

# Towards a neurophysiological foundation for cognitive neuromodulation through deep brain stimulation

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## Abstract

It may soon be possible to adapt the use of deep brain stimulation (DBS) technologies developed to treat movement disorders to improve the general cognitive function of brain-injured patients. We outline neurophysiological foundations for novel neuromodulation strategies to address these goals. Emphasis is placed on developing a rationale for targeting the intralaminar and related nuclei of the human thalamus for electrical stimulation. Recent anatomical and physiological studies are compared with original neurophysiological recordings obtained in an alert non-human primate. In this context we consider neuronal mechanisms that may underlie both clinical observations and cognitive rehabilitation maneuvers that provide theoretical support for open and closed-loop strategies to remediate acquired cognitive disability (ACD).

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## 1. Introduction

Electrical stimulation of the human brain is a rapidly advancing therapy for several otherwise intractable neurological conditions. As scientific understanding of the basic mechanisms underlying this technique unfolds, the opportunity to extend its use to patients for whom no treatment strategy currently exists will enlarge. Herein, we address the possible use of electrical stimulation of deep brain structures to treat acquired cognitive disability (ACD). ACD accompanies most complex brain injuries due to traumatic brain injury (TBI) or stroke (Cicerone et al., 2000; NIH Consensus Development Panel, 1999); additionally, anoxic, hypoxic, ischemic, degenerative, and other mechanisms of brain injury lead to ACD. The public health dimensions of this problem and the medical need to develop novel therapies for these conditions have been previously reviewed (Schiff et al., 2000, 2002a). Later we review relevant anatomical and neurophysiological data supporting the development of both open- and closed-loop neuromodulation strategies for treatment of ACD.

## 2. Scope of the problem and possible therapeutic opportunities

Acquired brain injuries produce permanent total or near-total disability due to impaired cognitive function in >100,000 patients per year in the United States, leading to an estimated 5–6 million persons suffering chronic effects, which are dominated by ACD (NIH Consensus Development Panel, 1999; Winslade, 1998). A broad spectrum of cognitive capacities is identified in patients recovering consciousness following severe to moderate brain injury. Patients with limited evidence of awareness or only fragments of interactive behavior are considered to be in a minimally conscious state (MCS; Giacino et al., 2002). Functional abilities in MCS patients range from a lowest level where patients may demonstrate little difference from the persistent vegetative state (PVS), to a ‘high’ level where patients may demonstrate infrequent, very high level responses such as command following or context-appropriate verbalizations that functionally are closer to communication. PVS patients demonstrate recovery of cyclic alteration of an eyes closed sleep-like state and an eyes open “wakeful” state that is devoid of any evidence of awareness of self or the environment (Jennett and Plum, 1972). A patient in a PVS may rarely demonstrate a behavioral fragment consistent with residual

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cerebral activity; multi-modal brain imaging studies reveal that small modular networks can occasionally be preserved in these patients (Schiff et al., 2002b). Functional activation paradigms in PVS patients, however, fail to activate poly-modal association cortices with natural stimuli (Laureys et al., 2000). This finding is consistent with a breakdown of communication across distributed large-scale networks in these patients. A ‘low’ functioning MCS patient, on the other hand, may exhibit an isolated minimal response that demonstrates a level of sensory-motor integration not present in a PVS. For example, such a patient may reproducibly but inconsistently show efforts to push a ball rolled toward them. Functional magnetic resonance imaging (fMRI) studies of high level MCS patients reveal preservation of widely distributed cerebral networks (Hirsch et al., 2001). This physiological result is consistent with the clinical finding that the bedside performance of the patients revealed an element of higher integrative brain function. Reliable and consistent interactive communication or functional use of objects indicates emergence from a MCS (Giacino et al., 2002).

Patients who recover to functional levels near the threshold of emergence from MCS are likely to be the first group of potential candidates for cognitive neuromodulation with a goal of establishing consistent communication. The prevalence of MCS is estimated at 112,000–280,000 adult and pediatric patients in the US (Strauss et al., 2000). Further development of patient selection criteria and ethical frameworks, however, are required before such studies can be pursued (Schiff et al., 2000; Fins, 2000; Fins and Miller, 2000). We discuss MCS as a model here for interventional cognitive neuromodulation using deep brain stimulation techniques; if such techniques can be developed their use could extend to less overwhelmingly brain-injured patients, e.g. those near the borderline of independent function but limited by ACD (see Fig. 1 for hypothetical points of intervention).

### 3. Possible mechanisms underlying partially reversible cognitive disability following brain injury

Most MCS patients demonstrate preserved but fluctuating capacities for command following, attention, intention, and awareness of self and environment. The fluctuations suggest that their limited functional capacities might be augmented if their highest functional performance level was stabilized. In some cases MCS patients fluctuate quite widely, revealing marked residual cerebral function including capacities for receptive and expressive language (Burruss and Chacko, 1999). The neurological literature suggests several possible neurophysiological mechanisms that may underlie fluctuation in cognitive function following complex brain injuries. Although it has generally recognized that some aspects of ACD may result from functional disturbances disproportionate to the extent of structural injuries, systematic approaches to identify the mechanisms underlying this dissociation in brain-injured patients have not been developed.

Fig. 2 provides a heuristic guide to several such typically interrelated mechanisms. Pathological mechanisms producing both persistent and paroxysmal functional alterations may contribute to partially reversible impairment of integrative forebrain function. A relatively common finding following focal ischemia or TBI is a reduction in cerebral metabolism measured using positron emission tomography (PET) in brain regions remote from the site of injury. This phenomenon, known as ‘diaschisis’, reflects a crossed (trans-)synaptic downregulation of distant neuronal populations (Nguyen and Botez, 1998). Crossed-synaptic downregulation results from the loss of excitatory inputs to a remote brain region that originate at the site of original injury or focal disturbance. Gold and Lauritzen (2002) recently showed that such crossed-synaptic changes are functionally reversible, and only marginally reported by changes in cerebral blood flow; neuronal firing rates can be markedly reduced without proportionate changes in

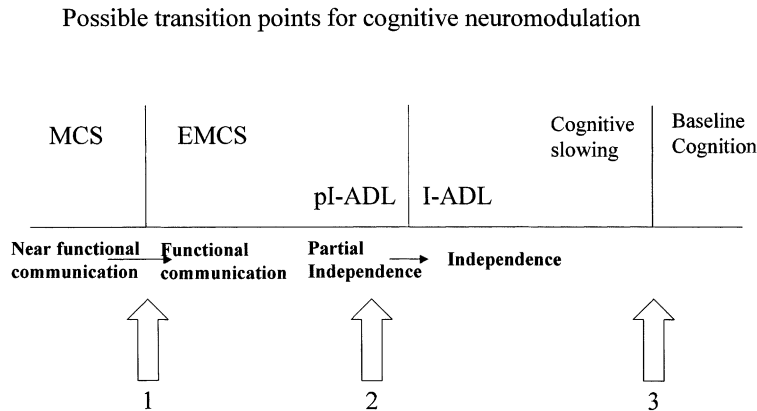


Fig. 1. Three possible transition points for cognitive neuromodulation. Figure diagrams potential entry points for cognitive neuromodulation strategies each at a transition representing a significant functional change. MCS, minimally conscious state; EMCS, emergence from minimally conscious state; pI-ADL, partial independence of activities of daily living; I-ADL, independence in activities of daily living.

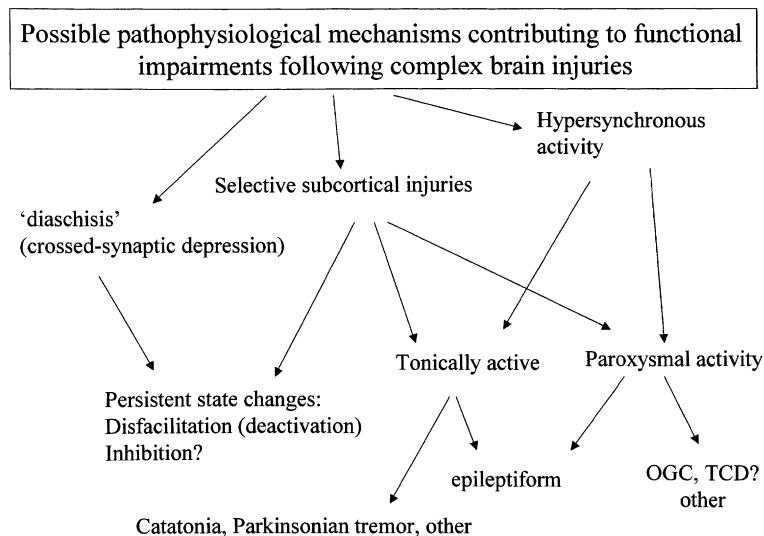


Fig. 2. Possible pathophysiological mechanisms contributing to functional impairments following complex brain injuries. OGC, oculogyric crisis; TCD, thalamocortical dysrhythmia; see text for further discussion of figure.

cerebral perfusion. Loss of excitatory drive to neuronal populations in such instances likely results in a form of inhibition known as disfacilitation in which hyperpolarization of neuronal membrane potentials arises from absence of excitatory synaptic inputs allowing remaining leak currents (principally potassium) to dominate (Timofeev et al., 2001).

In addition to persistent decreases in neuronal firing, widespread hyperpolarization of thalamic membrane potentials may lead to different forms of abnormal hypersynchronous activity (c.f. 'thalamocortical dysrhythmia,' Llinas et al., 1999). The alteration of excitation and inhibition producing hypersynchrony within relatively restricted networks may also play a role following structural brain injuries. For example, hypersynchrony restricted to the thalamostriatal system may account for the forms of catatonia (Wilcox and Nasrallah, 1986, c.f. Kamal and Schiff, 2002) and obsessive-compulsive disorder infrequently observed after TBI (Berthier et al., 2001). Similarly, relatively isolated injury to the thalamostriatal system (Kakigi et al., 1986) may also generate unusual paroxysmal disturbances of consciousness such as the oculogyric crisis (Leigh et al., 1987). Increased excitability following direct brain damage also plays an important role in predisposing widespread areas to epileptiform activity (Santhakumar et al., 2001). Such epileptiform activity, however, can also remain restricted to subcortical regions and manifest only surface slow waves in the electroencephalogram (Williams and Parsons-Smith, 1951).

Importantly, as indicated in Fig. 2, selective subcortical structural injuries alone can produce marked functional disturbances (Schiff and Plum, 2000). In particular, injury to the paramedian mesodiencephalon can induce disproportionate changes in cerebral integration (Castaigne et al., 1981; Steriade, 1997; Schiff and Plum, 2000; Schiff et al., 2002b). Among several established patterns of diaschisis across long-range cortico-cortical and thalamocortical

networks (Nguyen and Botez, 1998), injury to the paramedian thalamus (intralaminar and related thalamic nuclei) is unique in producing widespread functional effects following focal lesions (Szeliés et al., 1991; Caselli et al., 1991). Focal injuries to these regions are also associated with production of epileptic seizures (van Domburg et al., 1996) and other paroxysmal phenomena (Kakigi et al., 1986). Thus, the presence of paramedian mesodiencephalic lesions in combination with other cerebral injuries may lead to a variety of partially reversible mechanisms of dysfunction. Damage to the paramedian mesencephalon commonly accompanies both TBI and stroke as result of the selective vulnerability of this region to the effects of diffuse brain swelling leading to herniation of these midline structures through the base of the skull (see Plum and Posner, 1982).

#### 4. Mechanisms of deep brain stimulation

The use of chronic electrical stimulation of subcortical brain regions (deep brain stimulation or DBS) was initially developed as a more flexible and reversible alternative to traditional functional neurosurgical lesioning methods (Benabid et al., 1993). Patients with severe movement disorders are being successfully managed with DBS by placing the electrodes in selected subcortical structures including the thalamus, globus pallidus interna, and subthalamic nucleus. Present clinical practice is restricted to 'open-loop' DBS in which the stimulator is adjusted by manipulating the frequency and amplitude of an electrical pulse train to achieve a steady stimulation rate that can be carefully titrated to the response profile of an individual patient (Volkman et al., 2002). Investigational studies have also applied open-loop systems for the treatment of chronic pain, obsessive-compulsive disorder, and epilepsy. In each

of these cases the intent is to suppress abnormal activity. In addition, recent efforts to extend DBS to ‘closed-loop’ systems in which particular events or signals trigger a ‘contingent’ or ‘demand’ pacemaking have begun in small clinical studies of refractory epilepsy (Osorio et al., 2001). Such closed-loop methods will extend the flexibility and range of applications of neuromodulation.

The basic mechanisms of DBS remain a topic of debate (e.g. Vitek, 2002). Brain imaging studies show evidence of selective activation of both cortical and subcortical regions including fMRI activations of sensory cortex following thalamic Vim nucleus stimulation and functional PET (fPET) studies of vestibular cortex modulation following globus pallidus interna stimulation (Rezai et al., 1999; Ceballos-Baumann et al., 2001). A series of recent studies by Hammond and co-workers show that high-frequency stimulation of neurons in a slice model of the subthalamic nucleus elicits activation of action potentials with high fidelity (Garcia et al., 2002), that is, in a one-to-one fashion with one pulse producing one burst of action potentials. The burst pattern may be converted to tonic firing after blockade of calcium currents. The one-to-one response of the firing of action potentials following stimulation pulses, however, is independent of synaptic integration mechanisms, as shown by persistence of action potential firing despite broad excitatory or inhibitory neurotransmitter blockade (Garcia et al., 2002). These findings demonstrate that DBS represents a new type of therapeutic modality. The similar clinical effects of DBS and lesioning for the treatment of movement disorders do not reflect a common mechanism of action. The *in vitro* studies are complemented by *in vivo* demonstrations in alert primates that DBS activates target neurons (Postupna et al., 2001; Hashimoto et al., 2001). Since, thalamic neurons share most of the essential intrinsic membrane properties found in subthalamic neurons (Steriade et al., 1997), thalamic neurons are likely to respond similarly to DBS techniques. A recent modeling study of the effect of thalamic DBS on the thalamocortical system is consistent with the experimental findings of subthalamic nucleus stimulation and suggests that widespread activation will typically accompany electrical stimulation of the thalamus (McIntyre and Grill, 2002).

Modulation of neuronal firing rates, however, may only represent part of the mechanism underlying clinical improvements with DBS (Levy et al., 2002; Farmer, 2002; Montgomery and Baker, 2000). In addition to increasing or decreasing neuronal activity within a distributed network (both of which may result depending on synaptic and network connectivity, see later), changes in the correlation structure of background activity produced by DBS may also play causal role. Dostrovsky and co-workers recently demonstrated that modulation of a background rhythm plays a key role in segmentation of active movement (Levy et al., 2002). In their studies, local field potentials (LFPs) and pairs of neurons in the subthalamic nucleus of patients with Parkinson’s disease demonstrated high-frequency

(15–30 Hz) oscillations that showed increased synchronization in the paired recordings of single neurons. These oscillations were suppressed both by movements and by introduction of dopaminergic agents that improved the patient’s symptoms. Importantly, several pair recordings showed changes in the synchronization of neuronal firing pattern independent of a change in firing rate. Thus, the findings support a complementary, or possibly alternative mechanism for the effects of DBS in changing the gating of background oscillatory activity (Farmer, 2002; Levy et al., 2002; Brown et al., 2001). Several studies in the non-human primate MPTP model of Parkinson’s disease also suggest that such correlation structure changes may represent the underlying pathophysiological mechanism (Bergman et al., 1994).

## 5. Role of paramedian thalamic nuclei in forebrain integration and arousal

Though originally considered to form the core of forebrain arousal systems along with the thalamic reticular nucleus and the tegmental mesencephalon (Moruzzi and Magoun, 1949) the thalamic intralaminar nuclei (ILN) are no longer considered exclusively in terms of arousal functions (Steriade, 1997; Groenewegen and Berendse, 1994a; Llinas et al., 1994). Although these thalamic nuclei play an essential role in supporting the state changes of corticothalamic systems that generate sleep–wake cycles (Steriade et al., 1990; McCormick and Bal, 1997) and their pathologies (c.f. Seidenbecher and Pape, 2001), their functional role in the wakeful forebrain appears to be to organize cortico–cortical and thalamocortical networks that are engaged in behaviorally relevant long-range interareal cortico–cortical interactions.

Several unique anatomical features of the intralaminar and related thalamic nuclei allow for such a role. Their specialization is evident in having both wide, but regional selective, projections across the cerebrum and within the cortical microcircuitry. Importantly, the ILN are strongly innervated by subcortical brainstem nuclei that are recognized as the arousal systems (McCormick, 1992; Steriade et al., 1997; Parvizi and Damasio, 2001). The ILN receive strong inputs from the brainstem cholinergic, noradrenergic and other neuronal populations that themselves establish the large-scale pattern of arousal states through their mutual interactions and their projections to the thalamus and cortex (Steriade et al., 1997). In addition, these nuclei receive a variety of sensory afferents including a very heavy innervation from the brainstem vestibular nuclei (Shiroyama et al., 1999, and see later), strong inputs from the superior colliculus (Krout et al., 2001), nociceptive afferents, mesencephalic reticular afferents (Steriade and Glenn, 1982), as well as internal pallidal and substantia nigra (pars reticulata) innervation.

The ILN project widely to both basal ganglia and cortical targets and provide the largest thalamic efference to

the basal ganglia (Gimenez-Amaya and Scarnati, 1999). Recent anatomical studies demonstrate that individual ILN subdivisions project to selected cortical and subcortical regions (van Der Werf and Mitter, 1999; Groenewegen and Berendse, 1994a,b; Macchi and Bentivoglio, 1999; Sidibe et al., 2002). The rostral intralaminar nuclei (central lateral, CL; paracentralis, Pc; and central medial, CeM) tend to project to prefrontal, posterior parietal, and primary sensory areas and provide more diffuse innervation of the basal ganglia (Macchi and Bentivoglio, 1985); the caudal intralaminar nuclei are the centromedian–parafascicular complex (Cm–Pf) which form several strong, in most cases topographically organized, connections with the basal ganglia and include cell populations projecting to pre-motor and anterior parietal cortices (Groenewegen and Berendse, 1994b; Sadikot et al., 1992). In the rat thalamocortical system these nuclei collectively provide a map of large distributed networks roughly corresponding to the cortico–striatopallidal–thalamocortical ‘loop’ systems described in non-human primates by Alexander et al. (1986) (including a ‘visceral,’ ‘motor,’ ‘limbic’ and ‘cognitive’ loop, van Der Werf and Mitter, 1999). Groenewegen and co-workers have proposed that the ILN provide an anatomical substrate for interactions among these relatively segregated loop pathways under the control of the prefrontal cortex (Groenewegen and Berendse, 1994b). Although similar comprehensive mapping of the primate ILN systems is not available, these systems are highly conserved across species (Jones, 1985). Of note, a recent multi-dimensional scaling model of the entire cat thalamocortical system identifies that the ILN (CL, Pc, Cm–Pf) form a unique central cluster among all the otherwise segregated thalamocortical loop systems (frontal, limbic, temporal, and parietal), providing a potential shortest path of connection among them (Scannell et al., 1999).

Complementing their multi-regional projections across forebrain cortical and subcortical structures, ILN neurons have a unique pattern of innervation of the cortical microcircuit (Macchi, 1993). Most intralaminar thalamic neurons synapse in layer I on the apical dendrites of pyramidal cells located in layers II–III, and layer V. In addition, ILN neurons synapse on cell bodies within layers V and VI (Macchi, 1993). Studies of direct electrical stimulation of ILN subdivisions reveal selective depolarization of both the supragranular and infragranular cortical layers (Sukov and Barth, 1998; Llinas et al., 2002). This pattern of dual innervation within a cortical column has been proposed to provide a coincidence detection mechanism that can facilitate inputs from the specific thalamic inputs to the granular layers (Llinas et al., 1994, 1998). Larkum et al. (1999) demonstrated that co-activation of the apical dendrites (in layer I) and soma of layer V pyramidal neurons (unusual in having projections to all cortical layers and in their capacity to generate both distal dendritic and somatic action potentials) induces a back-propagating action potential leading to the generation of burst firing. The mechanism may provide

a biophysical basis for synaptic modification around coincident firing patterns. Llinas et al. (2002) recently demonstrated that combined stimulation of CL and the ventrobasal nucleus (a specific thalamic relay nucleus projecting into cortical layer IV) in a mouse slice model generated a supra-linear summation of local evoked potentials consistent with this mechanism. Depolarization of the supragranular layers by ILN afferents as demonstrated in this study may promote sustained cortical activity (Vogt, 1990; Mair, 1994) and activate mechanisms of long-term potentiation dependent on NMDA receptors (Mair, 1994, Purpura and Schiff, 1997) or other mechanisms (McCormick and von Krosigk, 1992).

The strong projections of the ILN and other related thalamic nuclei to layer I of cortex formed the basis of earlier classifications of thalamic nuclear subdivisions as ‘non-specific’ (Jones, 1985). Jones (1998a, b) has recently redefined the intralaminar and other thalamic subdivisions into two classes of neurons on the basis of differential calcium-binding protein expression. This classification scheme parallels the ‘striosome’ concept of basal ganglia organization developed by Graybiel (1984). One class of thalamic neurons, the “matrix” neurons, expresses calbindin D<sub>28K</sub> and demonstrates superficial cortical projections to layer I across relatively wide cortical territories. The other class of thalamic neurons, the “core” neurons, expresses parvalbumin; core neurons have more area-specific cortical projections and form synapses in the middle, or granular, layers of the cortical microcircuit. Jones identifies a large number of matrix neurons in most ILN subdivisions, but also demonstrates their existence throughout the thalamus, even within primary sensory relay nuclei. He proposes that the matrix neurons act collectively as a functional system to organize global corticothalamic synchrony (Jones, 2001).

Unique clinical pathologies associated with injury to ILN subdivisions in humans, however, suggest a disproportionate importance of the intralaminar and adjacent ‘paralaminar’ thalamic nuclei in forebrain integration (see Schiff and Plum, 2000 for review). Consistent with this viewpoint, Jones’ anatomical parcellation of the primate thalamus has been extended by Munkle et al. (1999, 2000) in studies of the human thalamus where the addition of a marker for the calcium-binding protein calretinin identifies a pattern of co-expression unique to most intralaminar subdivisions. These authors interpret their findings as evidence for a privileged role of the human ILN in forebrain gating. The matrix concept also provides a possible substrate for the rare recovery of cognitive function following bilateral injury to the ILN (van Domburg et al., 1996; Krolak-Salmon et al., 2000).

Arousal states reflect varying degrees of corticothalamic synchronization that are under well-established physiological control by brainstem modulation of the interactions of thalamic reticular neurons, thalamocortical relay neurons, thalamic inhibitory interneurons and cortical pyramidal cells (Steriade, 2000). Stimulation of either Cm–Pf or CL desynchronizes the electroencephalogram and generates arousal

(Glenn and Steriade, 1982; Steriade et al., 1990, 1996). A bi-directional monosynaptic connection between CL and the mesencephalic reticular formation has been demonstrated to underlie this phenomenon (Steriade and Glenn, 1982). The background activity changes during arousal states can be precisely identified as shifts in spectral content of the activity of distributed forebrain networks (Contreras and Steriade, 1995; Steriade et al., 1996), with spectra showing a shift in power away from low frequencies to a mixed state including increased synchronized high-frequency activity in natural awake attentive states (Steriade et al., 1996). Such long-lasting changes of ongoing background activity, however, are episodically shaped at a finer temporal scale by brief phasic modulations of the rhythms. In wakeful states, for example, modulation of high-frequency oscillatory activity in the 30–80 Hz range has been correlated with several cognitive functions including perceptual awareness (Joliot et al., 1994), motor preparation and exploration (Murthy and Fetz, 1996), and working memory (Pesaran et al., 2002). These ongoing background rhythms likely play a role in structuring cognitive activity within corticothalamic networks similar to that of the 15–30 Hz rhythms identified for organizing activity in motor systems (see earlier sections).

An important issue is whether the modulation of background rhythms by ILN neurons has a functional role in controlling forebrain information flow beyond that of a simple bias signal to promote depolarization of neurons and consequently coincidence detection within the cortical columns. Several behavioral studies in animals indicate that these nuclei play an important role in the integration of sensory information (Matsumoto et al., 2001; Minamimoto and Kimura, 2002), and motor intentional signals (Burk and Mair, 2001) including an oculomotor efference copy signal (Schlag-Rey and Schlag, 1984a,b). Additionally they play a role in the maintenance of persistent neuronal firing patterns supporting sustained attention (Schiff et al., 2001) and working memory (Burk and Mair, 1998). These latter changes in persistent activity likely reflect signals rich in information and are further discussed later.

Amzica et al. (1997) showed that coherent high-frequency activity can be produced in CL, the lateral geniculate nucleus and primary motor and sensory cortices by instrumental conditioning in awake cats. This remarkable finding may depend on the unique connectivity pattern of CL which projects to the frontal eye fields (FEFs), and the anterior cingulate, dorsal lateral prefrontal, anterior parietal association, primary motor, and visual cortices (Leichnetz and Goldberg, 1988; Macchi and Bentivoglio, 1985; Minciacchi et al., 1993). The projections of CL and those of Pc, which has strong connections with temporal association cortex (Yeterian and Pandya, 1989), suggest a role for the rostral ILN in sensory information processing within overall sensorimotor integration. A recent lesion study of the rat ILN (primarily the rostral nuclei) demonstrated that failures of motor intention and not sensory attention account for impaired performance on a self-paced serial reaction-time task (Burk and

Mair, 2001). These findings suggest that the projections of the rostral intralaminar nuclei to the prefrontal, primary motor, and sensory cortices may provide an ‘intentional’ gating mechanism linking perceptual processing to the direction of action. The caudal ILN, i.e. the Cm–Pf complex, appears to be more centrally related to the gating of motor behavior around sensory information (Minamimoto and Kimura, 2002; Matsumoto et al., 2001). Consistent with this view two recent studies demonstrate that posterior intralaminar neurons signal several types of behaviorally relevant sensory events, such as the onset of a sensory cue (Matsumoto et al., 2001) and participate in attentional orienting to such sensory cues (Minamimoto and Kimura, 2002).

## 6. How might neuromodulation be linked to cognitive rehabilitation?

### 6.1. Open-loop strategies

For open-loop neuromodulation to find application in the treatment of cognitive disabilities it is necessary to develop rational strategies that build on the emerging mechanistic principles that underlie the technique. Accordingly, a role for modulation of neuronal firing rates and possibly modification of pathological background rhythms to treat impaired cognitive function must be articulated. In addition, to be practical, it is necessary that discrete subcortical structures are available to implement the stimulation strategies.

As reviewed earlier, complex brain injuries may lead to reversible disabilities as a result of decreased neuronal firing rates due to chronic crossed-synaptic depression of firing rates and varying types of abnormal rhythmicity. In addition, loss or impairment of widely broadcast signals used in normal forebrain integration mechanisms may also contribute to reversible deficits (see *closed-loop strategies*). The anatomical and physiological distinctions of the intralaminar and ‘matrix’ neuron rich subcomponents of related thalamic nuclei suggest that these unique subcortical structures are optimally placed to provide access to several large-scale networks underlying basic cognitive functions of intention, working memory and sustained attention.

Human neuroimaging studies support an interdependence of distributed forebrain networks during performance of tasks requiring working memory, sustained attention and motor intention. Specifically, a significant convergence of neuronal populations in prefrontal and parietal cortices is identified in several different paradigms (Fockert et al., 2001; Courtney et al., 1997; Klingberg et al., 1997; Kinomura et al., 1996; Paus et al., 1997). The short-term maintenance of active representations of information defines working memory. Human fMRI studies show sustained activity in multiple regions of prefrontal and extrastriate cortices during tests of visual memory (Courtney et al., 1997). Fockert et al. (2001) demonstrated interactions of selective attention and working memory within several of the same areas of the

prefrontal cortex. These investigators interpret their results as evidence that working memory resources in the frontal lobe control visual selective attention. Broad deficits in delayed conditional discrimination across sensory modalities are seen after experimental lesions of the rat rostral ILN (Burk and Mair, 1998). The deficits are not accompanied by impairment of sensory discrimination and have been attributed to loss of ILN modulation of analogous prefrontal cortical regions. Consistent with these findings from imaging of normal human subjects and rat lesioning experiments, long-lasting impairments of human frontal lobe function are correlated with discrete injury to CL (van Der Werf et al., 1999). As noted earlier, studies of lesions of the rat rostral ILN (CL, Pc) also demonstrate specific deficits in initiating motor behavior. The overlap of prefrontal and parietal regional activations seen in sustained attention and working memory paradigms is also found in human imaging studies of motor planning (Klingberg et al., 1997).

Roland and colleagues studied subcortical contributions to the short-term focusing of attention using fPET in normal human subjects performing a reaction-time task to a visual or somatosensory stimulus (Kinomura et al., 1996). They identified strong activation of both the rostral (CL) and caudal (Cm–Pf) ILN during the sustained attention component of the behavior. These thalamic nuclei co-activated with the tegmental mesencephalon consistent with their demonstrated bi-directional monosynaptic connections (Steriade and Glenn, 1982). Coincident with the increases in regional cerebral blood flow to these subcortical structures, regional cerebral blood flow in the cerebral cortex showed a diffuse elevation ( $\sim 3\text{--}4\text{ ml}/100\text{ g min}^{-1}$ ). A related study by the same investigators identified a strong correlation of activation of the anterior cingulate cortex with the speed of the reaction time in a similar paradigm (Naito et al., 2000). Recruitment of the anterior cingulate cortex appears to strongly correlate with engagement of the networks reviewed earlier in the face of increasing cognitive demands (Dehaene and Naccache, 2001; Duncan et al., 2000; Naito et al., 2000; Paus et al., 1997) and may reflect activation of reciprocal connections of the rostral ILN (CL) with this cortical region. Paus et al. (1997) studied cortical and subcortical contributions to a sustained vigilance task done over a 60 min test period and found covariation of blood-flow responses in the paramedian thalamus, caudate, putamen, basal forebrain (substantia innominata), ponto-mesencephalic tegmentum and the anterior cingulate cortex.

The studies of human vigilance reviewed earlier provide critical foundations for assessing the intralaminar thalamic nuclei as an entry point for modulation of basic cognitive functions. We have modeled the brief focusing of attention study done by Roland and colleagues (Kinomura et al., 1996) in the non-human primate (Schiff et al., 2001). Fig. 3A shows the timeline of the visuomotor attention experiment. The monkey initiates the trial by holding a bar. Following trial initiation a target appears in one of nine locations in a spatial array and is acquired by a saccadic eye movement.

The monkey is then required to hold fixation for a variable delay until the target changes color providing a ‘go’ signal to release the bar within 500 ms to receive a juice reward. Fig. 3B shows an example of single-unit responses from central thalamic structures activated during the sustained attention (variable delay) component of this reaction-time task. An elevation of firing rates during the variable delay period was identified in 23% of central thalamic neurons and was correlated with a shift of spectral content of the simultaneously recorded LFPs characterized by an enhancement of power in the 30–70 Hz frequency band and a reduction in power in the 10–20 Hz frequency band (Schiff et al., in preparation). Panel 3C shows an example of a single-unit recording from a site in the caudate/putamen from the same animal. A complementary reduction in delay period firing is seen in this striatal neuron at the same time as increase in firing of the central thalamic neurons. A strong reduction of population activity in the 15–20 Hz region of the frequency spectrum was identified, similar to that seen in the thalamic LFPs (not shown).

Persistent neuronal firing patterns appear during the delay periods of selective attention and working memory paradigms in the prefrontal cortex (Fuster, 1973; Goldman-Rakic, 1996), FEF (Schall, 1991) and the posterior parietal cortex (PPC) (Andersen, 1989; Pesaran et al., 2002). These regions are activated in human imaging studies using similar paradigms as noted earlier. The central thalamic recordings shown here may be recorded from rostral ILN subdivisions, CL or Pc (Schlag-Rey and Schlag, 1984a,b) or closely-related paralaminar regions of the median dorsalis nucleus rich in matrix cells (Jones (1998a) in fact has reclassified these areas of the primate median dorsalis nucleus as continuations of CL). Collectively the rostral intralaminar nuclei selectively project to prefrontal cortex, PFC (CL and paralaminar MD), FEF (CL and paralaminar MD), anterior cingulate cortex (CL) and PPC (CL)—placing them in a central position to participate in the integration of intentional gaze control with attentional and working memory systems (Purpura and Schiff, 1997).

Two complementary rationales for open-loop cognitive neuromodulation in the ILN can be articulated based on boosting endogenous short-lasting elevations in neuronal activity such as those seen in single-unit recordings (as illustrated in Fig. 3B). As reviewed earlier, persistent deactivation may play an important role in the failure of partially viable modular networks to express their function following complex brain injuries. Thus, increases in neuronal activity within the matrix subpopulation per se induced by DBS may help support and extend such ongoing distributed network activity. As discussed earlier, however, re-establishing normal patterns of coherence of neuronal activity, such as the episodic modulation of coherence of 15–30 Hz oscillations in Parkinson’s patients (Levy et al., 2002), may be equally important.

Periods of elevated neuronal activity, such as those illustrated in Fig. 3B, may play a causal role in the integration

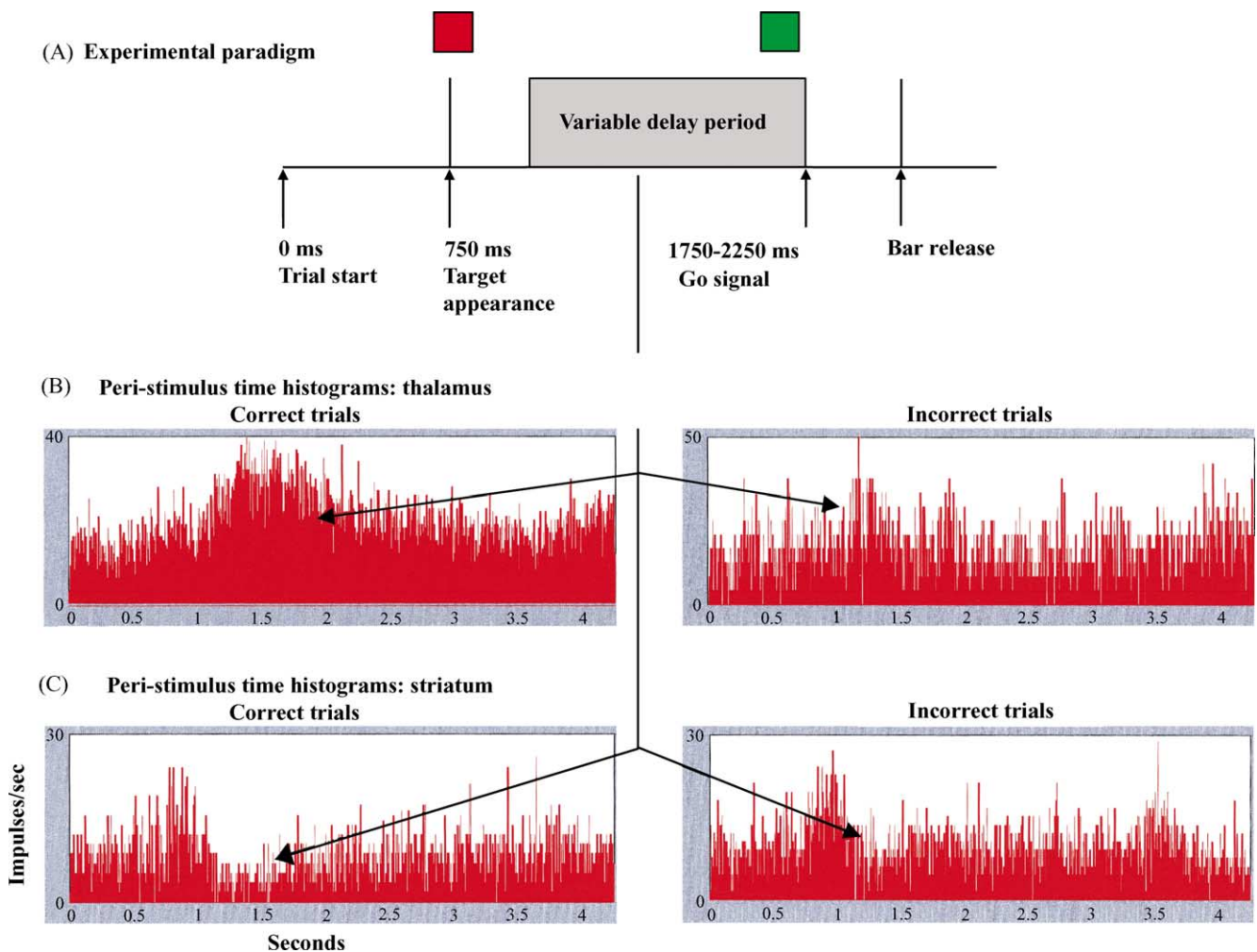


Fig. 3. (A) Experimental paradigm. Target appearance indicates appearance of red square in a location of the visual field that is acquired by a saccadic eye movement (see text). A 'go' signal (change of square color to green) appears after a variable delay period. Bar release is required within 500 ms of 'go' signal for correct performance. (B) Peri-stimulus time histogram indicating elevated firing rate in the central thalamic single-unit during delay period. A reduced response is seen in the delay period of the incorrect trials (C). Peri-stimulus time histogram indicating reduced firing rate in the single-unit recording from the striatum during delay period. The reduction of response is not seen in the delay period of the incorrect trials.

of separate distributed oculomotor networks underlying intentional gaze control with attentional and working memory systems (Purpura and Schiff, 1997). In studies of single-unit responses in the primate striate cortex, we earlier demonstrated that 'residual' neuronal activity, i.e. activity (recorded as spikes or continuous field potentials) that remains after the average of the event-related driven activity is subtracted, can be modulated by the presence of a repetitive stimulus (Schiff et al., 1999a). Such residual activity may therefore be related to an endogenous or externally generated signal providing a phase mark. Fig. 4 schematically illustrates the modulation of residual activity (here a hypothetical LFPs recording) by a background oscillation (sinusoid). Quantification of such activity envelopes allows for analysis of the dynamics of complex local network inputs that shape individual neuronal responses. These stimulus-dependent changes in brain activity are not restricted to narrow band, single population phenomena such as oscillations (Singer and Gray, 1995),

and might appear as bursts (Bullock, 1996; Lisman, 1997; Schiff et al., 1999a,b) or other types of transient neuronal responses to stimuli (Aertsen et al., 1989; Friston, 1995). The presence of stimulus-dependent residual activity provides a mechanism for the gating of interactions of substantially independent sources of ongoing activity within different forebrain structures (Schiff et al., 1999a). For example, the modulation of background population activity envelopes by phasic changes in the firing of ILN neurons, may simultaneously influence residual activity of neurons in cortical and basal ganglia networks and thereby alter the capacity of these individual single-units to gate signals from multiple neuronal assemblies.

Selective stimulation of intralaminar thalamic nuclei has been proposed as an open-loop DBS strategy for treating patients with ACD (Schiff et al., 2000, 2002a). In the MCS patients described earlier who demonstrate intermittent integrative forebrain activity, open-loop neuromodulation



## Heuristic model for gating of residual neuronal activity by episodic changes in background rhythms

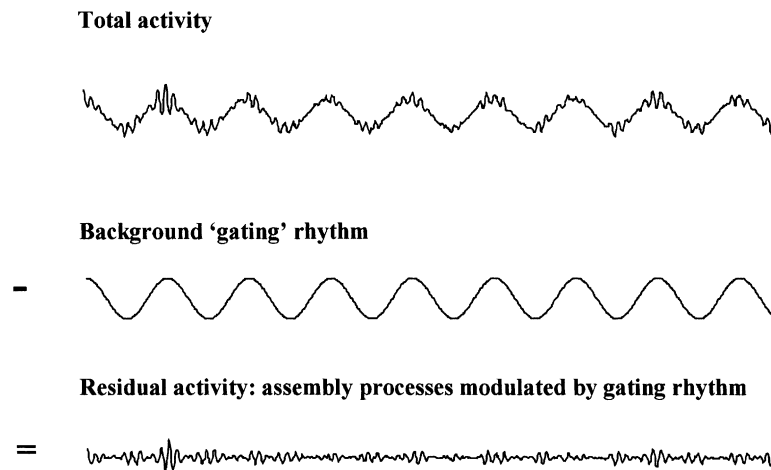


Fig. 4. Model of 'gating' mechanism (see text).

might help to extend endogenously generated elevations of neuronal activity and temporal patterns of firing rates (envelopes). The integrative network responses identified in MCS patients indicate that these distributed networks remain functionally connected, although the quality of neuronal activity is apparently insufficient to support consistent cognitive function. Open-loop stimulation of the intralaminar nuclei could both increase baseline firing of neurons in these paramedian structures that are incompletely damaged, for example, by herniation injuries, as well as to facilitate formation of population activity envelopes in the thalamus, basal ganglia and connected cortical regions. Appropriate stimulation parameters to achieve such goals are unknown. In vitro slice preparations (Llinas et al., 2002) demonstrate that electrical stimulation of intralaminar neurons can strongly induce cortical microcircuit activity in the 30–50 Hz frequency range, similar to what is seen in the EEG and LFP during attentive behaviors (Steriade et al., 1996). The influence of different DBS patterns on complex network dynamics, however, is also unknown; irregular, higher frequency stimulation rates could prove to be more effective in restoring appropriate network activity (Montgomery and Baker, 2000). To further develop open-loop strategies, primate experimental models of wakeful unresponsiveness using pharmacological inactivation methods and deep brain stimulation techniques along the lines of the MPTP model in Parkinson's disease are required (Schiff et al., 2002c).

### 7. Closed-loop strategies

Developing strategies for closed-loop cognitive neuromodulation depends on the identification of relevant, and widely distributed, internally-generated physiological sig-

nals that can be used to control the output from implanted deep brain stimulators. As noted earlier, the distributed forebrain networks co-activated by effortful cognitive tasks requiring sustained attention, high working memory loads and strong intentional/motivational drive have significant overlap with systems involved in the control of saccadic eye movements in humans and non-human primates (Paus et al., 1997; Kinomura et al., 1996; Morecraft et al., 1993). Paus et al. (1997) propose that this overlap may reflect a 'supramodal' involvement of these networks in controlling directed attention. Directed attention here is interpreted as an intention to move based on sensory information generalized across modality (c.f. Snyder et al., 1997; Sheliga et al., 1994). Studies of cognitive rehabilitation support the view that the brain's internal signals related to intended movements, particularly saccadic eye movements, represent a natural control signal that may underpin the efficacy of existing cognitive modulation maneuvers. For example, retraining of visual scanning in patients with ACD significantly correlates with general improvements in their performance of activities of daily living (Cicerone et al., 2000).

Many rehabilitation maneuvers elicit only a transient recovery of broad cognitive deficits including forced deviation of eye movements, vibration of the sternocleidomastoid muscles or deep tendon massage, forced truncal rotation, cold water irrigation of the ear canal and other methods that induce ocular nystagmus (Karnath et al., 1991, 1995, 1996; Nadeau et al., 1997). These maneuvers improve awareness of auditory, visual, and somatosensory stimuli, as well as re-establish awareness of limbs or neurological deficits. In addition, the recoveries of abilities to organize to motor behaviors (reversal of intentional neglect) and to direct attention in all sensory modalities are described with such maneuvers. Notably, most of these maneuvers introduce

vestibular and oculomotor stimuli (e.g. cold caloric testing, truncal rotations in three-dimensional space, and vibratory stimulation of muscle spindles). The principal outflow of the brainstem vestibular nuclei, in addition to cortical targets, is to paramedian thalamic nuclei, principally the intralaminar nuclei CL, Pc, and Pf (Shiroyama et al., 1999). The repetitive activation of a saccade-related signal distributed through the intralaminar nuclei as a result of the oculovestibular response induced by cold caloric stimulation is proposed as the mechanism producing transient reintegration of cortical function with this technique (Schiff and Pulver, 1999).

As reviewed earlier, the ILN receive a wide array of sensory afferents along with efference copy signals of oculomotor (Schlag-Rey and Schlag, 1984a,b) and likely other movements including the head, neck, and limbs. Another possible simplification of the integration of these wide inputs, in addition to the support of persistent activity envelopes (Purpura and Schiff, 1997; reviewed earlier), may be to bias activation around the intended direction of action. Interpreted in this way, the various rehabilitation techniques reviewed may all rely in part on re-establishing or enhancing these signals related to changes in the intended direction of movement, or perceived body coordinates, via ILN afferents to achieve improvements in cognitive function. The robust presence of signals related to saccadic eye movements in the ILN and related subcortical structures suggest they are good candidates for monitoring internally-generated signals and providing stimulation as part of a strategy for closed-loop neuromodulation (Schiff et al., 1999b).

Fig. 5 displays simultaneous recordings of LFPs from a population of central thalamic neurons that demonstrate elevation of neuronal firing rates during a delay period of sustained attention (see Fig. 3B) and a population of neurons in the extrastriate visual cortex of the alert monkey. The LFPs are obtained by averaging several trials around the time of the animal's first saccade (marked as zero time) onto the target screen (see Fig. 3A). In Fig. 5A, an extraretinal saccade-related signal is shown in the central thalamic recordings; this signal begins approximately 25 ms prior to the saccade onset. The LFP signal is seen to invert for right (red line) and left (blue line) directed saccades. In Fig. 5B, LFPs recorded simultaneously from the extrastriate cortex show an eye movement potential that reflects both visual afference from fixation following the saccade and an efference copy component (Purpura et al., in preparation). A sign inversion of the signal with respect to saccade direction is seen in an early component here with similar characteristics to the extraretinal signal recorded in the thalamus. In Fig. 5C these LFPs signals are plotted on the same scale and the early sign inversion of the potential is seen in both signals (arrows indicate thalamic potentials) with a possible slight latency shift evident for the LFPs averaged around rightward saccades (red lines). These findings add support for a central thalamic role in signaling intended direction of movements and raise the question of whether such signals may interact with the sustained activity

envelopes recorded in the same central thalamic neuronal populations.

Several studies demonstrate that delay period activity in the cortex (principally recorded in the frontal lobe and parietal cortices) contains directional information about intended movements—both in the spike activity and in the population activity recorded in the LFPs (Andersen, 1989; Fuster, 1973; Funahashi et al., 1993; Goldman-Rakic, 1996; Pesaran et al., 2002; Schall, 1991). We earlier proposed that signals from ILN afferents facilitate the formation and maintenance of delay period activity that may link arousal, attention, working memory and gaze control on a moment-to-moment basis (Purpura and Schiff, 1997). Taken together, combining the signaling of an intended direction of action (or preparatory change of coordinates, e.g. optokinetic reflexes) and the maintenance of sustained activity envelopes may identify an underlying organizational principle of the intralaminar system.

Physiological and psychophysical studies support an interaction of sustained activity supporting working memory and repetitive motor signals. Funahashi et al. (1993) earlier demonstrated interactions of delay period activity with saccades and other movements in recordings of neurons from the principal sulcus in the alert rhesus monkey; they proposed that the transient signal related to the movements terminated the delay period activity. Gutkin et al. (2001) recently proposed a model for these and other recordings of neuronal delay period activity in which promotion and dissolution of persistent activity envelopes depends on brief synchronous transients interpreted as efference copy signals of saccades and other motor events. An interesting and complementary neuropsychological observation along these lines is that gesturing in most normal subjects improves working memory during speaking (Goldin-Meadow et al., 2001). One interpretation of this finding is that the repetitive motor signal of the gesture provides a phase mark to reset and recruit additional activity envelopes to support the verbal task. Alteration of the interplay of brief formation and dissolution of activity envelopes on a time scale consistent with the intersaccadic interval may also account for failures of working memory across saccades in the parietal neglect syndrome (Husain et al., 2001). In the context of these studies, it is interesting to note that impaired simultaneous performance of cognitive and motor tasks is described following focal ILN injury (Mennemeier et al., 1997). As reviewed earlier, the ILN likely contribute directly to the formation and gating of extended activity envelopes around intentional motor behaviors including saccadic eye movements.

Finally, the precise timing characteristics of saccadic movements per se may be considered a fundamental mechanism of information acquisition in the human (and non-human primate) brain which, if linked by feedback neuromodulation systems, may allow further functional reintegration of cortical activity and cognitive function. Gilchrist et al. (1997, 1998) provide unique and well-documented

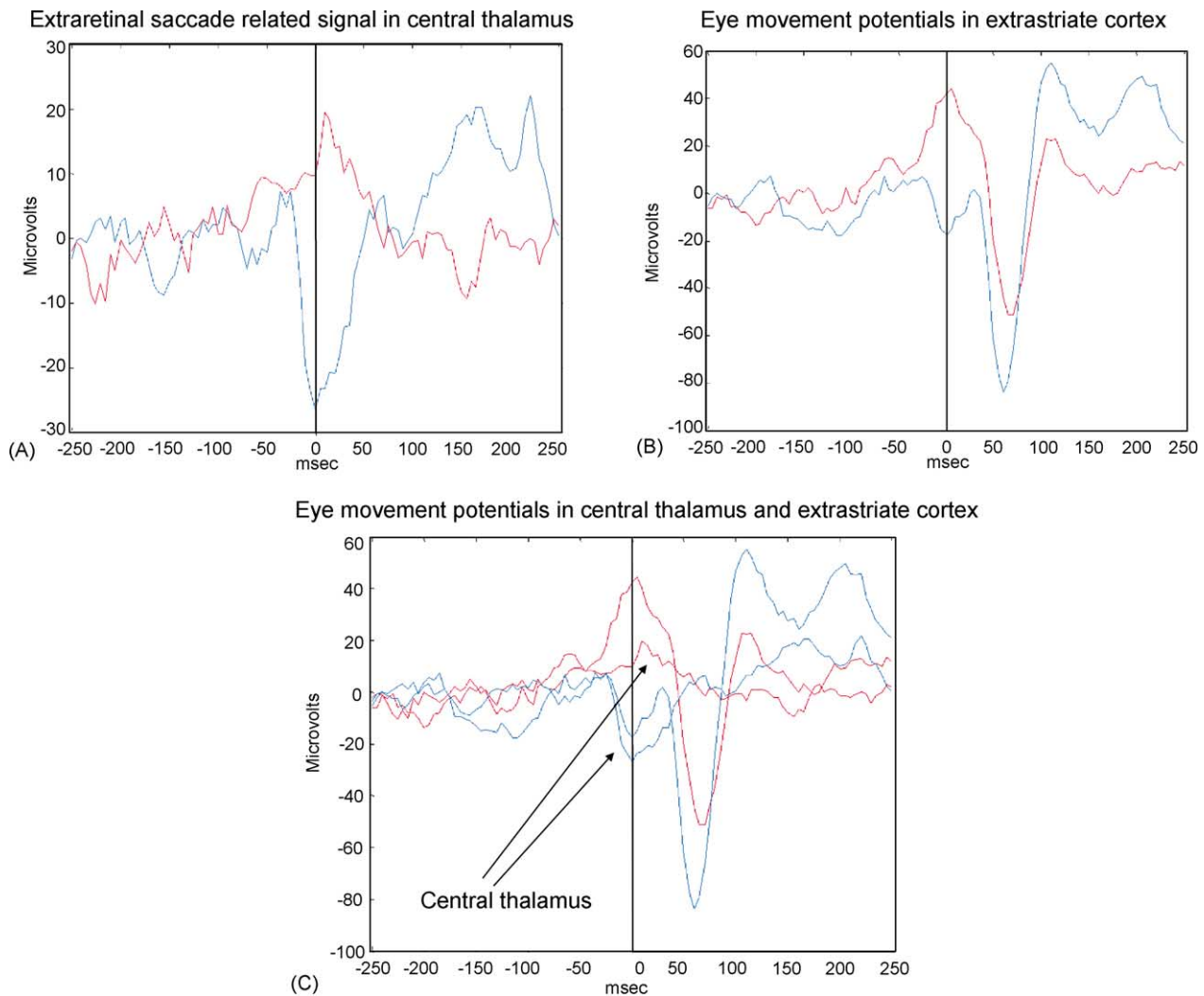


Fig. 5. (A) Extraretinal signal in central thalamus from local field potential (LFP) recordings averaged around saccade onset. Line colors indicate left directed saccades (blue) and right directed saccades (red). (B) Eye movement potential recorded in the extrastriate cortex. Line colors indicate left directed saccades (blue) and right directed saccades (red). (C) Combined figure of the simultaneously acquired recordings showing early sign inversion of field potentials around saccade onset (see text for further discussion). Arrows indicate central thalamic LFP signals. Line colors indicate left directed saccades (blue) and right directed saccades (red).

evidence for this proposal in their studies of a patient with congenital extraocular muscle fibrosis. The patient has made no eye movements since birth yet has developed 'saccadic' movements of the head that fit exploratory fixation patterns and intersaccadic interval distributions known for eye movements (Gilchrist et al., 1997). The head saccades qualitatively reproduce system characteristics identified in standard oculomotor paradigms including the phenomenon of reduced sensitivity to visual stimuli around the time of a saccade or 'saccadic suppression' (Gilchrist et al., 1998). An important quantitative difference of the patient's head saccades is the finding that the maximum saccadic suppression occurs 19 ms prior to the detected movement of the head. This observation supports a key role for a pre-motor signal (such as that shown in Fig. 5) in producing the perceptual change. Due to the greater inertial properties of

the head the timing of this signal is more clearly identified in this patient. The investigators interpret their results as providing clear evidence for the role of a signaled action in perceptual processes. The finding also provides a link to the perceptual improvements seen with movement related rehabilitation strategies discussed earlier. We propose that to increase the cortical and subcortical resources available for the execution of a cognitive task, DBS of subdivisions of rostral or caudal ILN (or possibly matrix neuron rich paralamina regions of median dorsalis and pulvinar) that demonstrate an oculomotor efference copy signals, should be gated by an impending saccadic eye movement. Patterning DBS in conjunction with endogenously generated saccades, or linked to body movements (such as hand gestures or head movements) using pulse parameters similar to saccadic eye movements, may more reliably reproduce the

transient remediative effects of rehabilitation maneuvers on cognitive deficits.

## 8. Postscript

We are now witnessing a re-examination and renewed appreciation of the role of the intralaminar thalamic nuclei, nucleus reticularis of the thalamus, and the basal ganglia in supporting cortical synchronization patterns. We argue that in concert with the rapid progress in clinical neuromodulation techniques, it will soon be possible to develop rational techniques for cognitive neuromodulation. Further understanding of the role of the intralaminar nuclei and the other thalamic nuclei containing significant subpopulations of ‘matrix’ cells in establishing normal patterns of episodic integration during behavior will be essential to these efforts. Any approach to modulating cognitive functions must be placed in the context of established understanding of integrative brain function. Open-loop strategies will require that stimulation sites provide benefit either via changing overall firing rates of target neuronal populations or constant alteration of ongoing background brain rhythms. Closed-loop strategies, however, may be able to come closer to provide relevant signals for coupling information gathering and processing with intention. It may be far more flexible and efficient to adapt brain stimulation to the moment-to-moment, ever-changing demands of a particular individual. Increased flexibility will also permit tackling a wider range of human brain injuries. As proposed earlier, particular transient activations around shifts of intention, indexed by internally-generated signals identified by reference to movements, may provide a practical entry point to develop closed-loop cognitive neuromodulation. 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.

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