A neuromodulation strategy for rational therapy of complex brain injury states

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We review initial efforts at neuromodulation in the vegetative state and organize several aspects of recent studies of the underlying neurobiology of catastrophic brain injuries. An innovative strategy for patient and target selection for neuromodulation of impaired cognitive function is outlined. Scientific and ethical issues that will attend future efforts to appropriately risk-stratify patients and initiate interventions with therapeutic intent are considered. [Neurol Res 2000; **22**: 267–272]

Keywords: Deep brain stimulation; impaired cognition; consciousness; intralaminar thalamus; brain imaging; brain metabolism

INTRODUCTION

This summary organizes several aspects of recent progress in understanding the underlying neurobiology of catastrophic brain injury. It also focuses on initial efforts at neuromodulation in the vegetative state. Accordingly, we first describe the results of these studies and then present a novel strategy for patient and target selection for neuromodulation of impaired cognitive function. Several complex issues are addressed that will attend future efforts to risk-stratify appropriate patients and initiate interventions with therapeutic intent.

Chronically impaired cognitive function remains the least explored area for neurological treatment. Despite the substantial public health need to develop and implement such therapies, progress has been slow and research support limited[1,2]. Development of new therapies is complicated by scientific, social and ethical problems[3]. Foremost among the scientific barriers is the neuroanatomical and functional complexity of brain injuries and the theoretical and practical challenges they present. Furthermore, the uncertainties of any improvement by potential interventions coupled with the overall vulnerability of injured patients have required an appropriately cautious approach. Nonetheless, it is a societal imperative to develop novel therapies aimed at this increasingly large, marginalized population.

The cognitive capacities of patients recovering consciousness following moderate to severe brain injury span a broad spectrum. Those who permanently remain 'minimally conscious' with limited evidence of awareness or only fragments of interactive behavior represent the lowest level[4]. Beyond that level, several relatively unclassified categories of functional outcome exist (*Figure 1*). Most patients who suffer severe brain damage regain arousal but too little capacity for memory, attention, intention and awareness to attain independent living. Many of these patients fluctuate widely, with periods of alert, responsive behavior alternating with out-of-contact states. Other patients who reach 'independent' functional levels often retain marked cognitive impairments. Many such persons deteriorate seriously in response to mild stresses such as colds, low-grade fevers, or interpersonal arguments. Even persons who regain seemingly full consciousness and a functional working memory sometimes find themselves unable to reach pre-traumatic cognitive levels[5].

At present, no scientific study has aimed at developing neurophysiological approaches to treat these severely brain injured patients. Nevertheless, several related phenomena have been examined in brain injured patients that suggest clues to the nature of fluctuations and the potential to further improve cognitive function in patients who exhibit them (see below).

SCOPE OF THE PROBLEM

Most patients with complex brain injury states have suffered traumatic brain injury. Anoxic, ischemic, degenerative, and other brain injuries also leave many patients with chronically impaired cognitive function. The public health dimensions of this problem are wide, with important economic and social impact (*Table 1*). Many of these patients are free of systemic disease and still more incur their injuries when young. Thus, gains made in the treatment of these illnesses will have a long-term impact.

As indicated in *Table 1*, in the United States alone, the costs of care for new patients each year following traumatic brain injuries are estimated at 10 billion dollars[2]. Serious brain injuries lead to residual cognitive impairment function in an estimated 200,000 Americans each year[1,6] and statistics indicate that as many as 90,000 patients a year may fail to reach independent living[7].

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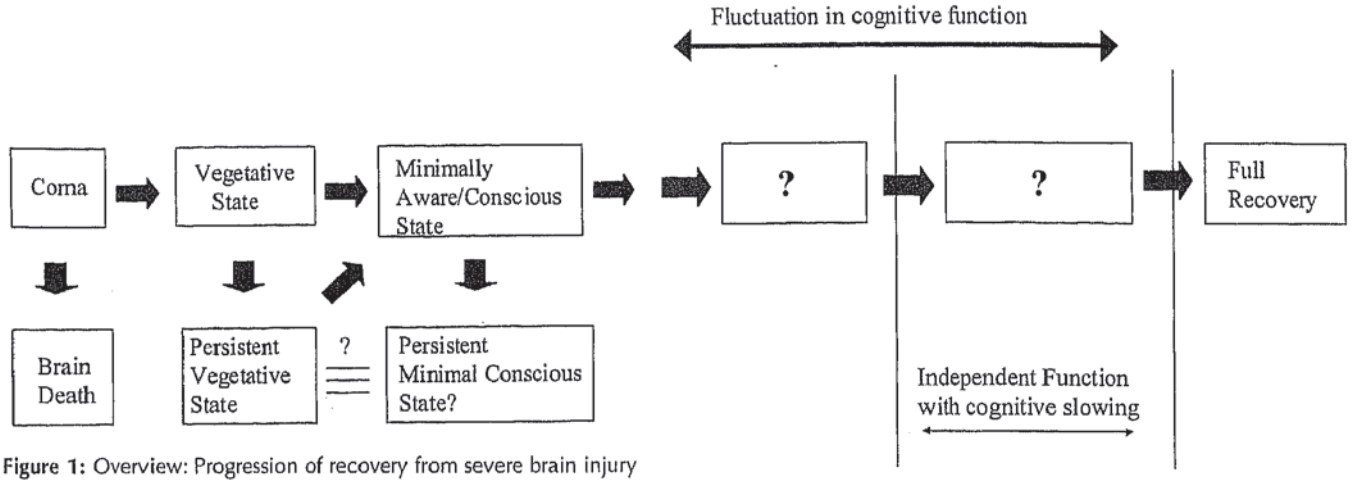


Figure 1: Overview: Progression of recovery from severe brain injury

Table 1: Scope of the problem

- Traumatic brain injury (TBI): Incidence 1.5–2.0 million persons/year in United States, prevalence 2.5–6.5 million impaired
- Leading cause of long-term disability among children and young adults
- Cognitive consequences often broad and occur in combination with other neurological disabilities
- No present therapy
- Costs for new cases per year in United States, $9–10 billion
- Estimated lifetime costs per individual, $600,000–$1,875,000

Source: NIH Consensus Development Panel on Rehabilitation of Persons with Traumatic Brain Injury. *JAMA* 1999; **282**: 974–983.

Table 2: Background: DBS and brain injury

- A few early studies of DBS and catastrophic brain injury (McLardy *et al.*, 1968 [$n=1$], Hassler *et al.*, 1969 [$n=3$], Sturm *et al.*, 1979 [$n=1$])
- In the early 1990s DBS studies in PVS were done using relatively modern techniques (Tsubokawa *et al.*, 1990, 1998 [$n=20$], Deliac *et al.*, 1993 [$n=25$], Hosobuchi *et al.*, 1993 [$n=4$])
- Taken together the 49 recent cases represent Phase I safety data
- Results of DBS were either equivocal or negative in all cases
- All patients were chronically unconscious, without fluctuations in functional level

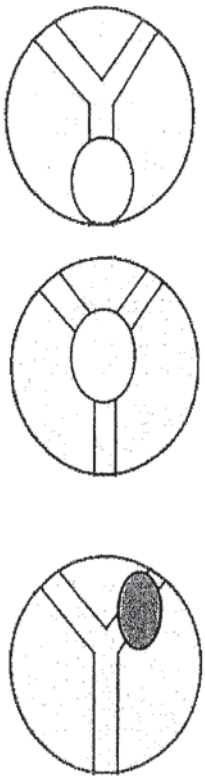
STUDIES OF DBS AND CATASTROPHIC BRAIN INJURY

Efforts to apply neuromodulation to brain injury states have mostly been restricted to patients in a persistent vegetative state (PVS), *Table 2*. A few studies in the 1960s and 1970s introduced electrical brain stimulation of the paramedian thalamus (intralaminar nuclei (ILN) typically the centromedian nucleus) and the tegmental midbrain (mesencephalic reticular formation (MRF)) as a therapy for chronic unconsciousness[7–9]. These early studies of deep brain stimulation (DBS) in PVS patients demonstrated that application of electrical current to mesodiencephalic[7,8] and allied targets[9] produced a physiological and behavioral arousal pattern. The activation of the electrophysiological and behavioral signature of arousal confirmed the earlier observation that electrical stimulation of these structures induced arousal in experimental animals[10]. In the small number of patients studied however, stimulation evoked no evidence of sustained recovery of interactive awareness.

In the last 20 years several studies of deep brain stimulation in PVS have been done using relatively modern techniques[11–14]. These studies also demonstrated robust brain activation with DBS in mesodiencephalic targets associated with arousal and, possibly in some patients, recovery of a minimal level of interactive awareness, allowing a degree of "interpersonal relationship and goal directed behavior"[12,14]. In general, however, physiological changes accompanying brain stimulation proved to be more substantial than the associated clinical improvement. This observation was important in the context of their rationale for attempting DBS in the PVS patients; in all cases intervention was based on the possibility that absence of functional recovery might be due to a lack of 'nonspecific cortical activation'. The presence of arousal responses in all patients demonstrated that despite overwhelming forebrain damage, it was in fact possible to activate the cortex significantly with the artificial signal. The second implication is that generally increased activation of the cortex alone is insufficient to restore any element of interactive awareness in most of the PVS patients studied. These studies were directed at catastrophically brain injured patients. Improved understanding of the underlying neurobiology of protracted vegetative function indicates that these patients are not the best candidates. The studies do demonstrate comparable safety profiles with other present DBS uses[14].

NEW BRAIN IMAGING STUDIES OF CATASTROPHIC BRAIN INJURY AND RELATED TECHNIQUES

Functional brain imaging techniques are increasingly utilized for mapping the human brain in both normal physiological and pathological conditions. Alone and in combination, the use of functional MRI (fMRI), positron emission tomography (PET) and magnetoencephalography (MEG) offers insights into the circuits that



Posterior ILN — **Cortical Targets**

Centromedian (Cm), Parafasicularis (Pf) — Pre/frontal, premotor, posterior parietal association cortex

Anterior ILN

Central lateral (CL), Paracentral (Pc), Paralamellar MD — Pre/frontal, frontal eye fields, anterior cingulate, anterior parietal, temporal association cortices

Midline related ILN

Central medial (CeM), Related midline nuclei — Limbic, orbito-rhinencephalic cortices, amygdala, hippocampus

Schematic Thalami

Figure 2: Selective targeting. (Adapted from Schiff, 1997 USPTO 5,938,688)

Table 3: Strategy for deep brain stimulation to remediate cognitive disabilities following brain injury

1. Selection of conscious patients.
2. Identification of patients who show evidence of fluctuation, either spontaneously or reliably induced by stimulation.
3. Selective targeting of intralaminar thalamic nuclei subdivisions based on the pattern of cortical injuries, regions of hypometabolism, or neurobehavioral criteria.
4. Rationale of DBS in these patients: To support specific distributed brain network (long-range cortico–cortical and cortico–striatopallidal–thalamocortical loop) interactions as opposed to arousal *per se*.

underlie several brain disorders. Recent functional brain imaging studies of patients in a vegetative state has brought out several new findings[15–18]. The vegetative state denotes the recovery of cyclic arousal without the recovery of consciousness[19]. This definition, however, allows for a variety of complex stereotyped responses to be encountered in PVS. Occasional fragments of behavior that may appear semi-purposeful or inconsistently related to processing of environmental stimuli are left unexplained by previous neurobiological models[20]. Past studies of the persistent vegetative state have correlated the state with a global reduction of brain metabolic activity as measured quantitatively by FDG-PET[21–23]. All of these past studies found that vegetative patients expressed metabolic rates of ~40%–50% of normal awake subjects, comparable to rates found in normal subjects undergoing deep anesthesia[24]. None of these prior reports have identified preserved modular function in the vegetative state or regional variations in the profoundly depressed metabolism.

Recent studies of vegetative patients using the combined technologies of PET, MRI, and MEG have revealed several new observations[16,18,25,26]:

1. Evidence of isolated metabolic and physiologic activity may be identified with preserved networks in overwhelmingly damaged brains by coregistration of PET/MEG/MRI data and clinical correlation.
2. These remaining networks reflect functionally segregated systems that appear to correspond to cortico–strato–pallidal–thalamocortical or thalamocortical networks that retain connectivity and partial functional integrity.
3. In some cases, clinically evident, function of a remaining network could be identified despite the lack of integration in the brain reflected by a state of permanent unconsciousness.
4. A single patient studied demonstrated widely preserved cortical metabolism but expressed severe hypometabolism in the mesodiencephalon.

These findings imply that selective injury to the mesencephalic reticular formation and paramedian thalamus (predominantly intralaminar and related structures) and long-range white matter tracts may result in

permanent unconsciousness. The findings support the view that paramedian mesodiencephalic systems (ILN, MRF and related structures) play a critical role in the precise functional integration of many segregated parallel networks and their modulation by state changes mediated by brainstem and allied arousal systems. These preliminary data in PVS support the use of brain imaging techniques in other patients with less severe injuries to characterize areas of preserved function. Such multimodal imaging data seem necessary to organize an approach to deep brain stimulation for individual patients.

Recent combination of functional brain imaging and deep brain stimulation demonstrates unique opportunities for identifying circuits and underlying mechanisms of neurological disorders[27]. These studies, presently focused on movement disorders and pain studies, consistently demonstrate selective activation of cortical and sub-cortical regions with deep brain stimulation. For example, Rezai *et al.*[28] demonstrated functional MRI activations at thalamic and pallidal sites with stimulation via implanted electrodes in the ventro intermediate (VIM) nucleus. The combined fMRI/DBS approach offers further rationale for the strategy developed below. The technique also gives promise that such investigations may further elucidate the mechanism of action of deep brain stimulation.

AN EXPLICIT STRATEGY FOR SELECTIVE NEUROMODULATION IN COMPLEX BRAIN INJURY STATES

We propose a different strategy for deep brain stimulation in brain injury states: stimulation of selected subdivisions of the intralaminar thalamic nuclei in cognitively impaired conscious patients[29]. This novel approach is supported by a newly recognized role for the intralaminar nuclei that emphasizes facilitating long-range cortico–cortical and thalamocortical interactions rather than arousal *per se*[30–37].

The rationale is based on selectively supporting, impaired but partially functional brain networks. In persistently vegetative patients, their complete loss of integrative cortical function probably underlies the lack of efficacy of deep brain stimulation in ILN and allied targets. That is, the targets of ILN modulation have been overwhelmingly damaged in this patient population and ILN stimulation cannot be effective. The rationale of ILN deep brain stimulation in conscious patients with moderate to severe cognitive impairment is to amplify their remaining cortical integrative functions. Stimulation of specific ILN subdivisions may functionally re-establish particular long-range cortico–cortical connections that may be associated to specific behavioral and cognitive functions[29]. Further clinical and experimental evidence for the role of the ILN *per se* in cognitive function is rapidly accumulating[38]. This approach is particularly suited to traumatic brain injury, which includes a mix of shear injury of ascending arousal inputs and multiple focal cortical and subcortical injuries. In the early stages of clinical application this technique would likely target more seriously impaired patients, rather than those with moderate cognitive dysfunction who recover to independent functional levels but remain significantly impaired.

Chronic electrical stimulation of subcortical brain targets using deep brain stimulation (DBS) is an increasingly utilized mode of therapy in stereotactic and functional neurosurgery. The potential advantage of DBS in contrast to traditional lesioning procedures, is its adjustability and reversibility, allowing for maximal clinical efficacy while minimizing complications. Currently the most common application of DBS is in movement disorders. The improved safety and the striking benefits of DBS have expanded the possibilities of intervention into novel targets including the thalamus, the subthalamic nucleus (STN) and the globus pallidus[39–42]. In addition, the combination of selective application of pharmacologic agents via microcannula systems is extending the clinical armamentarium[43]. Hopefully currently adapted techniques of intracranial anatomical and physiological localization and implantation of DBS devices can be effective in treating brain injury conditions. Already, the selective anatomical and physiological targeting of subdivisions of the intralaminar nuclei have been performed in humans[44–46].

SUPPORT FOR THE PROPOSED INTERVENTION

Most of the clinical data on modulation of cognitive function in brain injury originates in the study of the neglect syndrome[47,48]. This disorder includes a variety of neuropsychological deficits that typically involve a hemi-spatial dissociation of either awareness of the self or environment (anosognosia or sensory neglect) or impaired capacity to initiate a response or decision process (nonsensory neglect). In many of these patients, external sensory stimuli or specific internally generated behaviors[47–49] can modify their unawareness. Sensory stimuli that can elicit a transient recovery of multi-modal deficits in these patients include caloric stimulation, sternocleidomastoid muscle vibration, truncal rotation, forced eye movements, induction of optokinetic nystagmus, and others[47,48]. Transient recovery of many different modular functions, including neglect of auditory, visual, and somatosensory modalities, personal unawareness (asomatognosia), unawareness of deficits (anosognosia), and motor neglect (intentional loss) have all been described[48]. Most of these methods represent vestibular stimuli, such as cold caloric testing (irrigation of the external auditory canal with ice water), rotations in three-dimensional space, and vibratory stimulation of muscle spindles[47]. Direct activation of the intralaminar nuclei by vestibular stimulation, leading to repetitive cortical activations, has been proposed as the mechanism underlying the observed transient recovery of cognitive functions[50].

Several additional patient-based observations show that alterations in the large-scale patterns of neuronal activation can permanently or transiently ameliorate apparently 'fixed' deficits including recovery of function after a second stroke[51], improved verbal fluency observed during DBS therapy for pain control[52], and

others[38]. That modular cognitive functions (that is, functions that are believed to have specific cortical localization) can be selectively or in combination restored, albeit transiently, suggests that the relevant neuronal populations may retain their ability to function but are aberrantly excluded from integrated brain activity.

Patterns of connection of the human intralaminar nuclei are known primarily on the basis of clinical–pathologic correlations[37] and detailed primate anatomical studies[53]. Functional mapping of the human intralaminar nuclei confirms the regional specificity seen in these studies[45,54,55]. In addition, studies of crossed synaptic changes in cortical metabolism following paramedian (intralaminar and related nuclei) thalamic injury show evidence of selective, large scale networks that express decreased metabolism[56–59]. Similarly, results of regionally specific changes are obtained in human MEG signals following selective paramedian thalamic injury[60].

Clinical evidence already supports the identification of patients with reliable fluctuations and the ability to isolate and correlate anatomical and functional deficits using brain imaging. In addition to baseline resting metabolism, either functional PET or fMRI images obtained during sensory activation (e.g. calorics) might be employed to optimize the approach and guide selection of ILN areas for stimulation (e.g., regionally selective activation with caloric stimulation[61]).

CURRENT LIMITATIONS AND CAUTIONS

Several important limitations impede the strategy outlined above. Presently, few available scientific outcome measures have been developed for patients with marked cognitive impairment. The Glasgow Outcome Scale, the FIM and FAM test battery[62] and the Coma Recovery Scale are most frequently applied but are insufficient to fully quantify the degree of cognitive impairment among many patients with severe to moderate brain damage. More precise evaluations of patient's cognitive, motor and emotional capacities will be required before interventional cognitive neuroscience based on quantitative probabilities of outcome can be applied. Developing selection criteria to appropriately categorize patients, based on effective outcome measures, will be critical for risk stratification when considering possible interventions in this diverse population.

Patients with severe brain injuries and prolonged functional limitations resulting from their disabilities create difficult ethical challenges[3]. An early concern raised in studies of DBS and catastrophic brain injury related to producing a 'half-way recovery' characterized by poor performance and possibly increased inter- and intra-personal suffering[11]. Before clinical neuroscience approaches such efforts it will be critical to develop an informed dialogue among clinicians, researchers, bioethicists, policy makers, families, patients and the public[3]. The reversibility of deep brain stimulation technique may help to ameliorate some of these concerns but to conduct this line of therapeutic research will require consensus.

CONCLUSION

The devastating outcomes of severe brain injury create an impetus for compassionate but vigorous attempts at amelioration. Under these circumstances, the need to innovate must clearly be balanced against the uncertainties of outcomes. Ethical considerations are imperative in such necessarily empirical neuromodulatory approaches. Improved neuroimaging techniques are now available that will greatly enhance our capacity to risk-stratify patients for potential therapeutic trials. Early studies of DBS in PVS patients who lacked all signs of cognitive function demonstrated significant physiological but not clinically efficacious effects. We propose a novel strategy for rational therapy of complex brain injury based on the selection of conscious patients and selective modulation of large, distributed forebrain networks. Optimization of patient selection is based upon selection of patients with identifiable spontaneous or induced fluctuations in cognitive function. Some such patients demonstrate by clinical criteria alone that at least some aspect of their functional deficit remains dynamic and potentially supportable. Several steps must be taken to guarantee adequate risk-stratification of patients and professional and public consensus to develop these innovative therapies. To leave these possibilities unexplored, however, would be unfair to marginalized patients and families. As neuromodulation techniques advance we must ensure strong efforts to bring the benefits of this emerging science to historically underserved individuals.

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