognitive function. In this context, the choice of "minimally conscious" seems most appropriate and closest to mechanism when compared with other proposals.[2,3] Minimal responsiveness, as indicated in the Table, does not suggest any mechanism and may be consistent with the locked-in state, which is not a disorder of consciousness. Alternatively, "minimal awareness" may be misleading and imply a reflective self-awareness that is not present. The term "minimally conscious" suggests that a minimal architecture for staging distributed neuronal activity correlated with wakeful behavioral states is preserved. Thus, the term invites further clarification of the diagnostic category based on brain mechanisms underlying cognitive capacities and functional limitations.

Alongside the nosological and pathophysiological implications of neuroimaging findings in the severely brain-injured are several ethical considerations. The limitations of the clinical examination of MCS patients are well recognized,[1] and as it becomes possible to better identify mechanisms in an individual patient, we will need frameworks for consideration of palliative goals (eg, communication despite dementia vs MCS) and to provide additional diagnostic and prognostic information that can guide surrogate decision-making. Fins[26] has recently commented on the historical and present societal context in which these studies will be received. As he notes, we must also safeguard the patient's right-to-die as we move forward in understanding the biological underpinnings of disorders of consciousness.

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