Developing prosthetics to treat cognitive disabilities resulting from acquired brain injuries

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Persistent cognitive disabilities represent the most troublesome consequences of acquired brain injury. Although these problems are widely recognized, few neuroprosthetic efforts have focused on developing therapeutic strategies aimed at improving general cognitive functions such as sustained attention, intention, working memory or awareness. If possible, effective modulation of these neuropsychologic components might improve recovery of interactive behaviors. The emerging field of neuromodulation holds promise that technologies developed to treat other neurological disorders may be adapted to address the cognitive problems of patients suffering from acquired brain injuries. We here discuss initial efforts at neuromodulation in patients in the persistent vegetative state and aspects of recent studies of the underlying neurobiology of PVS and other severe brain injuries. Innovative strategies for open-loop and closed-loop neuromodulation of impaired cognitive function are outlined. We discuss the possibilities of linking neuromodulation techniques to underlying neuronal mechanisms underpinning cognitive rehabilitation maneuvers. Ethical considerations surrounding the development of these strategies are reviewed. [Neurol Res 2002; **24**: 116–124]

Keywords: Deep brain stimulation; neurorehabilitation; consciousness; intralaminar thalamus; closed-loop systems; forebrain gating

INTRODUCTION

Many thousands of Americans annually suffer acquired brain injuries that result in permanent total or near-total disability due to impaired cognitive function. Brain injuries producing lasting cognitive deficits can result from trauma, strokes, cardiac resuscitation, encephalitis, sequelae of chemotherapy and radiation treatments and other causes. Despite the substantial public health need to develop therapies for chronically impaired cognitive function, this area remains the least explored for neurological treatment. The cognitive capacities of patients recovering consciousness following severe to moderate brain injury span a broad spectrum (*Figure 1*). Those who permanently remain in a minimally conscious state (MCS) with limited evidence of awareness or only fragments of interactive behavior represent the lowest level of recovery beyond the vegetative state[1]. Nevertheless, those in a MCS possess minimal but definite behavioral evidence of self or environmental awareness. Reliable and consistent interactive communication or functional use of objects demonstrates emergence from a MCS[1]. Many of these patients demonstrate preserved but fluctuating capacities of command following, basic communication, memory, attention, intention, and awareness of self and environment. These fluctuations provide clinical evidence that their limited functional capacities may not represent entirely irreversible damage. These and other clinical observations suggest that mechanisms of plasticity and dynamic reorganization are available to the brain that might be harnessed for therapeutic advantage for treating chronic cognitive and perceptual disorders. Several scientific challenges and ethical concerns complicate the development of such new therapies[2–4]. Foremost among scientific barriers are the neuroanatomical and functional complexities of brain injuries and the theoretical and practical challenges they present. The uncertainties of any improvement by potential interventions coupled with the overall vulnerability of cognitively impaired patients require an appropriately cautious evaluation and approach. Nonetheless, it is a societal imperative to develop novel therapies aimed at these increasingly large, marginalized patient populations.

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MEDICAL NEED FOR COGNITIVE CAPACITY PROSTHETICS

Most acquired cognitive disabilities result from complex brain injuries due to traumatic brain injury (TBI) or stroke[5]. 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

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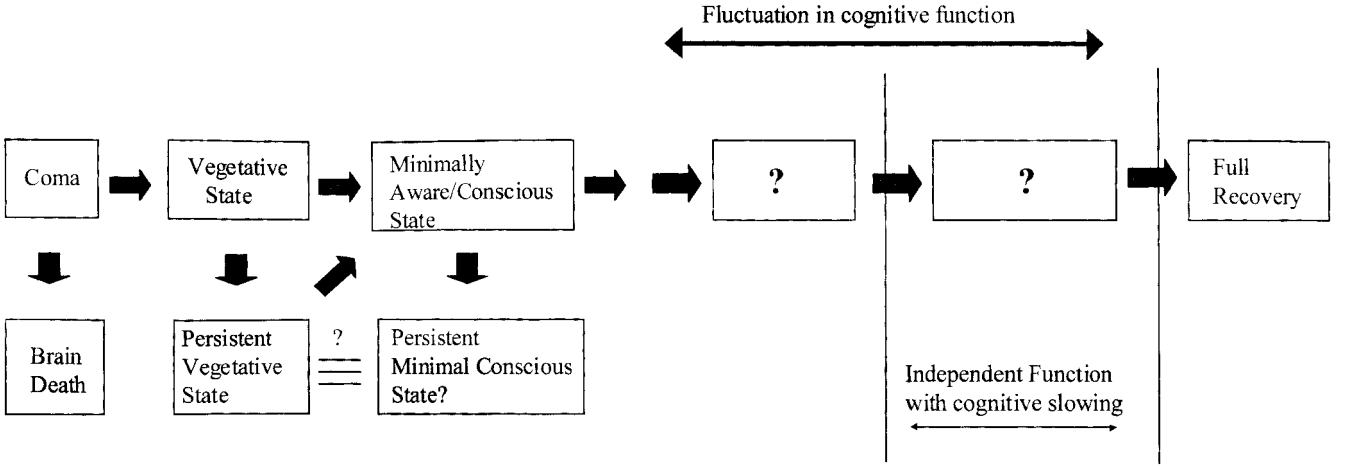


Figure 1: Overview of recovery of cognitive following acquired brain injury

and social impact[6,7]. It is estimated that TBI represents the majority of the patient population with a prevalence of patients suffering long-term consequences estimated at ~ 5–6.5 million, or approximately 2% of the US population. It is estimated that each year an additional 200,000–300,000 patients (out of 2 million new US TBI cases annually) acquire chronic cognitive disabilities[8]. Worldwide it is estimated that the incidence of TBI is 10 million annually[7]. Most of these patients incur their injuries at young ages (peak 18–24 years) and remain free of systemic disease. Accordingly, TBI represents the leading cause of long-term disability among children and young adults. The cognitive consequences are often broad and occur in combination with other neurological disabilities. The medical need to create new therapeutic strategies in this large area is presently unmet.

What would a cognitive capacity prosthetic provide? If such assistive devices can be developed they would be aimed at improving sustained attention, intention (initiation, planning, executive functions), awareness (self-monitoring, spatial), and working memory. To achieve these results a cognitive capacity prosthetic would need to be able to augment known cognitive rehabilitation strategies by supporting underlying neuronal mechanisms.

NEUROMODULATION

Chronic electrical stimulation of subcortical brain regions 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 disorder surgery. The improved safety and the striking benefits of DBS have expanded the possibilities of intervention into novel targets including the thalamus[9], the subthalamic nucleus (STN) and the globus pallidus[10–12]. In addition, modifications of the DBS technique including combination of selective application of pharmacologic agents via microcannula systems[13] and development of closed-loop systems[14] will extend the flexibility and range of applications of neuromodulation. The recent resurgence of DBS has mainly followed the strategy of replacing permanent lesioning of subcortical structures with chronic stimulation at high frequencies believed to functionally suppress neuronal activity by over-riding synaptic mechanisms[15]. The basic mechanisms of DBS, however, are not yet well-understood and the technique also involves selective activation of both cortical and subcortical regions as demonstrated in both fMRI[16] and fPET[17] activation paradigms. At present, clinical studies have focused on open-loop systems for the treatment of tremor, Parkinson's disease, pain, obsessive compulsive disorder, and epilepsy[18] all with an intent to suppress abnormal activity. In addition to providing functional blockade with DBS, it has long been recognized that direct brain stimulation can activate widely distributed brain regions.

Studies of deep brain stimulation and the persistent vegetative state: why vegetative patients are not reasonable candidates for deep brain stimulation

Over the past 15 years several neurosurgical groups have pioneered neuromodulation efforts in patients with severe brain injuries[19–21]. Most patients included in these studies were in a persistent vegetative state (PVS). Earlier studies in the 1960s and 1970s, introduced electrical brain stimulation of the paramedian thalamus (intralaminar nuclei, ILN, typically the centromedian nucleus) and the midbrain tegmentum (mesencephalic reticular formation, MRF) as a therapy for chronic unconsciousness[22–24]. These early studies of DBS in PVS patients demonstrated that application of electrical current to mesodiencephalic[22,23] and related targets[24] produced a physiological and behavioral arousal pattern. 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. Nevertheless, in both the early and more recent attempts at DBS in PVS patients, electrical stimulation evoked no evidence of sustained recovery of interactive awareness. The physiological changes accompanying brain stimulation proved to be more substantial than the associated clinical improvement.

The rationale provided for attempting DBS in the PVS patients in these studies was that absence of functional recovery might be due to a lack of 'nonspecific cortical activation' or arousal. PVS, however, is defined by the recovery of cyclical arousal without any evidence of interactive awareness. The majority of patients in a PVS have sustained overwhelming cerebral injuries from trauma or anoxia secondary to cardiac arrest[25]. Accordingly, pathological studies demonstrate that few cortical or even thalamic neuronal populations remain in these badly injured persons[26,27]. The failure of generally increased activation to restore a process of forebrain integration in any of the PVS patients studied is therefore not surprising.

Recent functional imaging studies of vegetative patients have demonstrated a lack of forebrain integration for even simple sensory processing[28]. In collaborative studies we have characterized cerebral activity in several PVS patients including three patients with unusual fragments of behavior[29,30]. Despite finding apparently isolated networks that may generate such fractions of behavior, no findings suggested that any PVS patients could be brought to higher functional levels. The more recent DBS studies in PVS patients demonstrated comparable safety profiles with other present DBS uses in 49 cases[19–21]; these data suggest that risks of implanting DBS devices in severely brain injured patients are not greater than in other conditions.

Recent pathological studies by Jennett *et al.*[31] have compared brain pathology in autopsies of conscious patients with severe disability with those of patients remaining in a vegetative state following brain injuries. Of note, in over half of the severely disabled group, this study identified only focal brain injuries without accompanying diffuse axonal injury or thalamic injury. These findings suggest that significant variations in both underlying mechanisms of cognitive disabilities and residual brain function accompany these severe but less disabling brain injuries. The observations may provide a clinical–pathologic foundation for wide fluctuations in functional capacities of some patients.

Fluctuations of cognitive function in patients with acquired brain injury

Many patients with severe brain injuries demonstrate significant fluctuations in cognitive performance. These variations of behavior are well-known but not frequently described in the medical literature. The phenomenon is illustrated by a recent isolated case reported by Burruss and Chacko[32]. Their patient, a 52-year-old man, remained in state characterized by loss of volitional movement and mutism following a 4-week coma resulting from the rupture of a basilar artery aneurysm and secondary strokes in the thalamus and basal ganglia. The patient's 'akinetic mutism' was characterized by sitting motionless, staring forward with his hands on his thighs. He was passively rehabilitated to the point of recovering ambulation and stamina without spontaneous movement or speech. This behavioral state persisted without change for 17 months when he spontaneously experienced a fluctuation in his behavioral state described as a return to his 'premorbid state, with full return of his demeanor and affect'. This remarkable clinical change lasted throughout one day and relapsed after sleeping through the night. One year later the patient had a second 'awakening' after suffering a *grand mal* seizure. Several additional wide fluctuations were reported following seizures and two rounds of electroconvulsive therapy but no mechanism was proposed. Other brain-injured patients have been observed to exhibit similarly wide flucutations of their underlying capacities for cognitive function. One plausible mechanism behind such wide variation of functional capacities is the presence of significant abnormal subcortical activity not recognized clinically as seizures or other related phenomena (for example, persistent paroxysmal activity[33] or other forms of hypersynchronous disturbances[34,35]). In an interesting early study by Williams and Parsons-Smith[36] in the 1950s, a patient with a widely, and sometimes rapidly fluctuating minimally responsive state secondary to brain injuries resulting from encephalitis, was studied with thalamic depth electrodes. *Figure 2* illustrates electrographic tracings of local field potentials recorded from the posterior paramedian thalamus and scalp EEG recordings from their original report. In this patient, periodic paroxysmal discharges (*Figure 2*, top panel) were identified in the thalamus during an akinetic mute state (characterized by alert appearance, purposeful withdrawal to noxious stimuli and visual tracking) with minimal change of scalp EEG outside of the presence of slow waves. After administration of deep pentobarbitol anesthesia, these discharges were suppressed and both the thalamic LFP and scalp EEG normalized coincident with the patient emerging into an interactive and oriented state and later full recovery.

The wide fluctuations that these severely brain-injured patients demonstrated indicated that they harbored residual cerebral capacities. The question arises whether or not cerebral networks may remain widely preserved in other such patients who show less dramatic but evident fluctuation. A recent study of two patients in minimally conscious states using functional magnetic resonance imaging techniques suggests that this may be the case. Functional imaging in the two patients identified the integrity of widely distributed cortical networks underlying human language function despite a failure to establish communication with either patient[37]. These findings indicate that forebrain networks may remain functional, yet fail to engender consistent interaction or communication. The identification of fluctuations in cognitive function in patients with acquired brain injuries indicates that at least some

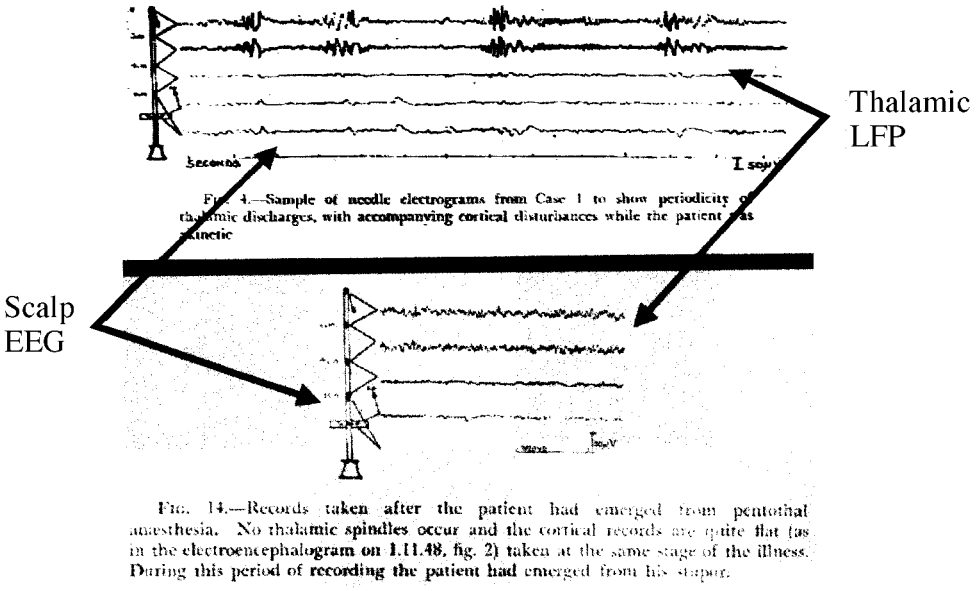


Fig. 4.—Sample of needle electrograms from Case 1 to show periodicity of thalamic discharges, with accompanying cortical disturbances while the patient was akinetic

Fig. 14.—Records taken after the patient had emerged from pentothal anesthesia. No thalamic spindles occur and the cortical records are quite flat (as in the electroencephalogram on 1.11.48, fig. 2) taken at the same stage of the illness. During this period of recording the patient had emerged from his stupor.

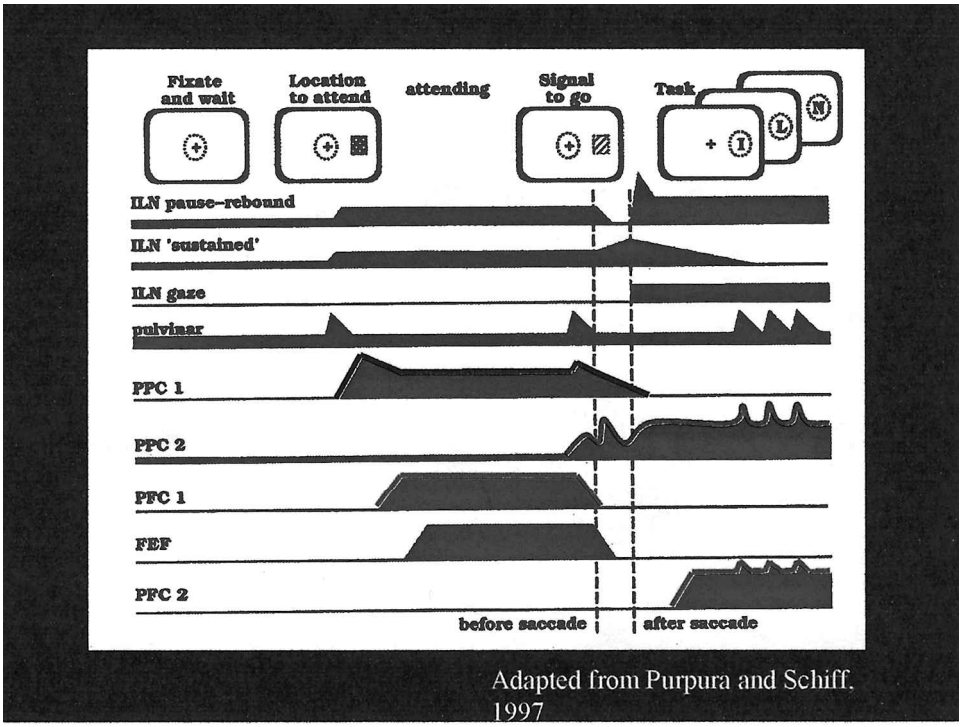
Figure 2: Local population recordings from the intralaminar thalamus of a patient with akinetic mutism (Williams and Parsons-Smith, *Brain*, 1951)

component of their disability is dependent on the dynamics of underlying neuronal activity; thus, functional aspects of forebrain integration may potentially be targeted in such patients to improve function. Such variations in performance are often seen in patients recovering from severe to moderate brain injuries and, when present, limit rehabilitation efforts. The underlying mechanisms of fluctuations are poorly understood. Abnormal subcortical activity resulting from reorganization of neuronal connectivity following complex brain injuries is only one possibility. Other possible mechanisms include decreased neuronal firing rates secondary to deafferentation of cortico–cortical or thalamo–cortical connections despite preserved integrative functions (see below) or loss of specific endogenous signals used to organize on-line forebrain integration[38–40] (see below).

An open-loop neuromodulation strategy and rationale

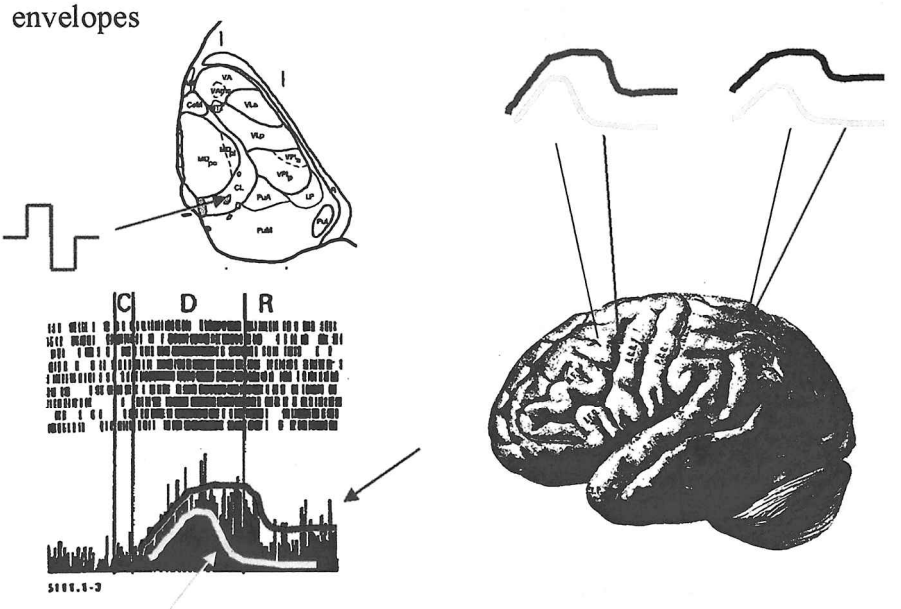
We have proposed that deep-brain stimulation of selective targets in the thalamic intralaminar nuclei (ILN) of conscious patients with moderate to severe cognitive impairment may amplify their remaining cortical integrative functions[2]. This strategy is based on converging evidence that specific ILN subdivisions gate particular long-range cortico–cortical connections that may functionally support specific behavioral and cognitive functions[41–43]. Based on a gating model of ILN function and the differences in underlying brain function, the failure of DBS in vegetative patients should not be interpreted so broadly as to exclude its utility in minimally conscious patients. The rationale for attempting open-loop DBS for cognitive impairment is to selectively support impaired but partially functional brain networks.

To develop novel neuromodulation strategies it is necessary to consider both the mechanism of brain injuries and the underlying neurophysiological mechanisms supporting cognitive brain activity. At present, the knowledge of the former derives primarily from pathologic studies, whereas understandings of the neurophysiological foundations of cognition are based largely on studies in nonhuman primates. We briefly sketch a motivation for open-loop deep brain stimulation in the ILN drawing inferences from these two sources of information. The mechanism of injury in many TBI and stroke patients includes compression of paramedian mesodiencephalic regions due to brain swelling, partially disabling these regions. Compression of the thalamus and brainstem is combined in many instances with shearing injury of cortico–cortical and reciprocal cortico–thalamic connections. These injuries may produce cognitive deficits through a common mechanism by reducing experimentally identified 'cortical persistent activity' associated with on-line wakeful behavior[44–47]. *Figure 3A* illustrates a hypothesis by Purpura and Schiff[38] for how populations of ILN neurons in nonhuman primates may play a role in selectively gating such cortical persistent activity in addition to facilitating tonic changes in arousal states. In this hypothetical experiment, recordings from several cortical and thalamic (ILN and pulvinar) sites are illustrated. The responses are modeled from recordings in the alert primate as reviewed below. The figure illustrates a hypothetical experiment in which a normal subject fixates a cue (upper panels *Figure 3A*) and after a 'go' signal makes a saccadic eye-movement to a target in which a series of letters appear to be identified by the subject. The dark



Adapted from Purpura and Schiff, 1997

Hypothesis: DBS of ILN mediates extension of endogenous activity envelopes



sustained activation in cortical neurons between presentation of a peripheral target and a subsequent saccade to the target's location (similar activity associated with working memory[45] is illustrated in the lower left corner of *Figure 3B*). Such attention shifts relate closely to saccadic eye-movements and may reflect similar transient activation patterns in the forebrain. Different ILN subdivisions selectively project to prefrontal cortex, PFC (Pf, CL and paralaminar MD), frontal eye fields FEF (CL and paralaminar MD), anterior cingulate cortex (CL) and posterior parietal cortex, PPC (Cm–Pf, CL). Through these specific projections, ILN neurons may facilitate, and possibly trigger such sustained activations[37]. These sustained neuronal responses may act as 'activity envelopes' that underlie such general cognitive functions. Kinomura *et al.*[53], using normal subjects performing a sustained attention paradigm, provide evidence that both anterior (CL) and posterior (Cm–Pf) intralaminar thalamic nuclei participate in maintenance of these activity envelopes. Recent studies modeling this task in nonhuman primates identified central thalamic neurons that demonstrate selective elevations of activity during the task-related period of sustained attention[54].

The selective activation of these thalamic populations by cognitive tasks supports the open loop strategy of DBS in patients who have been able to demonstrate integrative forebrain activity. For those patients, DBS might extend endogenously generated activity enveloped as cartooned in *Figure 3B*. The red arrow points to a hypothetically reduced activation in a patient with an acquired brain injury. In this cartooned version, we have reduced the cortical persistent activity in the prefrontal cortex (modeled from reference 45) in amplitude and duration. We speculate that open-loop DBS in the ILN may extend endogenous activity to approximate the normal response cartooned by the green line (see green arrow). In PVS patients, no evidence exists that such integrative forebrain processes remain intact.

Figure 3A also indicates the selectivity of some ILN populations to parameters of saccadic eye-movements. Schlag and Schlag-Rey[55] demonstrated that intralaminar neurons signaled an efference copy of the saccade to the multiple cortical regions identified in the figure. These pioneering observations support the role of the ILN In several interesting techniques developed to assist in cognitive rehabilitation (see below). More recently, Matsumoto *et al.*[56] demonstrated that posterior intralaminar neurons signal several types of behaviorally relevant sensory events such as the onset of a sensory cue. The selective physiological characteristics of these populations suggest additional adaptations of neuromodulation strategies to possibly assist cognitive function.

Linking neuromodulation techniques with mechanisms of cognitive rehabilitation: toward closed-loop strategies

Several present cognitive rehabilitation techniques rely on forms of induced fluctuations of cognitive function to establish therapeutic effects[5,57–59]. Many of these clinical studies focus on the neglect syndrome following focal strokes. This disorder includes a variety of neuropsychological deficits that typically involve a left hemi-spatial loss of awareness of the self or environment (anosognosia or sensory neglect) or impaired capacities to initiate a response or decision process (nonsensory neglect). Among maneuvers found to elicit transient recovery of multi-model deficits in these patients are cold caloric stimulation, sternocleidomastoid muscle vibration, truncal rotation, forced eye-movements, indication of optokinetic nystagmus, and others[58]. 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. Brief recoveries of function can also be observed with caloric stimulation in acute strokes demonstrating that a significant suppression (or 'gating out') of partially viable cortical regions can occur as a result of immediate dynamic reorganization[39]. Additional patient-based and experimental observations indicate that alterations in the large-scale patterns of neuronal activation can permanently or transiently ameliorate apparently 'fixed' deficits[60,61].

Most maneuvers used to alleviate neglect 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. The brainstem vestibular nuclei project strongly to several cortical regions and prominently to paramedian thalamic targets, principally in the intralaminar nuclei[62]. As noted above, the intralaminar thalamic nuclei are also known to receive and signal a variety of sensory transients[56] as well as efference copy signals of oculomotor activity[55]. Direct activation of these nuclei as a result of oculovestibular response induced by cold caloric maneuvers has been proposed as a mechanism to evoke the transient reintegration of cortical regions[39].

The pathological mechanisms underlying strokes producing unawareness and the broad cognitive disabilities following TBI are clearly different. The induced fluctuations achieved in patients with the neglect syndrome, however, may hint at a general principle underlying many rehabilitative techniques: the utilization of an internally generated efference copy signal to provide an organization for weakly established neuronal activations in partially viable brain regions[63]. While nonspecific increases in neuronal firing rates might be proposed to underlie these changes, the selectivity of these maneuvers argues against a general arousal effect (e.g., from the first observations of caloric stimulation the effect has been established to be lateralized with no effect or worsening observed with ipsilesional irrigation[64]). The repeated activation of widely distributed signal generated within the brain such as the efference copy of the saccade (or more generally, of an internally selected, directed movement) may exert strong influence on the correlation of neuronal activity in distributed

networks. Such changes in the correlation structure alone may facilitate the reintegration of still viable cerebral tissue. A similar mechanism of transient improvement may underlie phasic alerting techniques[65], training of visual 'scanning', and interesting strategies of head and hand circling alighted upon by patients with visual agnosia to directly improve perception[66].

Cicerone *et al.*[5] recently constructed a small number of evidence-based practice standards for cognitive rehabilitation and identified retraining of visual search to have significant positive effects. Similar improvements were seen with this technique in combination with truncal rotations[67]. Reviews of the rehabilitation literature identified six Class I studies (286 patients) and eight Class II studies (248 patients) in which visual scanning training improved compensation of unawareness and was superior to conventional occupational and physical therapies. In addition, the treatment effects generalized to more effective performance of activities of daily living, and shorter stays in acute rehabilitation programs. It is likely that the high impact of retraining of visual scanning reflects the key role of eye movements in gating of forebrain integration. While several externally driven techniques have been effective in producing eye-movement related brain activations including cold calorics[59] and forced eye movement techniques[68] it may also be possible to adapt stimulation of selective subcortical structures around this endogenous phase mark of neuronal processing[63].

The maneuvers used to rehabilitate cognitive function in patients with acquired brain injuries suggest strategies for developing closed-loop neuromodulation. As noted above, most current applications of neuromodulation strategies involve empirical trials of open-loop systems with early efforts now underway to use closed-loop approaches. Development of this new area of research will require careful attention to the underlying mechanisms of the acquired brain injuries and better understanding of physiological mechanisms of maneuvers generating partial recovery.

ETHICAL CONSIDERATIONS

Patients with severe brain injuries and prolonged functional limitations resulting from their disabilities present unique ethical challenges for development of novel therapeutic interventions[3,4]. Most important is the need to balance risks of invasive therapies against a lack of access to emerging technologies[3]. The issue of appropriate protections is particularly important given the vulnerability of this patient population. Although several issues will necessarily arise in course of developing the strategies suggested above, none will be more critical than establishing appropriate criteria to categorize patients into risk-stratified groups. Assessments of risk will require studies based on proven outcome measures for these populations and a consensus about reasonable therapeutic goals. For example, what may not be considered acceptable palliative treatment for a MCS patient might be acceptable as a partially restorative treatment for a patient with nearly independent function. Along these lines, a more nuanced approach to the consent process for patients with varying degrees of decision-making incapacity is needed[4]. Moreover, efforts at developing both investigational and experimental therapeutics in these patient populations will require the development of an informed dialogue among clinicians, researchers, bioethicists, policy makers, families, patients and the public[3].

CONCLUSION

We have outlined several strategies to extend current neuromodulation efforts toward a large unmet medical need for prosthetic systems aimed at improving cognitive capacities. As identified above, many new diagnostic techniques are needed as well as consideration of appropriate therapeutic goals and risk stratification of patients with acquired brain injuries. Current efforts with open-loop deep brain stimulation suggest that selective modulation of neuronal population firing rates may allow significant functional control of brain states: either by suppression of abnormal subcortical activity or activation of distributed neuronal activity. In addition to direct modulation of neuronal firing rates, specific induced changes of the correlation structure of neuronal activity across wide populations may allow known cognitive rehabilitative techniques to be assisted by neuromodulation. Cautious exploration of these possibilities is warranted because of the present lack of alternative therapies and clinical clues that some patients might significantly benefit if such approaches can be developed.

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