JOURNAL OF NEUROTRAUMA
Volume 23, Number 10, 2006

Pp. 1436–1449

Measurements and Models of Cerebral Function in the Severely Injured Brain

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ABSTRACT

We review the emerging applications of functional and structural neuroimaging techniques for the assessment of patients with disorders of consciousness. Measurements of brain function from patients in the vegetative state (VS) and minimally conscious state (MCS) are compared, and a conceptual organization is developed that suggests models of brain mechanisms associated with different functional levels of recovery. We emphasize developing strategies to place complex brain injuries on a more equal footing using global and regional quantification of resting or activated brain activity using functional imaging techniques alongside more detailed structural assessments of neuronal integrity and axonal connectivity now available. Preliminary studies from several investigative groups suggest that some MCS patients may harbor a functional reserve in the form of recruitable cerebral networks. These findings support developing systematic characterizations of the severely injured brain and suggest that some patients may benefit from improved diagnostic assessments.

Key words: consciousness; functional neuroimaging; minimally conscious state; vegetative state

INTRODUCTION

DISORDERS OF CONSCIOUSNESS resulting from severe brain injuries present several daunting challenges for clinical neuroscience. Among the many etiologies of diffuse brain damage that may produce impaired consciousness, traumatic brain injury (TBI) poses the greatest difficulties. In many cases, overwhelming structural injuries are relatively easily identified by neuroimaging techniques and well correlated with permanent unconsciousness. However, even modest clinical evidence of awareness in the face of marked structural injuries may herald a potential for further recovery. Wide variations in damage to cerebral structures and late neuronal loss due to secondary effects of axonal injuries are both thought to play an important although not currently well-defined role in outcomes. An early description from Wilder Penfield illustrates the problem. Penfield (1975) recalls examining the famous Russian physicist Lev Landau who had remained first in a coma and then in a vegetative state for 6 weeks following a TBI.

> On my first examination of the patient, I agreed that he was completely unconscious . . . His limbs were paralyzed; his eyes were open but apparently unseeing. Next morning, when I entered his room

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> to examine him again, I was accompanied by his wife. She preceded me and, sitting down at the bedside, she talked to him . . . As I stood silent, watching over her head, I became aware of a startling change in the patient. He lay unmoving still, as on the previous night. But his eyes, which had been deviated from each other then, were focused now in a normal manner. He seemed to be looking at her. He appeared to hear, and see, and to understand speech! How could this be? She came to the end of her explanation and was silent. His eyes then moved upward to focus quite normally on me. I moved my head from side to side. The eyes followed me. No doubt about it! Then they swung apart again and he appeared as he had the night before to be unconscious.

Penfield's lucid description exemplifies the kind of fleeting, yet unequivocal evidence of response to the environment that can indicate the transition from a vegetative state to what is now identified as the minimally conscious state (MCS). Although Landau made further significant recovery by nine months, the transition to MCS does not necessarily portend additional progress. For the physician asked to provide an accurate diagnosis and prognosis for a patient with severe traumatic brain injury this is disquieting information.

Several research groups have now taken on the challenge to develop neuroimaging tools and protocols to aid the neurological assessment of patients with severe brain injuries (Laureys et al., 2004). In the brief review below, some of the opportunities and limitations of these techniques are discussed. Ultimately, a satisfactory approach to this problem will require a better understanding of the differences in underlying mechanisms producing similar functional levels of recovery. A conceptual organization is developed from measurements of cerebral function that suggest models of brain mechanisms associated with different functional levels of recovery. A strategy for measuring cerebral function is proposed to confront the complexity of heterogeneous brain damage associated with TBI and to attempt to compare different patient's brains on more equal footing.

NOSOLOGY AND ASSOCIATED PATHOLOGY

Figure 1 presents an overview of the nosology of global disorders of consciousness following severe brain injuries. Coma is a state of unarousable unresponsiveness and is typically the initial brain state produced by a severe brain injury (Plum and Posner, 1982). Coma usually resolves within 1 or 2 weeks and is followed by recovery of a limited cyclical arousal pattern characterized by an eyes open "wakeful" appearance, alternating with an eyes closed "sleep" state. This limited recovery of arousal patterns indicates the transition to a vegetative state (VS). Like comatose patients, patients in VS demonstrate no evidence of awareness of self or their environment (Jennett and Plum, 1972). The term persistent vegetative state (PVS) is an arbitrary designation applied after 30 days of VS and is now less often used (Jennett, 2002).

VS lasting at least 1 month and persisting to death 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, often in combination with the paramedian thalamus (Schiff et al., 2002). Despite these variations a convergence of evidence supports VS in its early and chronic stages as a functionally distinct state associated with broad disruption of thalamocortical activity. Adams et al. (2000) re-

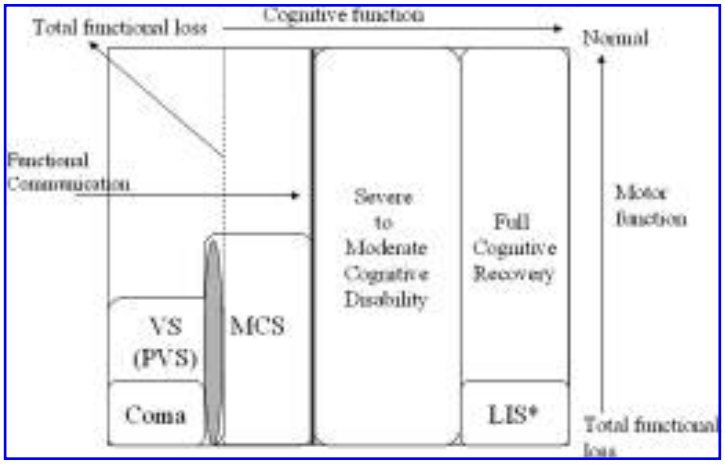

FIG. 1. Conceptual scheme for global disorders of consciousness. PVS, persistent vegetative state; MCS, minimally conscious state; LIS, locked-in state. (Reproduced, with permission, from MIT Press.)

viewed autopsy specimens from VS patients with traumatic brain injuries and found that the majority of patients demonstrated grade 2 and 3 diffuse axonal injury (DAI) and severe thalamic degeneration in (96% of patients). The investigators noted that damage to the thalamus following DAI is indirect as a result of transneuronal degeneration and that at least initially the neuronal substrate in the thalamus remains intact. Accordingly, delayed neuronal death 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; although VS is generally considered permanent after 3 months following anoxic injuries, recovery up to 1 year post-TBI is accepted (Multisociety Task Force, 1994).

The gray zone to the right of VS in Figure 1 reflects the uncommon observation of VS patients who may exhibit fragmentary behaviors that may be generated from isolated intact cerebral networks (Schiff et al., 1999, 2002). Close to this minimal level of behavioral interaction, patients enter into MCS once they demonstrate unequivocal but inconsistent evidence of awareness of self or the environment as demonstrated by verbal or gestural output (Giacino et al., 2002). The phenotype of MCS is broad and patients may also show wide fluctuations in baseline behaviors (Giacino and Whyte, 2005). The upper boundary determining a patient's emergence from MCS is reliable communication. At present, no data support establishing a predictive time frame for emergence from MCS following severe brain injuries. In fact, recent studies demonstrate a lack of correlation of time in MCS and ultimate level of recovery (Lammi et al., 2005). As an endpoint, some carefully studied MCS patients have shown significant changes in their capacity to communicate arising years after the initial injuries (McMillan and Herbert, 2004; Voss et al., 2005). Invariably, to date, such very late recoveries have been associated with TBI. If motor function is severely impaired, recognition of intermediate states between MCS and the locked-in state (LIS; not a disorder of consciousness) is very difficult.

Few studies of specific anatomic pathologies associated with MCS are available. Jennett and colleagues (2001) reported 65 autopsies of patients with traumatic brain injury leading either to a vegetative state or severe disability. Among patients within the severe disability group, 12 patients had clinical histories consistent with MCS at the time of death. Approximately one third of the overall group of severely disabled showed anatomic pathology consistent with findings in post-traumatic VS, that is, Grade 2 and 3 DAI and diffuse thalamic injury. The majority of the severely disabled patient group, however, did not show this type of pathology. Importantly, over half of the severely disabled group demonstrated only focal brain injures, without DAI or focal thalamic infarction (including two of the MCS patients). These findings identify the potential for an underlying anatomical substrate for residual networks and possible functional capacity in some patients who remain severely disabled at the low level of function consistent with MCS.

ELECTROPHYSIOLOGICAL STUDIES

Electroencephalography (EEG) patterns reported in VS patients range across findings of focal or diffuse continuous slowing in the theta (4–7.5 Hz) and/or delta (1–3.5 Hz) frequency ranges, intermittent delta rhythms, and severe attenuation including isoelectric recordings (Li et al., 1993; Hansotia, 1985). These gross abnormalities in the overall frequency content of the EEG or even the lack of reappearance of an EEG signal index the profound thalamocortical disconnection underlying VS. In addition, the normal ultradian and nocturnal EEG pattern fluctuations, as well as the reactivity of the EEG to stimuli are typically absent or grossly abnormal in VS. Isono et al. (2002) studied the diurnal EEG patterns in 12 VS patients and found little variation during the course of the day and no changes in response to noxious sensory stimuli. Typically, the EEG patterns that normally occur during the different stages of sleep, are absent in PVS patients, such as rapid eye movements (REM), sleep spindles, and vertex waves. Thus, the crude alternating behavioral arousal observed in VS patients largely reflects only the preservation of brainstem function, the *sine qua non* of the vegetative state. The cyclic variability and reactivity of the EEG *per se* are features that depend on the interaction of brainstem arousal systems and intact corticothalamic systems. This dissociation provides a physiological correlate of the classical vegetative state. The integrity of the upper brainstem-mesencephalic components of the reticular activating system and thalamus are crucial to the normal cerebral activity underlying the EEG; in fact overwhelming injuries to these structures may lead to permanent VS (Schiff and Plum, 2000).

Magnetoencephalography (MEG) studies of VS patients show a mixed pattern of absent or abnormal evoked magnetic field responses to sensory stimuli with alteration of high frequency components in all patients if present at all (Schiff et al., 2002). Classical EEG measured evoked potentials (EPs) are variably present in VS patients (Hansotia, 1985). Somatosensory evoked potentials (SEPs) are typically abnormal in PVS patients with delay and attenuation, or absence of the N20 cortical response to median nerve stimulation (Hansotia, 1985; Isono et al., 2002; Li et al., 1993). In a recent study of

98 severely brain-injured patients, including VS and MCS patients of varying etiologies (including TBI), Kotchoubey et al. (2005) identified N100, P300, and MMN responses in all VS patients without severe EEG slowing. These findings raise questions about the specificity of preserved ERP responses in the absence of information correlating these potentials with longitudinal changes in clinical exam, particulary recovery past VS or MCS levels of function. The limited preservation of high-frequency evoked EEG responses and other features of cortico-thalamic interactions in some VS patients may index the continuum of structural damage between VS and MCS.

Only a few studies currently report EEG findings in MCS patients. In general, EEG patterns are better preserved than in VS patients and observed abnormalities depend more on the location and type of cerebral lesions. Findings include diffuse or focal slowing, often in the theta and delta frequency range, loss of an organization pattern across diurnal cycles with absence, diminution,

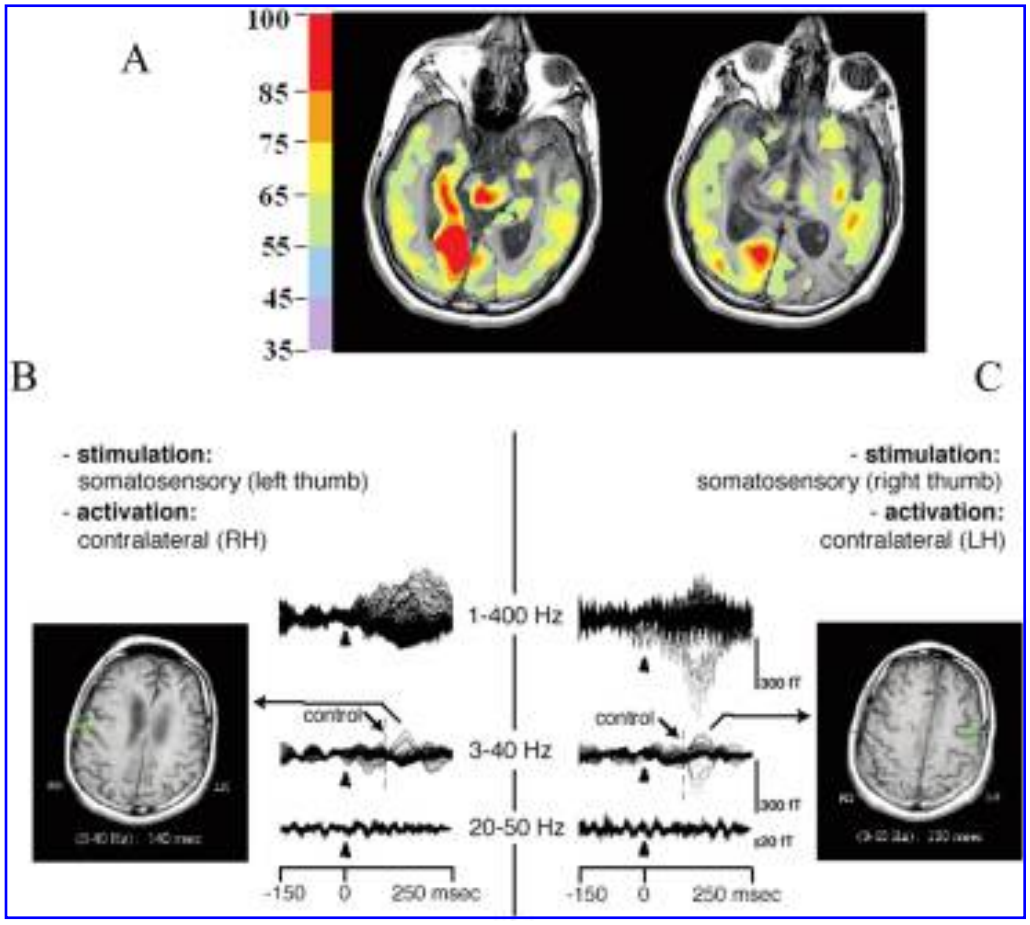

FIG. 2. Magnetic resonance imaging (MRI), positron emission tomography (PET), and magnetoencephalography (MEG) studies for patient described in text. (**A**) Co-registered MRI and PET images are displayed. PET voxels are normalized by region and expressed on a color scale ranging from 55% to 100% of normal. Marked reduction of metabolic activity across most brain structures is evident with preservation of posterior occipital metabolism near primary sensory cortex. (**B**) Contralateral somatosensory evoked magnetic fields (SEF) demonstrate a lack of time-locked activity in the gamma band in the right hemisphere following left thumb stimulation. Averaged waveforms are superimposed for all MEG channels and displayed unfiltered (1–400 Hz), and filtered at 3–40 Hz and at 20–50 Hz. Magnetic evoked field component is seen at around 140 msec (3–40 Hz; dashed line indicates main deflection seen in control subjects; note that control activation pattern is not shown here—see Schiff et al., 2002, for further details), localizing within sensorimotor areas. Goodness of fit: 99%. No evidence of time-locked activity in the gamma band (20–50Hz). (**C**) Left hemisphere activation are shown following right thumb stimulation. Averaged waveforms are superimposed for all MEG channels and diplayed unfiltered (1–400 Hz), and filtered at 3–40 Hz and at 20–50 Hz. Magnetic evoked field component is seen at around 130 msec (3–40 Hz), localizing within sensorimotor areas. Goodness of fit: 96%. No evidence of time-locked activity in the gamma band (20–50 Hz). (Reproduced, with permission, from *Brain*, Oxford University Press.)

and/or decreased reactivity of the posterior dominant rhythm (Boly et al., 2004; Kobylarz and Schiff, 2005).

FUNCTIONAL BRAIN IMAGING OF VEGETATIVE STATE AND MINIMALLY CONSCIOUS STATE PATIENTS AFTER TRAUMATIC BRAIN INJURIES

Although few functional neuroimaging studies have focused on severely brain-injured patients, important differences in cerebral function appear to separate VS and MCS patients (Laureys et al., 2004; Kobylarz and Schiff, 2004). A finding of profoundly depressed cerebral metabolism in VS/PVS patients has been replicated across several laboratories using fluoro-deoxyglucose positron emission tomography (FDG-PET) (Levy et al., 1987; DeVolder et al., 1990; Tomassino et al., 1995; Rudolph et al., 1999; Laureys et al., 2000, 2002; Schiff et al., 2002). In these studies, patients in VS associated with TBI show relatively higher resting brain metabolic rates despite overall reduction of global metabolic rate to ~50% of normal or less in an "eyes-open" state. Comparable levels of reduction in cerebral metabolism are typically only observed in pharmacologically induced coma (Laureys et al., 2004). Such sharp reductions of glucose metabolism can be interpreted as a proxy for widely reduced neuronal firing rates (Smith et al., 2002; Eidelberg et al., 1997).

Taken together with the pathological and electrophysiologic data reviewed above the metabolic profile of VS patients is consistent with a widely disconnected and inactive cerebrum. Figure 2 shows the results of multimodal neuroimaging studies for a TBI patient who had remained in VS for 7 months at the time of the studies (Schiff et al., 2002). On exam the patient exhibited classic features of VS, including wakeful appearance without evidence of awareness, intentional activity, or purposeful activity as assessed by command following, object pursuit, verbal or gestural communication, or other patterned responses.

MRI images revealed multi-focal shear injuries in the subcortical white matter with marked damage to the posterior splenium of the corpus callosum (cf. Kampfl et al., 1998) and multiple frontal and temporal lobe contusions. In Figure 2A, resting brain metabolism measured using FDG-PET imaging is shown overlaid on structural MRI slices. The color scale indicates the percentage of normal metabolic rate expressed regionally within the brain. Measurements across the brain show that metabolism was globally reduced in most regions to ~50% of normal metabolic rates. Nonetheless, some smaller regions expressed higher resting metabolism, such as the right occipital lobe shown in Figure 2A. MEG recorded somatosensory responses from the left/right hemisphere to unilaterally presented stimuli are shown in Figure 2B (left hemisphere, right hand) and Figure 2C (right hemisphere, left hand). Averaged evoked MEG recordings in this patient demonstrated a unique finding of a bilateral loss of high-frequency gamma band (20–50 Hz) activity, despite preservation of a low-frequency network response to sensory stimuli. In response to unilateral tactile stimuli, primary evoked magnetic fields (SEF) demonstrated weak and delayed contralateral brain activations at around 130/140 msec for the left and right hemisphere in the proximity of sensorimotor areas; for both hemispheres, there is no evidence of time-locked activity in the gamma band.

These findings suggest a loss of important integrative responses reflected in high frequency responses (Ribary, 2005). The bilateral loss of high-frequency MEG activity in the somatosensory cortex in this patient may also reflect the role of feedback from motor regions in this response (Ribary et al., 1999). Although the FDG-PET imaging studies shown in Figure 2A identify small islands of relatively preserved metabolism, the patient showed no behavioral variations, and it is not possible to infer any specific functional activity of these regions of occipital cortex with higher metabolic rates. Nonetheless, the relatively preserved metabolism may indicate that these regions represent clinically silent, but partially functional sensory circuits.

In some rare cases, VS patients may exhibit unusual behavioral fragments that cannot be correlated with environmental stimulation, nor appear to be purposefully directed. Such patients may be placed in the gray zone of Figure 1. Figure 3 shows correlations of FDG-PET and MEG findings in such a unique patient who suffered successive hemorrhages from a deep, central arteriovenous malformation (Schiff et al., 1999). Over the course of a 20-year period in PVS, this patient had infrequently expressed isolated words (typically epithets) in isolation of environmental stimulation. Structural brain imaging identified destruction of the right basal ganglia and thalamus, as well as severe damage to the left posterior thalamus and moderately severe cortical atrophy in both hemispheres. As shown in Figure 3A, resting FDG-PET measurements in this patient reveal a sharp reduction in global cerebral metabolism to levels less than 50% of normal across most brain regions. Isolated regions in the left hemisphere, however, expressed higher levels of metabolism; in the figure, only values greater than 55% of normal are displayed. Evoked MEG responses to bilateral auditory stimulation identified an abnormal time-locked gamma-band activity restricted to the left hemisphere (Fig. 3D) and no response in the right hemisphere (Fig. 3C) consistent with the absence of the right medial geniculate body to relay auditory inputs. Compared to normal controls, the left hemisphere auditory gamma-band response cortical response is reduced, desynchronized and

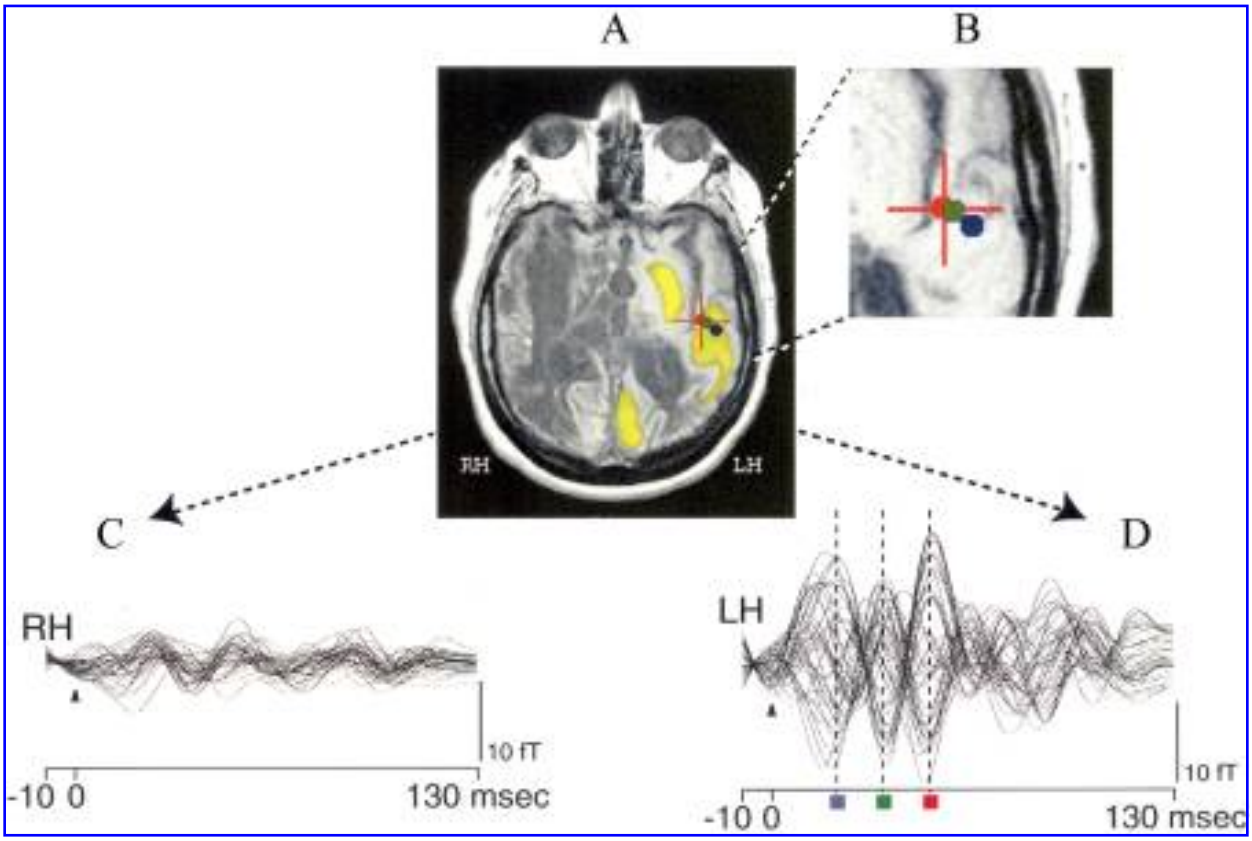

FIG. 3. (**A**) Positron emission tomographic (PET) regions of interest demonstrating metabolism above a threshold of 5.5 mg/100 g/mL (rCMRglc) are displayed (yellow regions) on co-registered MRI and overlayed with locations of MEG equivalent current dipoles having correlation of greater than 97%. Note the large area of damage to right hemisphere subcortical structures evident on MRI image with some sparing of the left anterolateral thalamus (**B**) MEG dipole locations. Cross-hair and red dot corresponds to dipole location of maximal response at a latency of 50 msec; other dipole fits at latencies of 21 msec (blue dot) and 35 msec (green dot) are also displayed (see D). (**C**) MEG waveforms for right hemisphere gamma-band (20–50 Hz filtered) mid-latency evoked activity in response to bilateral auditory stimulation. (**D**) MEG waveforms for left hemisphere gamma-band (20–50 Hz filtered) mid-latency evoked activity in response to bilateral auditory stimulation. (Reproduced, with permission, from *Journal of Cognitive Neuroscience*, MIT Press.)

incomplete (Joliot et al., 1994). Single-dipole analysis localizes this remaining evoked cortical component of the gamma-band activity to primary auditory areas within the left hemisphere as shown in Figure 3D. These locations corresponded to the island of higher resting brain metabolism observed by PET imaging in the left temporal lobe. In the aggregate, the small islands 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). The incompletely preserved MEG patterns of spontaneous and evoked gamma-band responses demonstrate that thalamocortical connectivity has been at least partially spared. Altogether the data support a sparing of thalamo-cortical-basal ganglia loops that underlie important aspects of human systems include the restricted regions of Heschl's gyrus, the frontal operculum (Broca's area) and cortico-cortical connections to the left temporal-parietal cortex (Wernicke's area), and the left caudate nucleus. This remnant functional circuit may account for the patient's occasional word production (Schiff et al., 1999). Other VS patients with behavioral fragments and evidence of isolated metabolic activity within defined cerebral networks have been described (Schiff et al., 2002).

Correlation of measurements of resting brain metabolism, patterns of structural injury, and MEG evidence of thalamocortical network preservation can only provide indirect support for preserved cerebral functional connectivity. To directly assess cerebral network integrity,

functional neuroimaging methods must be employed (Laureys et al., 2004). Menon et al. (1998) reported the first functional imaging study of a VS patient using functional positron emission tomography techniques (fPET) that showed evidence of preserved occipital cortical response to images of familiar faces compared with unstructured visual stimuli. A series of fPET studies by Laureys et al. (2000, 2002) have compared cortical activation patterns in response to simple auditory and somatosensory stimuli for PVS patients and normal controls. In these studies, PVS patients show brain activations restricted to the primary sensory cortices for both types of stimuli when compared against baseline resting conditions and do not activate higher-order cortical regions engaged by the same stimuli in normal control subjects. These observations are consistent with the understanding that there is widespread functional disconnection across cortical pathways in the PVS brain.

Recent functional imaging studies have included patients selected using the Aspen criteria for MCS (Giacino et al., 2002). Boly et al. (2004) 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 as well as strong correlation of the auditory cortical responses with frontal cortical regions. These observations provide evidence for preserved cerebral processing associated with higher-order integrative function in MCS patients. In other studies, Boly et al. (2005) have shown that MCS patients generate patterns of activation consistent with a normal pain network response.

In addition to evidence for cortical networks that process somatosensory and unstructured auditory stimuli, there is evidence for preservation of language responsive networks in MCS patients. We studied two patients who remained in MCS for greater than 18 months using functional magnetic resonance imaging (fMRI) and FDG-PET (Schiff et al., 2005). The patients and seven control subjects were studied with language activation paradigms similar to paradigms used in normal subjects and neurosurgical candidates to map language networks (Hirsch et al., 2000). Two 40-sec narratives were prerecorded by a familiar relative and presented as normal speech (yellow color), and also played time-reversed (blue color; red color indicates overlapping response to both forward and time-reversed stimuli). Forward presentations generated robust activity in several language-related areas in both patients. Figure 4 shows data from one MCS patient and a normal control subject. Regions of activation during presentation of the normal speech (shown in yellow color) included the inferior and medial frontal gyri, superior and middle temporal gyri, as well as primary and secondary visual areas including the calcarine sulcus, inferior and middle occipital gyri, precuneus, cuneus and inferior parietal lobule. The occipital region activations suggest possible visualization during presentation of the forward narratives. For the patient shown in Figure 4, the total volume and the specific regional cerebral activity overlapped with regions identified in control subjects for the forward narrative presentations. Importantly, large-scale network activations in both MCS patients were only seen for forward speech, and not for reversed speech; in normal controls, both presentations activated similar areas (compare yellow regions against blue for time-reversed only, and red for overlapping responses in Figure 4). Although the results demonstrate language-specific activations of large-scale networks in MCS patients, the implications of this difference between MCS patients and normals are unclear. One possibility is that the lack of activation for the time-reversed narratives reflects the loss of anticipatory, ongoing perceptual processing of environmental stimuli in MCS patients. FDG-PET measurements in both patients suggest a marker of baseline inactivity, with average resting eyes-open states averaging ~50% of normal metabolic rates—similar to values observed in VS patients. The time-reversed narratives may thus fail to overcome low resting neuronal activity in the MCS patients to engage dormant large-scale network processing capacities. The low resting metabolism of the MCS brain may reflect the loss of ongoing self-monitoring activity suggested to underlie high resting metabolic demands in normal subjects (cf. Gusnard and Raichle, 2001).

The demonstration of recruitable large-scale networks in MCS patients importantly 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 brain. Possible mechanisms underlying the apparent loss of ongoing activation of latent cerebral networks are reviewed below. For both MCS patients studied, it is proposed that impaired thalamocortical function resulting from transtentorial herniation injuries may account for an overall bilateral reductions of resting brain metabolism and bi-hemispheric dysfunction (Schiff, 2005; Schiff et al., 2005).

POSSIBLE UNDERLYING PATHOPHYSIOLOGICAL MECHANISMS OF RECRUITABLE COGNITIVE RESERVE

The imaging studies described above support the hypothesis that MCS reflects a chronically underactive

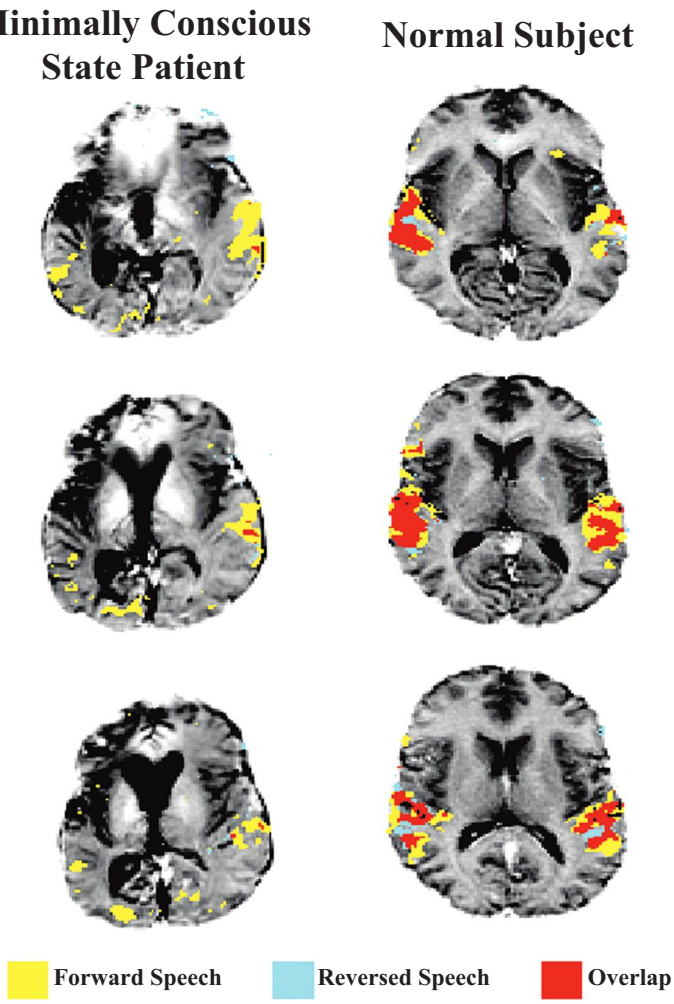

FIG. 4. Functional magnetic resonance imaging (fMRI) activation patterns of blood-oxygen-level-dependent (BOLD) signal in response to passive language presentations for a single patient in the minimally conscious state and a normal control subject.

brain that in some instances retains widely connected and recruitable cerebral networks (Schiff, 2005). Under not yet well-defined conditions these networks are capable of supporting sensorimotor integration, limited behaviors, and intermittent communication. Thus, the findings prompt consideration of partially reversible processes that could limit greater expression of latent cerebral networks. In addition, the variable time course of recovery from MCS and examples of very late recoveries suggest that currently unmeasured variables may play an important role. Accordingly we briefly review dynamical mechanisms and possible slowly evolving structural variations that may arise in the severely damaged brain.

REVERSIBLE DYNAMIC PHENOMENA

Several clinical observations indicate an important role for pathophysiological mechanisms producing abnormal brain dynamics in the context of severe brain injuries. Few diagnostic efforts are applied to assess the contribution of such mechanisms in patients recovering from severe brain injury. At least three different classes of phenomena may play a role as reviewed below. Donald Hebb (1949), in *The Organization of Behavior*, recognized the potential importance of such dynamic abnormalities grouping them in a concept of "hypersynchrony":

> A region in which the blood supply is interfered with, but not entirely shut off, usually shows some loss of cells and a number of remaining cells whose staining properties are changed. This indicates a change in the chemical properties of the cell, which in turn implies a change in frequency properties and obviously may account for the existence of a hypersynchrony which interferes with the functioning of the cell-assembly. A focus of hypersynchrony must act as a pacemaker that tends to wean transmission units away from the assembly. When hypersynchrony is not great, it would allow some as-

> semblies to function (particularly those that are long established) but would tend to interfere with recent memory, decrease responsiveness, and interfere with complex intellectual activities. When it is more extensive, it would prevent all higher functions.

Hebb's suggestion hints at several mechanisms now identified following brain injuries: (1) crossed synaptic downregulation (diaschisis), a relatively common finding of reduction in cerebral metabolism and blood flow in brain regions remote from the site of injury (Nguyen and Botez, 1998), (2) restricted hypersynchronous discharges reflecting subcortical epileptiform activity, and (3) alteration of subcellular processes without neuronal death through damage to specific pathways (Jenkins et al., 2004). Cross-synaptic downregulation produces disproportionately large reductions of neuronal firing rates in association with modest reduction of cerebral blood flow (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 neuronal membrane potentials are passively hyperpolarized due to a withdrawal of excitatory synaptic inputs (Timofeev et al., 2001). Disfaciliation may play a large role in changing resting brain activity levels given recent evidence that cortical neurons may change fundamental firing properties based on levels of cell membrance depolarization (Steriade, 2004). The degree of depolarization may be considered a proxy for excitatory drive. Multi-focal brain injuries may therefore result in wide passive inhibition of the cerebrum due to the loss of background synaptic activity across many networks. Among several large pathways that when damaged produce measurable cross-synaptic effects, selective injuries to the paramedian thalamus are unique in producing hemisphere-wide metabolic and blood flow reductions (Szelies et al., 1991; Caselli et al., 1991). This is a potentially important observation in the context of outcomes from severe TBI. The paramedian thalamus and upper brainstem are vulnerable to *en passant* damage in the setting of herniation during the acute swelling phase of severe TBI that arises in many cases. Such injuries may introduce hemisphere wide disfacilitation, contributing to reduced responsiveness of otherwise connected cerebral networks. In support of this potential mechanism, Kobylarz et al. (2005) identified broadband, hemispheric, reductions in EEG coherence across interregional electrode pairs that correlate with significant thalamic hypometabolism in the MCS patients studied by Schiff et al. (2005). It is proposed that these findings reflect ongoing functional alteration of common thalamic driving inputs to the cerebral cortex (Schiff, 2005).

Epileptiform or similar phenomena associated with "hypersynchrony" *per se* may often arise in the setting severe brain injuries. Experimental studies indicate an increased excitability following even minor TBI that could promote hypersynchronous activity in both cortical and subcortical regions (Santhakumar et al., 2002). Importantly, significant clinical effects could arise from such activity without obvious traditional EEG markers of epileptogenesis. Williams and Parsons-Smith (1951) reported a patient with a neurological exam alternating between a state consistent with MCS and interactive communication following an encephalitic injury and correlated local epileptiform activity in the human thalamus that appeared only as surface slow waves in the electroencephalogram with the MCS functional level. In this case, the patient recovered interactive communication after continuous IV phentothal treatment. A similar mechanism might underlie other cases of episodic recovery of communication in severely disabled patients that arise in the setting of generalized seizures or use GABA agonists (Burruss and Chacko, 1999; Clauss et al., 2000). Recent prospective studies of VS and MCS patients suggest that dopaminergic or gabaergic agents may promote recovery (Whyte et al., 2005). In addition, other phenomena can arise in severe brain injuries that remit with specific pharmacotherapies; these include syndromes with that share features with catatonia and dystonia such as oculogyric crises (Leigh et al., 1987; Kakagi et al., 1986), obsessive compulsive disorder (Berthier et al., 2001), and paroxysmal autonomic phenomena (cf. Blackman et al., 2004).

In addition to disfacilitation and epileptiform activity, other specific dynamical abnormalities may be associated with severe brain injuries. Isolated damage to pathways of the brainstem arousal systems may produce global impairment of consciousness, if the injuries impact the origin of fibers or points at which the tracts remain close together. Matsuda et al. (2003) reported a small series of VS patients with Parkinsonian features who showed isolated MRI findings of axonal injuries near the cerebral peduncle involving the substantia nigra and ventral tegmental area dopaminergic systems. These patients made late recoveries following administration of levodopa. Selden et al. (1998) propose that selective to damage to the ascending cholinergic pathways may cause clinically significant effects if injured as they exit the basal forebrain and travel through the ventral frontal white matter running in tight bundles at points along their trajectory to the cerebral cortex.

It is not yet possible to systematically characterize such reversible dynamical phenomena arising in the setting of novel connective topologies produced by structural brain injuries. Quantitative EEG methods may allow the dynamical signatures of such state-dependent phenomena

to be codified and used in conjunction with anatomical information to develop a better understanding of the prevalence and nature of these induced brain dynamics.

SLOW CHANGES IN BRAIN STRUCTURE

Structural brain imaging studies are an imperfect guide to the behavioral level ultimately achieved by a patient following severe TBI. Kampfl et al. (1998) described indirect volumetric MRI indices that provide reasonable predictive accuracy of approximately 84% (when combined with time in VS) for remaining in a permanent vegetative state. Unfortunately, patients fulfilling these criteria can recover after long intervals. We recently studied a patient who recovered interactive awareness and fluent but dysarthric speech after remaining in MCS for 19 years as judged by available medical records who nonetheless demonstrates extensive bi-hemispheric axonal degeneration as quantitatively measured using diffusion tensor imaging (DTI) (Voss et al., 2005). In this patient, the corpus callosum is reduced to one-third of the measured normal fractional anisotropy. McMillan and Herbert (2004) have reported 5- and 10-year follow-up on a well-characterized patient who had been at the center of a contentious legal debate in the United Kingdom. Their patient had remained in MCS for over a year following severe TBI but showed slow but continuous changes over a decade following injury. At 5 years, although the patient remained completely dependent, she had recovered the capacity for oral feeding, speech, some memory consolidation with retention, as well as improved insight into her condition. At the 10-year follow-up, the patient showed further improvement regaining the capacity to initiate conversation, express clear preferences and spontaneous humor. These observations suggest that some slow and presently unmeasured variables affecting brain function may exist and should be quantified if possible. It is unclear whether such slow changes depend exclusively on alterations of large-scale brain dynamics and synaptic plasticity (mechanisms for which evidence is available from the study of TBI and other neurological conditions) (Ward 2005). It is possible that alterations of brain structure may also play a role.

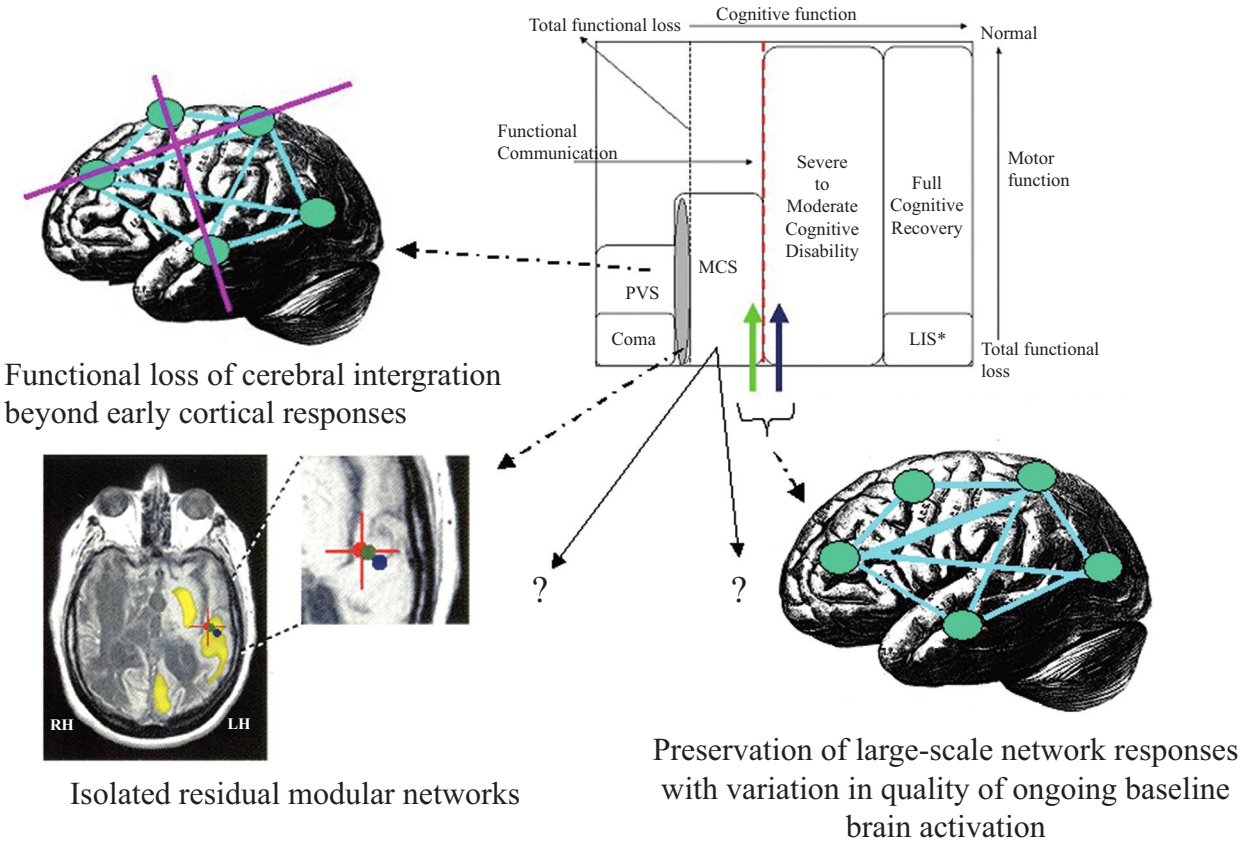

FIG. 5. Conceptual models for the mechanisms underlying brain function across spectrum of vegetative state and minimally conscious state patients. (Reproduced, with permission, from *Progress in Brain Research* 2005;150:477–947, Elsevier Press.)

To measure changes in brain structure will require assessment of both grey and white matter structures. Danielsen et al. (2003) report detailed MRI and magnetic resonance spectroscopy (^{1}H-MRS) findings from a patient with severe DAI measured over several timepoints while the patient remained in coma for 3 months and 21 months later when the patient had slowly recovered to a near independent functional level. In this patient, ^{1}H-MRS revealed characteristic regional reductions of NAA (*N*-acetyl-aspartate)/choline ratios within the white matter associated with severe DAI that later normalized in the study done at 21 months post-injury and correlated with evidence of cognitive recovery. Whether these MRS measured changes include structural alterations of the white matter is unclear. It is important to note, however, that there is evidence for a variety of mechanisms to allow for cortical rewiring (Chklovskii et al., 2004). This evidence includes large-scale cortical rewiring in adult monkeys following neurological lesions that could only be explained by axonal growth (Pons et al., 1991). Dancause et al. (2005) have provided evidence of extensive cortical rewiring in the adult primate brain after injury that originates from extensive proliferation of novel terminal fields produced by axonal sprouting. Longitudinal evaluations of changes in MRS and DTI measurements in patients recovering from severe TBI should provide further insight into these not well-understood observations.

MODELS OF BRAIN MECHANISMS ASSOCIATED WITH DIFFERENT FUNCTIONAL LEVELS OF RECOVERY

As detailed above, different levels of recovery from severe TBI can be modeled in terms of differences in underlying structural pathology and cerebral network function. In the aggregate, VS is associated with wide loss of functional integration of the thalamocortical system. In many cases, VS following TBI is associated with overwhelming cerebral functional disconnection that leads to permanent structural disconnection over time. A working model for VS is a widespread loss of integrative network function as measured by fMRI or fPET and absence or marked alteration of electrophysiological signs of cortical response from outside early sensory processing regions (Fig. 5) Exceptions to this model can be identified and new studies suggest that VS may be further divided by preservation of EEG background activity. For permanent VS, however, it seems reasonable to seek convergence of structural, functional, and clinical data supporting this model for unqualified use of the term in individual patients (particularly for research reports). For example, the heterogeneity of non-traumatic brain injuries such as paramedian thalamic infarcts producing a VS level of function are unlikely to follow similar natural histories (Schiff, 2004) or produce convergent structure function correlations (cf. Owen et al., 2005).

MCS patients may harbor considerably more cerebral network functional integration that may be strongly dissociated from normal resting metabolic activity levels. The failure of these networks to remain consistently active may reflect a baseline loss of the predictive, goal-directed state of normal wakeful consciousness (Schiff et al., 2005). Ultimately, even once identified, the underlying capacities of these networks identified in MCS patients are not known.

CONCLUSION: TOWARD A GENERAL STRATEGY FOR CHARACTERIZING THE SEVERELY INJURED BRAIN

The approach to measuring brain function in VS and MCS taken here aims at developing a functional characterization that treats the brain with multi-focal injuries from a physical systems viewpoint as distinguished from a more traditional neuropsychological approach. This strategy offers some hope of allowing complex brain injuries to be compared on a more equal footing. Starting with global and regional quantification of resting brain activity using PET and detailed structural assessments available from MRI, MRS, and DTI techniques, aggregate measurement of neuronal integrity and axonal connectivity can be used to provide benchmarks. It is expected that in many patients with very severe injuries some volumetric descriptors will be useful as suggested by the Kampfl et al. (1998) studies.

There are several methodological caveats to be noted, however, in using functional imaging and related techniques to evaluate patients with severe brain injuries (Laureys et al., 2004; Owen et al., 2005). The first issue is diagnostic clarity (Fins and Plum, 2004), which is often not found in the published literature. Another critical point is providing sufficient historical detail to allow comparison of etiologies of injury, time in the evolution of the course the patient's illness and other key facts such as details of concurrent pharmacotherapies that may confound measurements. Most importantly, it will be essential to establish vetted paradigms that can more unambiguously evaluate the level of cognitive function assayed as suggested by Owen et al. (2005).

Eventually fMRI and fPET evaluations in combination with more standard neuropsychological methods may be developed to guide rehabilitation efforts (cf. Giacino, 2005). These techniques, however, already offer an im-

mediately available opportunity to assess the integrity of cerebral network responses against the background level of ongoing activity and structural substrates. Finally, more detailed and integrative assessments of dynamics of the ongoing EEG are likely to be of considerable value. These measures can provide very statistically robust guides to recovery of brain states and functional correlates of goal directed behavior and communication that may eventually help to index cognitive capacity and graded recovery over time. Such a thoroughgoing approach to characterization is likely to be necessary to ultimately understand which patients may harbor recruitable cognitive reserve. Identifying this possibility is a pre-requisite for future efforts aimed at developing therapeutics and tracking recovery of consciousness in the severely brain-injured individual.

ACKNOWLEDGMENTS

Sections of this paper were presented at the 14th Annual Conference of the Rotman Research Institute, Toronto, Canada, on March 14, 2004. We thank Drs. Brian Levine and Donald Stuss for the invitation to speak at the conference. The support of the Charles A. Dana Foundation and the NIH-NINDS (NS02172, NS43451) and WMC GCRC M01 RR00047 are gratefully acknowledged.

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