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CHAPTER 33

Modeling the minimally conscious state: measurements of brain function and therapeutic possibilities

Nicholas D. Schiff*

Laboratory of Cognitive Neuromodulation, Department of Neurology and Neuroscience, Weill Medical College of Cornell University, 1300 York Avenue Room F610, New York, NY 10021, USA

Abstract: The minimally conscious state (MCS) defines a functional level of recovery following severe brain injuries. Patients in MCS demonstrate unequivocal evidence of response to their environment yet fail to recover the ability to communicate. Drawing on recent functional brain-imaging studies, pathological data, and neurophysiological investigations, models of brain function in MCS are proposed. MCS models are compared and contrasted with models of the vegetative state (VS), a condition characterized by wakeful appearance and unconsciousness. VS reflects a total loss of cognitive function and failure to recover basic aspects of the normal physiologic brain state associated with wakefulness. MCS may represent a recovery of the minimal dynamic architecture required to organize behavioral sets and respond to sensory stimuli. Several pathophysiological mechanisms that might limit further recovery in MCS patients are considered. Implications for future research directions and possible therapeutic strategies are reviewed.

Introduction

The recent definition of the minimally conscious state (MCS) challenges neurologists to improve the rational basis of evaluation and treatment of severely brain-injured patients (Giacino et al., 2002; Giacino, this volume). The ultimate impact of this nosological distinction is likely to rival the importance of the definition of the vegetative state (VS) by Jennett and Plum (1972; Jennett, this volume). Unlike VS, a condition characterized by the dissociation of behavioral unconsciousness and wakeful appearance, MCS classifies patients with unequivocal evidence of contingent response to their environment. The range of clinical phenotypes in MCS is quite large (see Giacino and Whyte, in press) and includes patients with relatively high-level behavioral responses such as complex command following or intelligible verbalizations. Detractors have raised ethical concerns that distinguishing MCS will lead to undervaluing the patients by leading to their conflation with VS (Burke, 2002; Coleman, 2002) and alternatively, futility concerns that there is no point to drawing further distinctions with the category of severe disability. The later concern is often expressed as a conclusion that this patient population is uniformly hopeless. To support the need for the MCS category and further refinement of the severe disability category of the Glasgow Outcome Scale (Jennett and Bond, 1975), neurobiological models of VS and MCS are examined and contrasted below. The conceptual models are considered in light of new measurements of brain function in severely brain-injured patients. Despite a limited number of studies, significant differences in underlying brain function are already unfolding (cf. Kobylarz and Schiff, 2004;

*Corresponding author. Tel.: +1 (212) 746 2372;
Fax: +1 (212) 746 8532; E-mail: nds2001@med.cornell.edu

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Laureys et al., 2004). These advances make diagnostic clarity an imperative in the evaluation of severe brain damage (Fins and Plum, 2004). Furthermore, the potential that specific measurements of brain function may provide a basis for selective therapeutic interventions in some severely disabled patients supports continued efforts to identify the different pathophysiological mechanisms arising in this context.

Akin to the dissociation of arousal and consciousness observed in VS, MCS dissociates the appearance of wakefulness and some level of responsiveness from a capacity to communicate and organize goal-directed behaviors. Models of MCS must therefore consider the neurobiological basis for supporting continuous interactive behaviors. Below, conceptual models of MCS are advanced and contrasted to current models of VS. Patients near the point of emergence from MCS, where late recoveries are sometimes identified, are proposed to primarily suffer failures of the initiation, maintenance, and completion of behavioral sets. Similar, but less profound impairments of general cognitive function are common across a spectrum of outcomes of severe brain injuries. Identifying and quantifying the necessary and sufficient conditions to emerge from MCS will require a neuroscientific framework that accounts for basic mechanisms underlying consciousness and cognition in the human brain. Thus, another motivation for detailed studies and models of MCS is this set of fundamental questions in neuroscience.

Nosology

Figure 1 provides a schematic overview of the nosology of global disorders of consciousness following severe brain damage. The initial brain state produced by severe brain damage is coma. Coma is a state of unarousable unresponsiveness and reflects overwhelming functional impairment of the forebrain arousal mechanisms (Plum and Posner, 1982). Coma is typically a transient state that, if uncomplicated by intercurrent processes (e.g., infection, metabolic derangement), will resolve within 1 or 2 weeks, heralded by the return of a limited cyclical arousal pattern during which an eyes-open "wakeful" appearance alternates with an eyes-closed "sleep" state. This pattern identifies the VS, a period of indeterminate duration that is otherwise similar to coma in that patients demonstrate no evidence of awareness of self or their environment (Jennett and Plum, 1972).

Patients who remain in a VS beyond 30 days are considered to be in a persistent vegetative state (PVS) and VS that lasts at least 1 year following traumatic brain injuries (TBI) or 3 months following hypoxic-ischemic injuries is considered permanent (Jennett, 2002). Rarely, PVS patients exhibit fragmentary behaviors that appear to arise from isolated intact cerebral networks (Schiff et al., 1999, 2002a). These behavioral fragments are not appropriate or specific to a given behavioral context, nor can they be reliably influenced to establish any evidence of interaction. Such patients may be placed in the "gray zone" shown in Fig. 1. Close to this minimal level of behavioral interaction, patients enter into MCS once they demonstrate reliable but inconsistent evidence of awareness of self or the environment as demonstrated by verbal or gestural output (Giacino et al., 2002). MCS patients can show wide fluctuations in baseline behaviors. The upper boundary determining a patient's emergence from MCS is reliable communication. This clinical categorization scheme includes patients with a large variety of behavioral patterns suggesting the utility of further refinement, particularly if based on quantitative

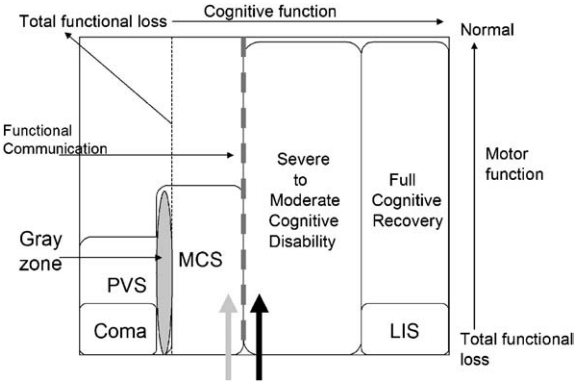

Fig. 1. Conceptual scheme for global disorders of consciousness. Abbreviations: PVS, persistent vegetative state; MCS, minimally conscious state; LIS, locked-in state. Gray and black arrows indicate functional levels just below and above emergence from MCS. Adapted from Schiff (2004), with permission from MIT Press.

indices. At present, no data support establishing a predictive time frame for emergence from MCS following severe brain damage (particularly if a result of TBI where well-documented cases demonstrate significant further recovery over long time periods; see Fins, this volume). Of note, if motor function is severely impaired, reliable identification of intermediate states between MCS and the locked-in state (LIS, not a disorder of consciousness; see Laureys et al., this volume) may not be possible. Across the range of clinical phenotypes encompassed by MCS, the gray arrow in Fig. 1 indicates a functional level from which some MCS patients may spontaneously emerge (black arrow) after long intervals (unpublished observations).

Models of the vegetative state

Before considering models of mechanisms underlying VS, it is useful to distinguish VS as a transient functional disturbance versus a permanent condition. VS often arises following an acute brain insult and can give way to significant further recovery. A wide range of outcomes, etiologies and structural injury patterns can be associated with transient VS. Similarly, the available literature of electrodiagnostic and functional imaging studies examining VS patients vary significantly with respect to time in VS, etiology of the condition, and underlying structural pathology. VS lasting at least one month and persisting to death, however, is associated with specific structural pathologies typically resulting in overwhelming damage to efferent and afferent cerebral connections (Adams et al., 2000). More rarely, permanent VS can be associated with extended bilateral damage to the paramedian mesencephalon, typically in combination with the paramedian thalamus (Ingvar and Sourander, 1970; Castaigne et al., 1981; Schiff et al., 2002a). Despite these variations a convergence of evidence supports VS as a functionally distinct state associated with common disruption of brain activity in the early and chronic stages.

Pathological studies

Adams et al. (2000) studied 49 patients remaining in a VS for at least 1 month until death and identified specific patterns associated with traumatic and non-traumatic etiologies. Non-traumatic injuries associated with VS showed severe bilateral thalamic damage in all instances and in the majority of cases was associated with diffuse cortical damage (64% of cases). Traumatic etiologies showed grade 2 and 3 diffuse axonal injuries and severe thalamic degeneration in the majority of VS patients (96% of patients who survived for 3 months before death). These and other pathological studies confirm the intuition that the chronic VS is characterized by overwhelming cerebral damage (cf. Dougherty et al., 1981). The conclusion that the most consistent and severe pathologies arising from both types of injuries are in subcortical structures, particularly the thalamus, is not widely appreciated. The investigators point out that damage to the thalamus following diffuse axonal injuries (DAI) is indirect as a result of transneuronal degeneration and that if delayed restoration of function in axons initially damaged is possible, the neuronal substrate in the thalamus remains in these situations. This difference is suggested to play a role in the very different expected time course of recovery and point beyond which permanence is expected in VS resulting from TBI compared to hypoxic-ischemic insults (see discussion below). An important related observation from these studies is that the cerebral cortex is generally spared in TBI resulting in VS, with only 11% of patients showing diffuse ischemic neocortical injury patterns and 37% showing any neocortical ischemic injuries (compared with 64% and 93% in VS of non-traumatic origins). Brainstem damage was uncommon in chronic VS patients emphasizing that VS is primarily a disorder of cerebral integration at the thalamocortical level (also see Graham et al., elsewhere in this volume).

Electrodiagnostic studies

Electroencephalographic studies in VS identify several patterns of abnormality limiting specific insights into mechanisms underlying this condition (Jennett 2002). In general, EEG findings in VS are comparable to findings in coma and typically show profound slowing with amplitude increases in delta and theta rhythms (e.g., Hansotia, 1985). Alternatively, very low amplitude, nearly isoelectric, EEG

may be recorded in the VS. Importantly, the recovery of arousal without consciousness in VS does not imply that the distribution of power across frequencies in the EEG is normal — as a rule the shape of the EEG power spectrum (the measure that quantifies this distribution) is markedly abnormal in VS. Thus, in addition to dissociating arousal and awareness on a behavioral level, VS dissociates cyclic activation of the cerebrum associated with eyes open and eyes closed states from the normal sleep–wake architecture despite cyclical alteration of aberrant EEG patterns associated with behavioral state changes (cf. Isono et al., 2002). Early evoked potential components are often preserved in VS but show abnormal central conduction times; the loss of sensory evoked potentials has been strongly correlated with diffuse ischemic injury of the neocortex and permanent VS (Rothstein et al., 1991; Guerit, this volume). Late components and mid-latency components of sensory evoked potentials are generally absent or show marked abnormality in VS (Kotchoubey, this volume).

Imaging studies

Initial studies of brain function in VS focused on measurements of cerebral metabolism and brain electrical activity in the electroencephalogram (EEG) and evoked potentials (EP). Levy et al. (1987) studied resting cerebral metabolism using fluorodeoxyglucose-positron emission tomography (FDG-PET) in the eyes-open "awake" state of 7 VS patients, 3 LIS patients, and 18 normal controls. In their studies, VS was associated with a 60–70% reduction in resting cerebral metabolism across most brain structures. This finding of profoundly depressed cerebral metabolism in VS has been replicated across several laboratories (DeVolder et al., 1990; Tomassino et al., 1995; Rudolf et al., 1999; Laureys et al., 2000a, 2002; Schiff et al., 2002). Comparable levels of reduction in cerebral metabolism are typically only observed in pharmacologically induced coma (reviewed in Laureys et al., 2004). Although significant reductions of glucose metabolism can be interpreted as a proxy for widely reduced neuronal firing rates (Eidelberg et al., 1997; Smith et al., 2002), improvements in the overall level of resting cerebral metabolism do not necessarily accompany recovery from VS (Laureys et al., 1999, see the discussion below).

FDG-PET, clinical EEG and EP studies can provide only limited information about cerebral processing in VS because these techniques cannot directly measure the presence or absence of distributed cerebral network responses. Functional brain imaging using $H_2^{15}O$ PET or magnetic resonance imaging (fMRI) or more quantitative analyses of brain electrical activity are required to examine the distributed activation of cerebral structures in the VS brain in response to selective stimuli. These methods are, however, more sensitive and require greater technical expertise (see Owen, this volume). Laureys and colleagues (Laureys et al., 2000a, 2002; Boly et al., 2004a, b) have studied patients unequivocally meeting the criteria for VS for at least one month using functional $H_2^{15}O$ PET (fPET) paradigms. Their studies included patients with both traumatic and non-traumatic etiologies and identified the loss of distributed activation across cerebral structures seen in normal subjects in response to the same simple auditory and somatosensory stimuli. In most of the patients studied, early evoked potential components (reflecting primary sensory cortical response) were preserved and correlated with fPET activations of primary sensory cortices. Late cortical evoked responses, as in other studies, were absent. These functional imaging findings are consistent with a general model that VS enduring for at least a month is the result of widespread disconnection of cerebral networks, usually on the basis of extensive structural injuries if enduring for at least one month. Taken together with the clinical features of VS, these findings support modeling of VS as a total loss of cerebral integrative activity. This loss is evident even at the earliest stage of cortical sensory processing reflected in the loss of late and midlatency electrical (magnetic) evoked potential components and distributed network activations measured by fPET.

Laureys et al. (1999) also reported changes in FDG-PET metabolism in one of their patients studied before and after recovery from VS. The patient had remained in a transient VS lasting 19 days after carbon monoxide poisoning but recovered to a level of only mild cognitive impairment 1 month after admission. FDG-PET studies done at 15 days

(while still in VS) and 37 days (recovery of consciousness with moderate short-term memory impairment) both showed a global metabolic rate of ~62% of normal values across the cerebrum. Although the overall metabolic rate did not change with recovery from VS, a clear difference in the pattern of metabolic activity was observed between the two scans (notably, the patient's metabolic rate in this transient VS was higher than typically associated with permanent VS where FDG-PET metabolic rate may be ~40% of normal levels). During VS significant metabolic reductions were observed in pre-motor, sensorimotor, and posterior parietal-occipital regions. Recovery of consciousness correlated with increased metabolism in the pre-motor and parietal-occipital regions. A follow-up study identified increased thalamocortical connectivity between the intralaminar regions of the thalamus and the prefrontal cortices following recovery (Laureys et al., 2000b). These findings can be compared to studies in normal subjects that identify the medial posterior parietal-occipital region as the most metabolically active area in the normal resting brain (Raichle et al., 2001; Vogt and Laureys, this volume). Thus, the observed shift in the pattern of resting metabolism may thus correlate with an overall normalization of brain activity associated with re-establishing frontal thalamocortical systems and related posterior networks (see discussion below); significant increases in correlation of intralaminar thalamic and prefrontal regions may also reflect a re-establishing of functional connectivity associated with elementary cognitive behavioral sets (cf. Paus et al., 1997). In a larger study, including patients with traumatic etiologies, Laureys and colleagues (2003) have identified a similar pattern of metabolic recovery in the medial posterior parietal region.

Unusual behavioral patterns in VS

Stereotyped responses to stimuli can be observed in VS patients such as grimacing, crying, or occasionally vocalization that originate primarily from brainstem circuits and limbic cortical regions. Very rarely, fragments of behavior that may appear semi-purposeful or inconsistently related to environmental stimuli may be identified in a patient who otherwise meets criteria for VS or PVS. In a multimodal imaging study using FDG-PET, structural MRI, and magnetoencephalography (MEG), we identified three such patients with unusual fragments of behavior. One, a 49-year-old woman, who had suffered successive hemorrhages from a vascular malformation of the right thalamus and basal ganglia, infrequently expressed single words (typically epithets) in isolation of environmental stimulation despite a 20-year period of VS (Schiff et al., 1999). MRI images showed absence of the right basal ganglia, right thalamus and severe injury to the left thalamus (Fig. 2A). Resting FDG-PET measurements showed marked reduction of global cerebral metabolism to $<50\%$ of normal across most brain regions with metabolic sparing in relatively small regions in the left hemisphere (Fig. 2B). MEG responses to bilateral auditory stimulation in this patient revealed an abnormal time-locked response in the gamma range (20–50 Hz) localized by single-dipole analysis to primary auditory areas in the left hemisphere alone (see Ribary, this volume). These locations corresponded to the islands of higher resting brain metabolism observed by PET imaging shown in Fig. 2. Taken together, the imaging and neurophysiological data indicate isolated sparing of left-sided thalamo-cortical-basal ganglia loops that normally support language function, including neuronal populations in Heschl's gyrus, Broca's area, and Wernicke's area. This finding and similar observations in other PVS patients (Schiff et al., 2002a) provide a model of brain function for patient's in the "gray zone" of Fig. 1: isolated cerebral networks may remain active and correlate with the occasional generation of fragments of behavior.

The asymmetry of subcortical injuries in this patient also provided a unique opportunity to examine the impact of removal of the thalamus and basal ganglia on the EEG (shown in Fig. 2C). We identified a sharp decline of coherence in the cerebral hemisphere deprived of both the subcortical gray matter structures and their return path through the thalamus (Davey et al., 2000). Coherence is a measure of cross-correlation in the frequency domain (Mitra and Pesaran, 1999). A high coherence indicates potential relationships

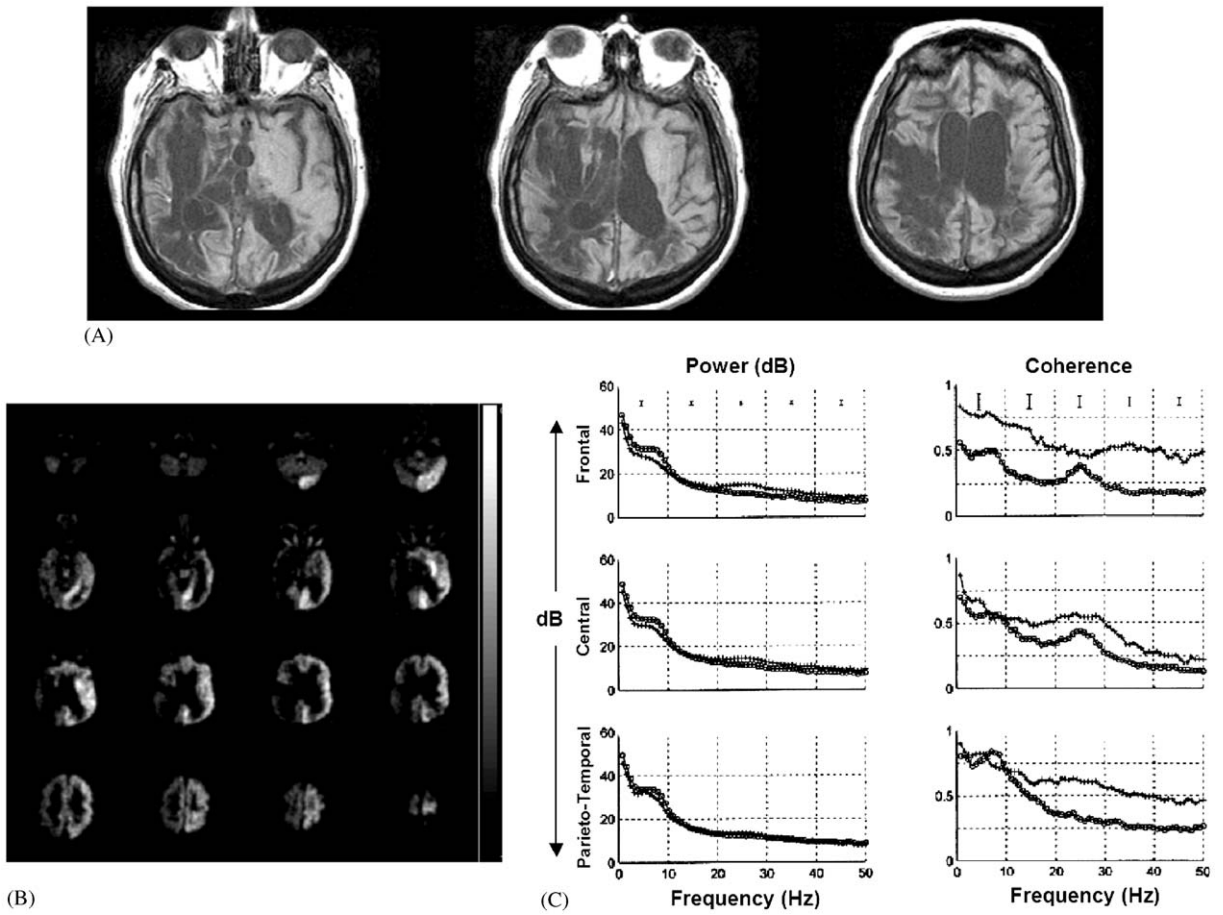

Fig. 2. Magnetic resonance imaging, positron emission tomography and electroencephalography studies for patient described in text. (A) MRI structural images show severe asymmetric brain damage with loss of right-sided basal ganglia and thalamic structures (Schiff et al., 1999). (B) Positron emission tomography images of resting glucose metabolism across entire cerebrum. Marked asymmetry of right and left hemisphere metabolism is seen. (C) Dissociation of hemispheric variations of coherence measurements and regional power spectrum measurements (from Davey et al., 2000). Reproduced with permission from Elsevier Press.

between two signals such as the presence of a common input signal, mutual driving of the signals, or one signal driving the other (cf. Bendat and Piersol, 2000). Coherence is a ratio of coherent power to total power and is therefore not sensitive to changes in the amount of power within frequency bands; significant coherence differences therefore reflect either the influence of common input or changes in functional connectivity *per se*. Theoretical studies of the origins of EEG coherence place strong emphasis on the role of corticocortical fiber pathways (Thatcher et al., 1986; Nunez et al., 1999).

As shown in Fig. 2C, EEG samples obtained over multiple episodes of an eyes-closed sleep-like state in this patient (from Davey et al., 2000) reveal a marked dissociation of differences in intrahemispheric coherence and regional power spectra. Regional power spectra and coherence from the left (+) and right (o) hemispheres are displayed in the figure (95% confidence limits are shown by brackets in top panels). The power spectra did not differ substantially between electrode pairs obtained from frontal regions (electrodes F3/F7 (left hemisphere) and F4/F8 (right hemisphere)), central regions (electrodes C3/T3 and C4/T4), or

parieto-temporal regions (electrodes P3/T5 and P4/T6). Of note, small differences of increased frontal and central theta band activity (5–10 Hz) and gamma band activity (here ~20–35 Hz) were evident in the comparison of the power spectrum obtained from pairs in each hemisphere. This finding correlated with the presence of residual spontaneous and evoked gamma band activity (20–50 Hz) isolated to the left hemisphere identified in MEG studies of the same patient (Schiff et al., 1999, 2002a). Intrahemispheric coherences, however, demonstrated marked differences between the left and right hemispheres, with broadband reduction of coherence seen across all right hemisphere electrode pairs. These findings are consistent with a critical role for subcortical structures in shaping coherence relationships in the EEG that are not reflected by changes in the regional power spectrum. Similar dissociations of the power spectrum and coherence spectrum have been observed in MCS patients (Kobylarz et al., 2003, discussed below).

The significance of this finding for the present discussion is that it represents a correlation with an unusual but straightforward anatomic difference in the cortical inputs to each hemisphere in this patient. It suggests that coherence spectra may provide important functional information not available in the power spectral characterization of the EEG that summarizes overall frequency content. More generally, the failure to recover the normal distribution of frequencies observed in the wakeful EEG in VS supports the view that the VS brain is not able to generate endogenous central states to prepare motor behaviors, and anticipate or process sensory stimuli.

Models of MCS

The diagnostic category of MCS canvasses a wider range of clinical phenotypes and structural pathologies than VS. At this time only a few studies have focused on patients fulfilling the diagnostic criteria for the condition and conceptual models must accordingly be seen as tentative. It is anticipated that as additional investigational studies are done this category will become further refined, hopefully based on mechanistic distinctions. Nonetheless, existing data provide evidence that brain function in VS and MCS may be well separated at the extremes if not more generally.

In considering the available data from functional imaging, pathology, and observational studies, a model is proposed that frames MCS primarily in terms of instability of the initiation, maintenance, and completion of behavioral sets. These critical functions depend on the interaction of brainstem arousal systems and mesencephalic and diencephalic "gating systems" (see below) with other cerebral structures. Pathological studies and observational data of fluctuations observed in severely brain-damaged patients suggest that relatively subtle measurements of brain function may be necessary to identify the underlying mechanisms of failure to organize goal-directed behaviors and communication in MCS. Mechanisms identified in MCS patients with limited structural injuries will likely also apply to understanding problems of cognitive recovery of patients with less severe or moderate disabilities following brain damage.

Correlations of MCS with structural pathology

Comprehensive studies of specific anatomic pathologies associated with MCS are unavailable. Autopsy studies of patients with severe disability following brain injuries show wide variations in underlying neuroanatomical substrates. Jennett and colleagues (2001) reported 65 autopsies of patients with traumatic brain injury leading either to a VS or severe disability. This study included 12 patients with histories consistent with MCS at the time of death. Over half of the severely disabled group demonstrated only focal brain injuries, without DAI or focal thalamic infarction (including 2 of the MCS patients). Structural brain-imaging studies also demonstrate that the behavioral level ultimately achieved by a patient following severe brain injuries often cannot be simply graded by the degree of vascular, DAI, and direct ischemic brain damage. Kampfl et al. (1998) described indirect volumetric MRI indices that provide reasonable predictive accuracy (~84%), when combined with time in VS, for a permanently vegetative outcome of overwhelming traumatic

brain injuries. Unfortunately, many patients fulfilling these criteria can recover after long intervals. In our own ongoing studies, we have identified one MCS patient, with a structural injury pattern on MRI fulfilling all of the Kampfl et al. criteria, who emerged at 8 months and is now near an independent functional level (unpublished observations). Danielsen et al. (2003) report detailed MRI and magnetic resonance spectroscopy (^{1}H-MRS) findings from a patient with severe DAI measured over several time points, while the patient remained in coma for 3 months and 21 months later when the patient had slowly recovered to a near independent level. In this patient, ^{1}H-MRS revealed characteristic regional reductions in NAA (*N*-acetyl-aspartate)/choline ratios associated with severe DAI that normalized by the study done at 21 months and correlated with cognitive recovery. McMillan and Herbert (2004) recently reported a 10-year follow-up on an MCS patient who continued to recover 7–10 years following a traumatic brain injury to a point of regaining the capacity to initiate conversation, and express clear preferences and spontaneous humor. These observations suggest that some slow variables of recovery may exist and should be quantified through further structural imaging and longitudinal analysis of brain dynamics (see below).

Attempts to correlate outcome with structural injuries is further complicated by the potentially disproportionate impact of certain focal injury patterns. It is well known that enduring global disorders of consciousness can result from relatively discrete injuries concentrated in the paramedian mesencephalon and thalamus (Schiff and Plum, 2000). The structures involved in these lesions include the thalamic intralaminar nuclei (ILN) and the mesencephalic reticular formation (MRF), which together with their connections to the thalamic reticular nucleus appear to play a key role linking arousal states to the control of moment-to-moment intention or attentional gating (Schlag-Rey and Schlag, 1984; Llinas et al., 1994, 2002; Kinomura et al., 1996; Paus et al., 1997; Purpura and Schiff, 1997; Steriade, 1997; Jones, 2001; Matsumoto et al., 2001; Minamimoto and Kimura, 2002; Schiff and Purpura, 2002; Wyder et al., 2003, 2004). These structures can be considered "gating" systems that control interactions of the cerebral cortex, basal ganglia, and thalamus through their patterns of innervation within the cortex as well as rich innervation from the brainstem arousal systems (Groenewegen and Berendse, 1994; Schiff and Plum, 2000; van der Werf et al., 2002). Patients who recover from bilateral paramedian thalamic injuries typically demonstrate persistent instability of arousal level and within-state fluctuations of the selective gating of different cognitive functions (Katz et al., 1987; Meissner et al., 1987; Mennemeier et al., 1997; van Der Werf et al., 1999). Thus, even incomplete injuries to the gating systems may produce unique deficits in maintaining adequate cerebral activation and patterns of brain dynamics necessary to establish, maintain, and complete behavioral set formation (Schiff and Purpura, 2002; see the discussion below).

Enduring VS or MCS produced by such focal injuries will typically include bilateral damage to the mesencephalic reticular formation extending bilaterally into the intralaminar thalamic nuclei (Plum, 1991; Schiff et al., 2002a). However, *en passant* damage to the thalami and upper brain stem commonly follows both traumatic brain injury and stroke as a result of the selective vulnerability of this region to the effects of diffuse brain swelling that leads to herniation of these midline structures through the base of the skull (see Plum and Posner, 1982). It is likely that most patients who recover from severe brain injuries may represent mixed outcomes resulting from intermediate pathologies that combine moderately diffuse injuries with limited focal damage to paramedian structures (Adams et al., 2001; Jennett et al., 2001). Pathophysiologic mechanisms arising in the setting of such mixed pathologies have not been the subject of systematic study. It is known, however, that damage to the paramedian brain stem worsens prognosis following TBI and is associated with MCS and other poor outcomes (Wedekind et al., 2002).

In the aggregate, clinical and pathological findings suggest significant variability in both the underlying mechanisms of cognitive disabilities and residual brain function accompanying severe brain injuries associated with MCS and other outcomes. It appears that severe disabilities may arise under at least two different conditions: (1) extensive,

relatively uniform diffuse axonal injury or hypoxic-ischemic damage and (2) focal cerebral injuries combined with minimal diffuse axonal or ischemic damage with possible coexisting functional alteration of subcortical gating systems and their interaction with cortical association areas.

Functional brain imaging in MCS

Recent functional imaging studies have examined patients using the Aspen criteria for MCS (Giacino et al., 2002). Boly et al. (2004a) studied five MCS patients using the same fPET auditory stimulation paradigm applied by Laureys et al. (2000) to study vegetative patients. In their studies, MCS patients and healthy controls both showed activation of auditory association regions in the superior temporal gyrus that did not activate in the PVS patients and strong correlation of the auditory cortical responses with frontal cortical regions, providing evidence for preservation of cerebral processing associated with higher order integrative function. The majority of the MCS patients were scanned approximately 1 month after initial injury and at a time when EEG examinations revealed significant bilateral abnormalities (mostly slowing in the theta and delta range). Preliminary data from Laureys and coworkers also show a near-normal pain network response to somatosensory stimulation in their MCS patients (Boly et al., 2004b).

Menon et al. (1998) described selective cortical activation patterns using a $H_2^{15}O$ PET subtraction paradigm in a 26-year-old woman described as in a PVS 4 months following an attack of acute disseminated encephalomyelitis. The patient later improved to an MCS level by 6 months; emergence from MCS occurred sometime after 8 months and the patient eventually made a full cognitive recovery (Macniven et al., 2003). Imaging studies done during the PVS period demonstrated selective activations of right occipital-temporal regions. This pattern of activity was interpreted as indicating a recovery of minimal awareness without behavioral manifestation. Such an interpretation is limited by the lack of any evidence of behavioral response from the patient. It is generally agreed that the present state of imaging technologies cannot provide alternative markers of awareness (Menon et al., 1999; Schiff and Plum, 1999; Schiff et al., 1999; Laureys et al., 2004). The findings of Menon et al. (1998) contrast with those of Laureys et al. (2000, 2002) and suggest that ultimately neuroimaging studies may be able to elucidate underlying differences between PVS and MCS patients. Bekinschtein et al. (2004) recently reported brain activations obtained using fMRI in an MCS patient recovering from traumatic brain injury. A subtraction comparison of responses to presentations of the patient's mother's voice and a neutral control voice revealed selective activation of the amygdala and insular cortex suggesting emotional processing associated with the mother's voice. As in the interpretation of "high-level" responses in VS, in patients without the ability to communicate we can only speculate about whether such activations indicate awareness.

We studied two MCS patients near the border of emergence more than 18 months after injury (gray arrow in Fig. 1) using fMRI, FDG-PET, and quantitative EEG (Schiff et al., 2005; Kobylarz et al., 2003). The patients and seven control subjects were studied with fMRI language activation paradigms similar to paradigms used in normal subjects and neurosurgical candidates to map language networks (Hirsch et al., 2000; Hirsch, this volume). Two 40-second narratives were pre-recorded by a familiar relative and presented as normal speech and also played time-reversed. Forward presentations generated robust activity in several language-related areas in both patients. Figure 3 shows cortical activity maps associated with the presentation of linguistic stimuli in a single patient. While wide network activation occurred with the forward presentations, time-reversed narratives only activated early sensory cortices in the left hemisphere. This pattern differs from that of normal subjects, where large activations for both stimulus types were observed, with time-reversed language presentation showing slightly more activation than forward presentations. These preliminary fMRI results have now been confirmed in further studies of MCS patients (unpublished data). The findings indicate that some MCS patients may retain large-scale cortical networks that underlie language comprehension and expression despite their inability to execute motor commands or communicate reliably.

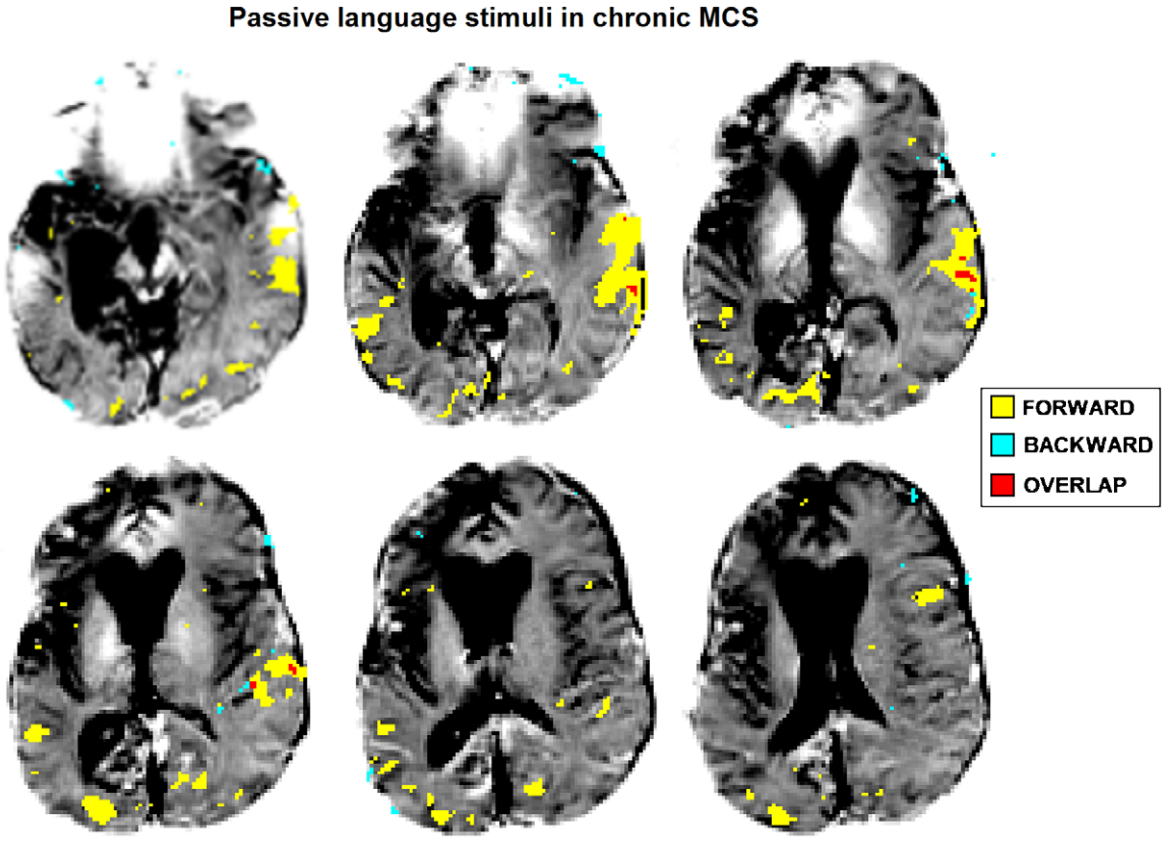

Fig. 3. Functional magnetic resonance imaging activation patterns of BOLD signal in response to passive language presentations. Reproduced with permission from MIT Press. See Plate 33.3 in Colour Plate Section.

In both patients studied we correlated fMRI findings with FDG-PET and quantitative EEG measurements. The patients demonstrated low global resting metabolic rates with significant differences in hemispheric resting metabolic rates and baseline thalamic activity. EEG studies in both patients revealed significant reductions in interregional coherence of the more damaged hemisphere in wakefulness (Kobylarz et al., 2003). In one patient this interregional coherence pattern showed a marked dependence on arousal state with coherence decreases observed across frequencies only in the state of wakefulness. The abnormalities of EEG coherence measures indicate a significant alteration of the functional integration of cortical regions in the more damaged hemisphere. This is all the more striking in that the EEG power spectrum showed no differences in the distribution of power across frequencies for both hemispheres in the two patients. Traditional EEG and MRI evaluations are known to be insensitive to detection of mild and moderate disabilities following brain injuries and to be poor predictors of gradation of severe TBI (Thatcher et al., 2001). The observation of marked coherence abnormalities is consistent with experimental studies that indicate that coherence measures can provide a more direct reflection of behaviorally relevant dynamics than changes in the power spectrum (cf. Vaadia et al., 1995).

Brain dynamics underlying behavioral fluctuations in MCS

It is notable that the low level of behavioral responses represented by MCS can be associated in

some patients with intact large-scale network responses as observed in normal human subjects (shown in Fig. 3). These observations lead naturally to the question of how to model the coexistence of recruitable large-scale networks and severely limited behavioral repertoires. A systematic approach to this question is likely to require both consideration of normal mechanisms studied in cognitive neuroscience and a variety of clinical neurological disorders. As noted above, correlations of structural injuries and functional outcomes are not as strong as naïve assumptions would suggest, as widely differing structural pathologies may correlate with the same poor functional level. Moreover, functional measurements offer only snapshots of brain function in time. Baseline metabolic assessments or functional activation studies cannot adequately identify the frequency of the resting brain state sampled or likelihood of response at the time the measurements are taken. In patients with widely varying responsiveness, these limitations present an important methodological concern and emphasize the need for more careful consideration of ongoing brain dynamics. What kinds of dynamical measures are needed? At least two different kinds of measurements suggest themselves. Dynamical structures arising in the EEG that correlate with elementary cognitive functions underlying behavioral set formation may quantify fluctuating responsiveness in MCS. Alongside these measurements there is also a need to develop more sensitive diagnostics that can identify dynamical signatures of several abnormal processes that may arise in the setting of severe brain damage and limit recovery.

Beginning with the observations above, the shape of the spectrum of the EEG can be relatively normal in MCS patients, and it is reasonable to next consider the fine correlation structure of the EEG as a potential indicator of mechanisms. In our preliminary studies discussed above, hemispheric coherence abnormalities have been identified (Kobylarz et al., 2003) but such observations are only starting points for more detailed consideration of markers of cognition. The background activity of ongoing EEG during different arousal states can be precisely described as shifts in spectral content of the activity of distributed forebrain networks (Steriade, 2000). Combined studies of intralaminar thalamic neurons and EEG power spectra show that these neurons in concert with the brain stem arousal systems support the shift away from low frequencies characteristic of sleep to a mixed state including increased synchronized high-frequency activity in natural awake attentive states (Steriade and Glenn, 1982; Steriade et al., 1996). A recent theoretical model of the EEG demonstrates that most of the features of the shape of the EEG spectrum as it evolves across wakefulness and sleep stages can be captured in a partial differential equation system constructed from physiologically realistic parameters and the connectivity of only three major neuronal populations: thalamic relay and reticular neurons and cortical pyramidal neurons (Robinson et al., 2002). This architecture is consistent with experimentally based models of EEG generation. Simply recovering the shape of the EEG spectrum may therefore only indicate that an essential substrate of thalamocortical connectivity remains to produce this signal — not that the brain has reestablished organized activity across widely distributed networks correlated with goal-directed behavior and cognition (also see John, this volume).

Importantly, the long-lasting changes of ongoing EEG background activity and thalamic firing patterns associated with the arousal state of wakefulness are episodically shaped at a finer temporal scale by brief phasic modulations of the rhythms that organize behavioral set formation. The aggregate abnormalities of resting coherence spectra observed in our two MCS patients likely reflect loss of this fine structure within their resting wakeful EEG. In wakeful states, quantitative EEG studies in normal subjects and experimental studies suggest several potential surrogate markers of elementary cognitive processes underlying the formation of behavioral sets. Among such measures that may prove relevant are regional excitation of high frequencies seen in primate cortical recordings in the 30–80 Hz range associated with working memory and attention (Fries et al., 2001; Pesaran et al., 2002). Similar patterns of frequency-specific, event-related synchronization and desynchronization events are identified in the human EEG (Pfurtscheller and Lopes da Silva, 1999) and in the dynamical structure associated with the contingent negative variation

(CNV), a measure of expectancy generated by paramedian thalamic structures, and medial frontal cortices in response to a warning cue (cf. Nagai et al., 2004; Slobounov et al., 2000).

Although most studies of the correlation structure of the EEG examine dynamic patterns elicited by specific goal-directed tasks, such activations may only reflect half of the necessary fine structure typically present in a normal subject (and therefore possibly required for emergence from MCS). Raichle and colleagues have proposed that the very high resting metabolic rates in the normal human brain reflect "default self-monitoring" activity that characterizes the conscious goal-directed brain (Raichle et al., 2001; Gusnard and Raichle, 2001). This baseline activity is identified by specific patterns of reduction of brain oxygen extraction fraction (OEF) measured at rest across brain regions in a wide variety of goal-directed tasks. Maximum reductions in OEF arise in midline regions of the posterior medial parietal cortex (posterior cingulate cortex and precuneus) and mesial prefrontal cortex. The baseline mode is proposed to depend on tonically active processing in these areas and to correlate with the overall metabolic demands of resting wakeful states. The very low overall resting cerebral metabolic rates in MCS patients may reflect a severe deficit of such tonically active processes. The dissociation of low resting cerebral metabolism despite recruitable networks raises the possibility that patients who remain near the border of emergence from MCS are characterized by a loss of ongoing self-monitoring with fluctuation of recruitment of these large-scale networks under varying internal conditions of arousal and appearance of environmentally salient stimuli.

In normal subjects, Laufs et al. (2003) correlated fMRI BOLD signal with spontaneous power fluctuations in EEG frequency bands during the "baseline" resting state. They identified a strong positive correlation of beta activity (17–23 Hz) with posterior medial parietal (retrosplenial), temporal-parietal, and dorsomedial BOLD activation. This regional grouping overlaps with Raichle et al.'s baseline network. In addition, they identified a strong negative correlation of alpha activity (8–12 Hz) and BOLD signal in lateral frontal and parietal cortices. These observations raise the possibility that it may ultimately be possible to isolate specific dynamical signatures of ongoing activity in the distributed networks deactivated by task performance against the signature of other systems activated during behavioral performances.

In a study including 10 MCS patients, Laureys and colleagues observed relatively increased metabolic activity in these medial posterior parietal regions compared with VS patients. As noted above, this may indicate a partial reestablishing of baseline metabolic activity. It is interesting that although these regions are the most metabolically active regions in the resting human brain, bilateral injuries in these locations are not known to produce global disorders of consciousness. Focal injuries producing states of globally impaired consciousness and cognition, such as VS, MCS, and other forms of severe disability, are typically associated with bilateral injuries of the paramedian mesencephalon and thalamus, medial frontal cortical systems, or posterior-lateral temporal-parietal regions (Schiff and Plum, 2000). A possible interpretation of this difference, consistent with the proposed functions of these cortical regions, is that the self-monitoring activity thought to drive this high metabolic demand may not be necessary for goal-directed behavior and awareness *per se*.

In addition to quantifying incompletely or insufficiently established dynamic phenomena associated with normal cognition, a systematic evaluation of abnormal dynamics arising in the severely injured brain will be required in evaluating MCS patients. A large variety of pathophysiological mechanisms producing abnormal dynamics have been catalogued in the context of severe brain injuries. At present few diagnostic efforts are applied to assess the contribution of such mechanisms in patients recovering from severe brain damage. A relatively common finding following focal brain lesions is a reduction in cerebral metabolism in brain regions remote from the site of injury (Nguyen and Botez, 1998). Disproportionately large reductions of neuronal firing rates are associated with modest reduction of cerebral blood flow produced by these crossed-synaptic effects (Gold and Lauritzen, 2002). The cellular basis of this effect appears to be a loss of excitatory

drive to neuronal populations that results in a form of inhibition known as disfacilitation in which hyperpolarization of neuronal membrane potentials arises from the absence of excitatory synaptic inputs allowing remaining leak currents (principally potassium) to dominate (Timofeev et al., 2001). Disfacilitation may play a major role in changing resting brain activity levels given recent evidence (Steriade, 2004) that cortical neurons may change fundamental firing properties based on levels of depolarization (considered here as a proxy for excitatory drive). Multifocal injuries may therefore result in wide passive inhibition of networks due to loss of background activity. Note that selective structural injuries to the paramedian thalamus are unique in producing hemisphere-wide metabolic reductions presumably through this mechanism (Szelies et al., 1991; Caselli et al., 1991). Similarly, herniation injuries may generally produce some level of hemisphere-wide disfacilitation. Thus, the broadband, hemispheric, reductions in EEG coherence observed in the MCS patients discussed above may reflect ongoing functional alteration of common thalamic driving inputs to the cerebral cortex (as opposed to complete structural thalamic injury as seen in Fig. 2).

In addition to disfacilitation, which may arise on the basis of non-selective injuries across many different cerebral structures, other specific dynamical abnormalities may be associated with severe brain injuries. In some patients selective structural injuries may damage pathways of the brainstem arousal systems where the fibers emanate or run close together. Consequent withdrawal of broad cortical innervation by a neuromodulator could produce significant dynamical effects on the EEG and behavior. In a small series of VS patients with isolated MRI findings of axonal injuries near the cerebral peduncle (including substantia nigra and ventral tegmental area) and parkinsonism, the patients made late recoveries following administration of levodopa (Matsuda et al., 2003). The ascending cholinergic pathway also runs in tight bundles at points along its initial trajectory to the cerebral cortex and a role for focal injuries along this pathway has been proposed (Selden et al., 1998).

Epileptiform or similar hypersynchronous phenomena may arise in severe brain damage without obvious traditional EEG markers. Williams and Parsons-Smith (1951) described local epileptiform activity in the human thalamus that appeared only as surface slow waves in the electroencephalogram in a patient with a neurological exam alternating between a state consistent with MCS and interactive communication following an encephalitic injury. A similar mechanism might underlie a case of episodic recovery of communication in a severely disabled patient that intermittently resolved following occasional generalized seizures (Burruss and Chacko, 1999). Clauss et al. (2001) described emergence from MCS in a 28-year-old man with diffuse axonal injury after a stable 3-year period following administration of the GABA agonist zolpidem that correlated with 35–40% increases in blood flow measured by single photon emission tomography (SPECT) in the medial frontal cortex bilaterally and left middle frontal and supramarginal gyri. Experimental studies have shown increased excitability following even minor brain trauma that may promote epileptiform or other forms of hypersynchronous activity in both cortical and subcortical regions (Santhakumar et al., 2001). Other observed phenomena in severe brain injuries include several syndromes with features of dystonia such as oculogyric crises (Leigh et al., 1987; Kakigi et al., 1986), obsessive compulsive disorder (Berthier et al., 2001), and paroxysmal autonomic phenomena (reviewed in Blackman et al., 2004). These phenomena typically show selective responses to different pharmacotherapies.

It is not yet possible to predict the presence and influence of reversible dynamical phenomena that may arise in the setting of novel connective topologies induced by structural brain injuries. However, it may be possible to begin to identify specific dynamical signatures of such state-dependent phenomena using quantitative EEG and MEG methods. Llinas et al. (1999) demonstrated examples of spectral abnormalities in cross-frequency interactions in several different disorders including epilepsy, dystonia, and tremor. At present, however, no systematic methods have been developed to screen for these mechanisms. The brief review above suggests that to accurately model recovery from severe brain damage it will be necessary to attempt to isolate brain

dynamics across different structural pathologies and possibly even patterns of resting metabolic activity. Available studies reviewed above indicate that structural pathology and resting metabolism may provide only limited guides to understanding cerebral integrative processes associated with consciousness and cognition in severe brain dysfunction. Given these limitations complementary EEG measures need to be developed to track longitudinal changes in correlation with behavioral patterns and functional imaging.

Summary

Figure 4 organizes the proposed mechanisms for the clinical spectrum arising across VS and MCS patients. The common feature across all MCS patients is the preservation of contingent response to the environment even if infrequently observed. As suggested in Fig. 4, some MCS patients who remain behaviorally near the gray zone, where unusual VS patients can exhibit isolated fragments of behavior, might only retain a limited number of modular sensorimotor networks that nonetheless can show a patterned response. In such cases the patient's limited behavioral repertoire may not reflect greater residual cognitive capacities. Conversely, functional imaging studies already provide evidence that patients closer to emergence from MCS may harbor multiple, responsive large-scale networks. These functional differences likely underlie the rare instances of patients who spontaneously emerge late in the course of MCS. An accurate model of MCS for patients near this upper boundary will require understanding the mechanisms underlying endogenous recruitment of these distributed networks to form and stabilize behavioral sets. It is proposed that unstable interactions of the arousal and gating systems may underlie the fluctuations observed in MCS patients. Emergence from MCS (blue arrow) may then reflect recovery of sufficient ongoing dynamics to support communication and goal-directed behaviors in brains that have remained widely functionally connected but dynamically impaired.

Possible therapeutic strategies

Spontaneous emergence late in the course of MCS indicates that some patients with non-progressive encephalopathies retain reserve capacities. The observations raise the question of how these capacities might be recruited in MCS patients and others with less severe cognitive disability. Recent efforts have begun to examine the effects of dopaminergic and other neuromodulators early in the course of treatment of MCS patients (Giacino, this volume). As discussed above, in some patients, single-agent pharmacologic interventions may lead to dramatic improvements. Another direction for experimental therapeutics is the development of deep brain-stimulation (DBS) strategies.

DBS of selective intralaminar thalamic nuclei (ILN) has been proposed as a strategy for treating patients with acquired cognitive disabilities (Schiff et al., 2000, 2002b; Schiff and Purpura, 2002). Appropriate DBS stimulation parameters to produce clinically meaningful effects are unknown. At present DBS therapies are "open-loop" applications in which the frequency and amplitude of electrical pulses generated by the stimulator are empirically adjusted to achieve a steady-state stimulation rate that is titrated to clinical response (Volkmann et al., 2002). At least two complementary rationales for open-loop cognitive neuromodulation in the ILN can be articulated: increases in cortical neuronal activity induced by DBS might help support and extend ongoing distributed network activity. In addition, or alternatively, reestablishing normal patterns of coherence of neuronal activity may be important. Effective cognitive rehabilitation strategies suggest that special synchronizing signals also play a key role in reestablishing cognitive functions suggesting a basis for closed-loop DBS strategies as well (reviewed in Schiff and Purpura, 2002).

Initial experimental studies of open-loop DBS in primates and rodents provide some support for this research direction. We modeled a human vigilance paradigm (Kinomura et al., 1996) in the nonhuman primate to study central thalamic contributions to the formation and completion of behavioral sets (Schiff et al., 2001). Figure 5 shows the timeline of this experiment. The animal initiates the trial by holding a bar, and following a

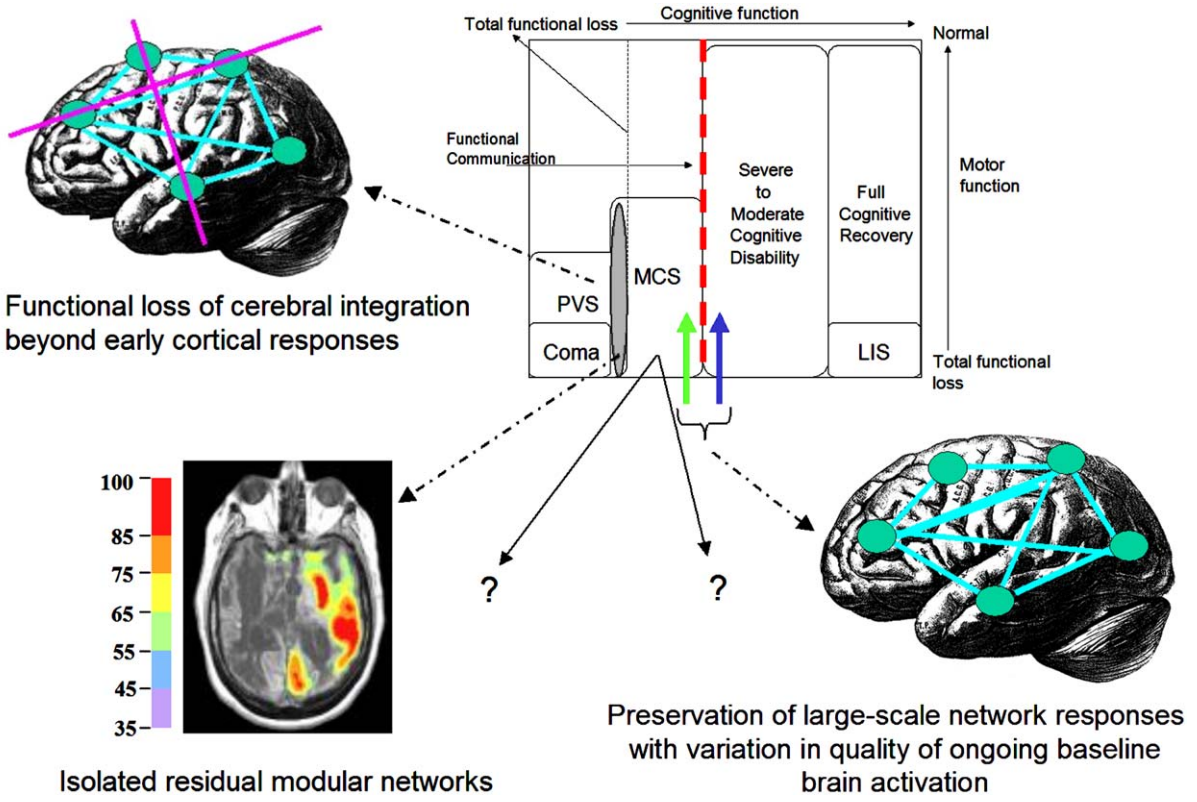

Fig. 4. Mechanisms underlying functional levels across spectra of vegetative state and minimally conscious state patients. Coregistered FDG-PET and MRI image from patient in Fig. 2 with color scale indicating percentage of normal regional metabolic rates (from Schiff et al., 2002; see text for further discussion). See Plate 33.4 in Colour Plate Section.

fixed delay a target appears in one of nine locations in a spatial array. After acquiring the target by a saccadic eye movement, the animal is then required to hold fixation for a variable delay until the target changes color providing a "go" signal to release the bar within one second to receive a juice reward. Figure 5B illustrates a peri-stimulus time histogram of single-unit responses from a central thalamic location during the sustained attention (variable delay) component of this reaction-time task. The persistent neuronal firing pattern seen is similar to the delay-period activity recorded during both selective attention and working memory paradigms in the prefrontal cortex (Fuster, 1973; Goldman-Rakic, 1996), frontal eye fields (Schall, 1991), and the posterior parietal cortex (Andersen, 1989; Pesaran et al., 2002). The central thalamic recordings shown here may be recorded from rostral regions of the ILN (Schlag-Rey and Schlag 1984) or closely related paralaminar regions of the median dorsalis nucleus. Collectively these regions selectively project to prefrontal cortex, frontal eye fields, and anterior cingulate cortex and lateral parietal areas placing them in a central position to participate in the integration of intentional gaze control with attentional and working memory systems (Purpura and Schiff, 1997).

The recordings from incorrect trials show that initiation of the persistent firing activity may arise but fail to build up to the same level and maintain activation over the course of the trial. Figure 6 illustrates the conceptual basis for the possible use of open-loop central thalamic DBS in selected MCS patients. If the patient can initiate behavioral set formation across distributed networks spontaneously, it is proposed that activation of these pathways may support increased firing rates at target cortical locations and improve the maintenance

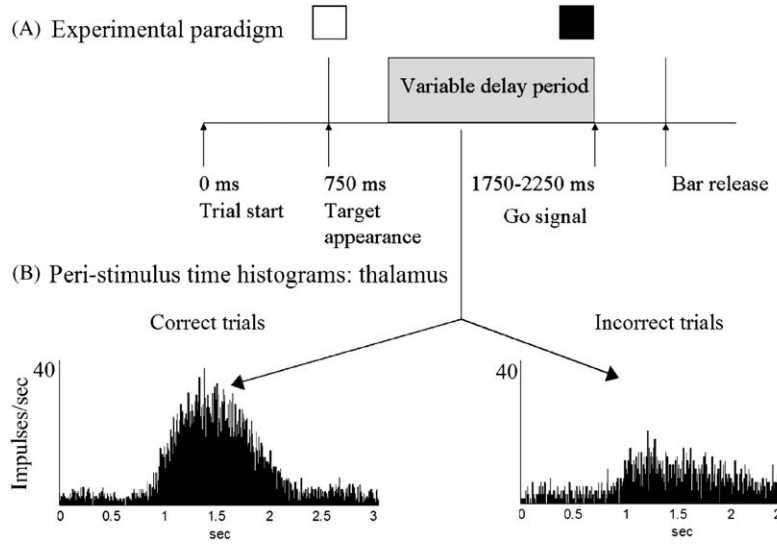

Fig. 5. (A) Behavioral paradigm for elementary visuomotor attention task. (B) Peri-stimulus time histograms for central thalamic neurons during correct and incorrect performance of the task.

and completion of behaviors that are initiated. In pilot studies using the same cognitive paradigm in conjunction with DBS in recording sites that showed elevation of single-unit firing rates (as shown in Fig. 5), the percentage of correct performances was significantly improved at the end of the day when large performance decrements arise (Schiff et al., 2002c). These findings are comparable to improvements in the performance of object recognition tasks during stimulation of the central lateral intralaminar nucleus in rats (Shirvalkar et al., 2004). These initial studies support further investigations into the contributions of central thalamic populations to elementary cognitive operations (cf. Wyder et al., 2004) and effects of direct electrical stimulation.

Implications and research directions

Why should we carefully study MCS patients and others with severe brain dysfunction? The most general answer is that it appears that functional disabilities may often exceed the obvious burden of structural brain injuries and that neuroimaging studies may show more distributed functional activation of cerebral networks than anticipated by the bedside examination. Further research efforts must focus on what these activations may mean, when the data present reasons to expect potential improvement or a reasonable basis to pursue the use of experimental therapeutics, and related diagnostic and prognostic concerns.

It is an empirical question whether residual cerebral capacities in some MCS patients can be augmented to achieve a palliative care goal. Fins (this volume) articulates a framework for palliative care in the context of severe brain damage. One apparently defensible palliative goal would be to help MCS patients reliably communicate. Communication presents a ''bright-line'' distinction that immediately places the patient into a different functional category. It may also be that reliable communication is the boundary where most would agree that concerns about futility are largely resolved. Along these lines, it is increasingly recognized that placing all patients with apparently nonprogressive encephalopathies into custodial care without further consideration of brain mechanisms is not consistent with basic principles of clinical ethics (Fins, 2003).

It is anticipated that understanding brain mechanisms underlying MCS will extend to insights into other less devastating outcomes of

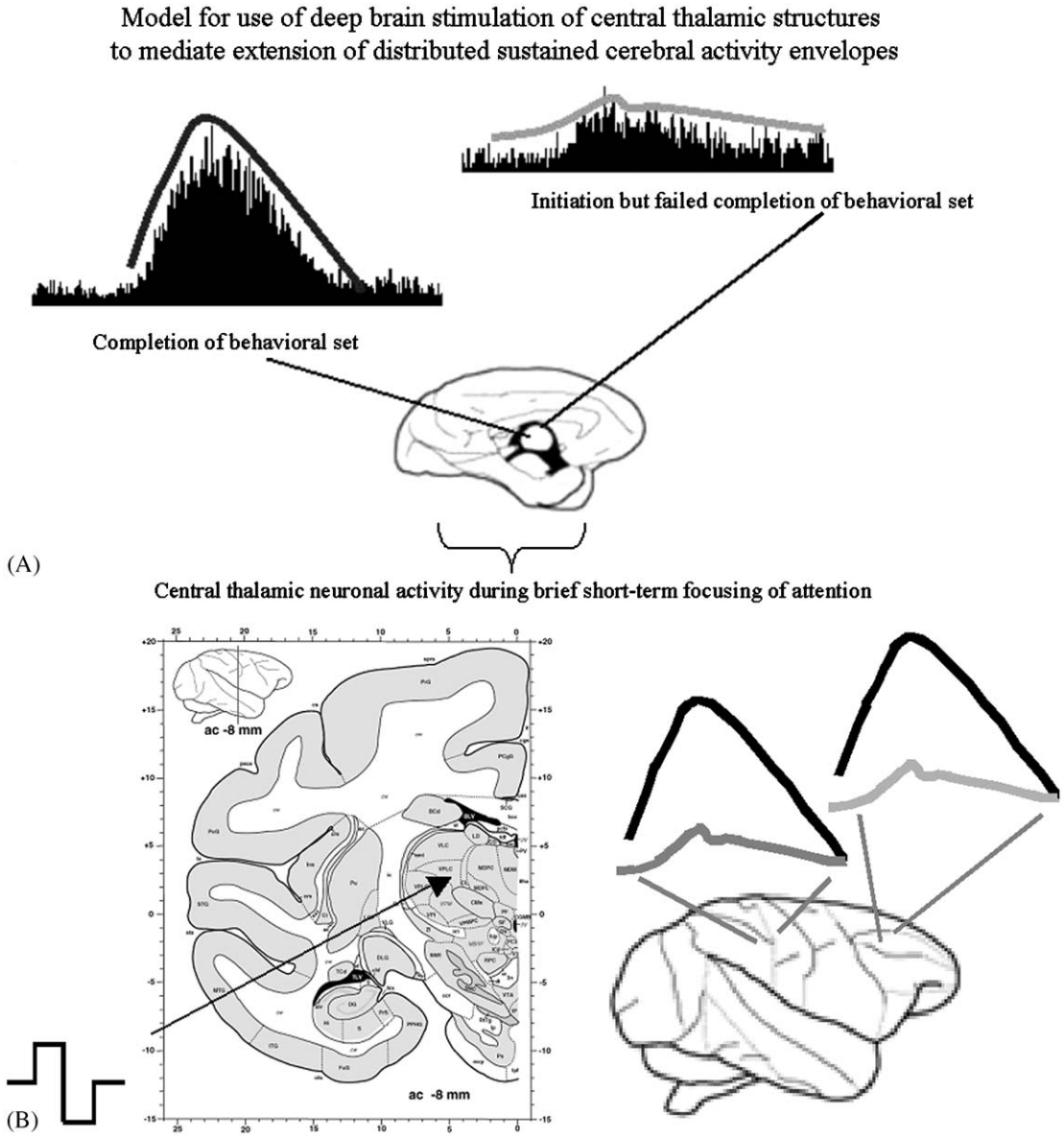

Fig. 6. Illustration of the theoretical basis for the proposed use of open-loop deep brain stimulation as a cognitive neuromodulation strategy (see text).

severe brain damage and potentially more significant palliative goals, if still falling short of restoring normal brain function. Patients suffering less severe brain injuries than those producing MCS will likely share similar pathophysiological mechanisms. For example, pathological studies in patients remaining with only moderate disabilities following brain injury identified post-traumatic epilepsy in 75% of the patients but no diffuse thalamic damage and only mild diffuse axonal injuries (Adams et al., 2001), suggesting that functional (dynamical) disturbances may play a greater role in outcome. To date, few studies have considered accessing

potential cognitive reserve in patients with non-progressive encephalopathies.

Finally, it should be recognized that studies of patients with severe brain damage are particularly vulnerable to dismissal by neurologists as irrelevant and hopeless, and by neuroscientists as too diffuse to fit into nicely packaged research projects. Unfortunately such attitudes have led to a continuing lack of scientific and medical infrastructure available to study brain function in these disorders (Laureys et al., 2004). Hopefully, the large number of new scientific contributions reflected in this volume will promote further curiosity and intellectual engagement of these issues.

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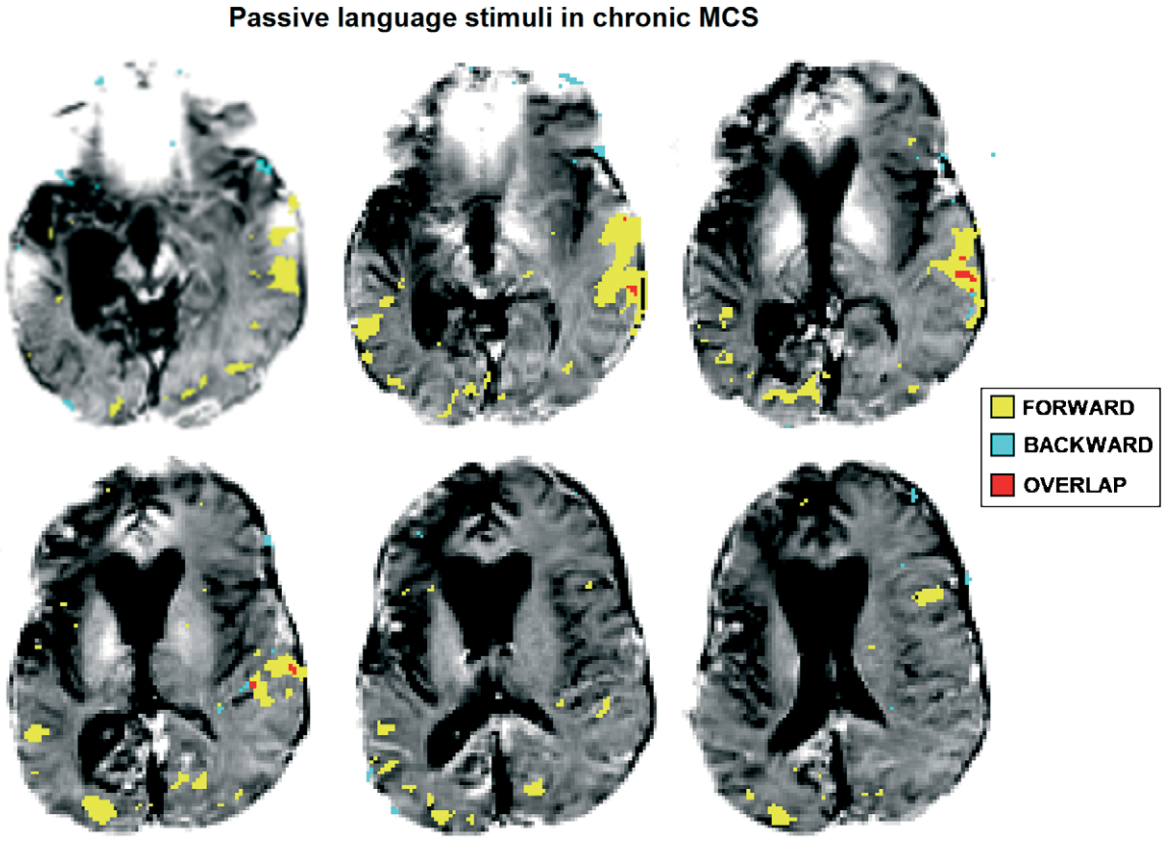


Plate 33.3. Functional magnetic resonance imaging activation patterns of BOLD signal in response to passive language presentations. Reproduced with permission from MIT Press.

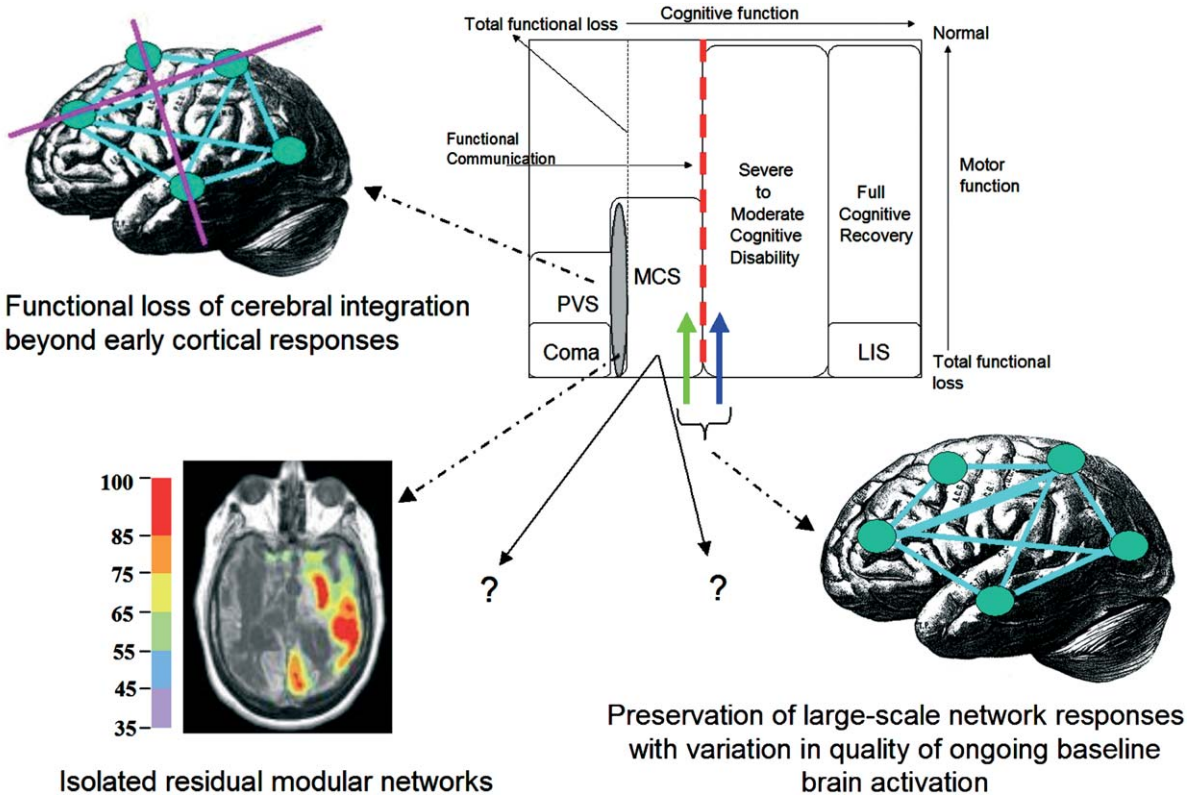
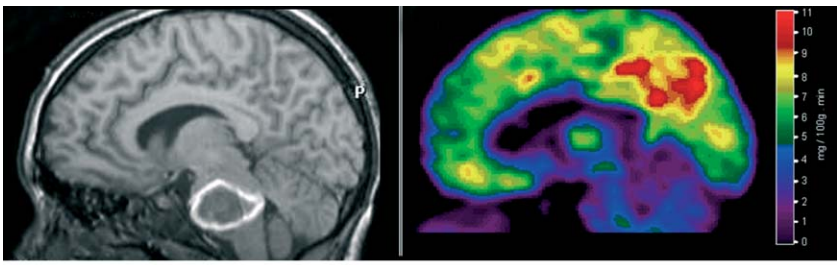


Plate 33.4. Mechanisms underlying functional levels across spectra of vegetative state and minimally conscious state patients. Co-registered FDG-PET and MRI image from patient in Fig. 2 with color scale indicating percentage of normal regional metabolic rates (from Schiff et al., 2002; see text for further discussion).



(A) (B)

Plate 34.2. (A) Magnetic resonance image (sagittal section) showing a massive hemorrhage in the brainstem (circular hyperintensity) causing a locked-in syndrome in a 13 year-old girl. (B) ^{18}F-fluorodeoxyglucose — Positron emission tomography illustrating intact cerebral metabolism in the acute phase of the LIS when eye-coded communication was difficult due to fluctuating vigilance. The color scale shows the amount of glucose metabolized per 100 g of brain tissue per minute. Statistical analysis revealed that metabolism in the supratentorial gray matter was not significantly lower as compared to healthy controls (Adapted from Laureys et al., 2004a).