Central Thalamic Deep-Brain Stimulation in the Severely Injured Brain

Rationale and Proposed Mechanisms of Action

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This review outlines the scientific rationale supporting the potential use of deep-brain electrical stimulation (DBS) in the central thalamus as a method to improve behavioral responsiveness following severe brain injury. Neurons within the central thalamus are selectively vulnerable to disconnection and dysfunction following severe brain injuries because of their unique geometry of cerebral connections. Because the central thalamus plays a key role in forebrain arousal regulation, impaired function of these cells has a broad impact. Prior clinical investigations, however, have targeted some components of the thalamus and related subcortical structures to improve behavioral responsiveness after severe brain injuries without providing evidence of sustained and clinically meaningful behavioral effects. Here important differences in conceptual framework, consideration of diagnostic categories for patient selection, and anticipated mechanisms of effect that distinguish earlier approaches and current studies are reviewed. As opposed to targeting chronically unresponsive patients, current efforts focus on identification of conscious patients with significant preservation of large-scale integrative cerebral networks. The potential mechanisms and limitations of this evolving strategy are discussed, including the need to develop frameworks to calibrate patient selection to potential clinical benefits, range of potential effect size, and other present unknowns.

Key words: **intralaminar nuclei; minimally conscious state; medium spiny neuron**

Introduction

Several clinical observations demonstrate that some severely brain-injured patients may harbor greater functional reserve than indicated by conventional neurologic assessment.[1–3] In some cases, marked limitations of observed behavior or even the absence of overt behavior present over months, years, and even rarely, decades, has not excluded significant recovery.[3,4] Although infrequent, recovery of verbal communication, ambulation, and other capacities that require integrative cerebral function has occurred either spontaneously or in response to introduction of selective pharmacologic agents.[1,2,5] More commonly, many severely brain-injured patients show marked fluctuations in behavioral responsiveness. Collectively, these observations prompt consideration of physiological mechanisms that both limit the recovery of integrative brain function after severe injury and yet provide a potential substrate for further rehabilitation. Specifically, they raise the question of whether a "circuit"-level description of the instability of brain function after severe injuries might help to account for these phenomena. As argued later in this chapter, common underlying mechanisms may play a role in different types of severe brain injury at a "mesocircuit" level of description.[6] Importantly, neurons within the central thalamus may play a key role in circuit mechanisms

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underlying forebrain dysfunction after severe injury[7] (see Ref. 7 for review) and possibly also provide a substrate for interventions aimed at partial restoration of brain function. These neurons are specialized anatomically and physiologically to support distributed mechanisms of arousal regulation in the forebrain. Electrical stimulation of these neurons, or deep-brain stimulation (DBS), has been proposed as an approach to assisting recovery from severe brain injury.[8–10] In the following sections we outline the clinical–pathologic foundations for the unique vulnerability of the central thalamus to disconnection and dyfunction in nonselective, diffuse brain injuries and the details of proposed circuit mechanisms underlying the possible role of DBS in the central thalamus.

Involvement of Central Thalamus in Severe Brain Injuries: Pathological Studies

It is well known that focal brain injuries within the central thalamus can produce coma and residual long-standing disturbances of consciousness in humans if the lesions are bilateral and large in their rostrocaudal extent.[7,11,12] However, it is less well appreciated that central thalamic (CT) neurons have a critical involvement in nonselective brain injuries such as hypoxia-ischemia, anoxia, and diffuse axonal injury.[13–16] Kinney and Samuels[16] originally noted in the autopsy study of Karen Ann Quinlan that nuclei within the central thalamus appeared to be more severely affected than other brain regions, although widespread cerebral atrophy was evident that had also resulted from her anoxic brain injury. Adams and colleagues[13] identified similar observations of widespread thalamic neuronal death in a larger group of autopsy studies of ~50 patients in vegetative state (VS) (examining autopsy data from a patient who remained in VS for at least one month after anoxic injury and 3 months after traumatic injuries). These investigators went on to carefully examine in detail the differential cell loss within the thalamus in a group of patients with diffuse multifocal brain injuries against varying outcomes following severe traumatic brain injuries.[14] In this assessment, patterns of cell loss within individual CT nuclei correlated with functional outcomes ranging from moderate disability to VS. In these studies (see Fig. 1A), patients with the highest-level functional outcomes of moderate disability demonstrated neuronal loss within the anterior intralaminar nuclei (central lateral [CeL] and central medial [CeM]). A continuing progression of cell loss that involved more posterior and lateral components of the intralaminar regions (centromedian–parafasicularis [CeM–Pf]) associated with outcomes of severe disability or VS (in VS the centromedian nucleus showed marked cell loss). These observations are consistent with earlier anatomical studies that identified the intralaminar and paramedian nuclei within the central regions of the thalamus as showing the greatest cell loss associated with nonselective, widespread cerebral ablations experiments.[17,18]

The selective vulnerability of neurons within the central thalamus can be understood as a simple consequence of their unique pattern of geometrical connectivity. The central thalamus has widespread point-to-point connections across cerebral cortical regions. Individual nuclei project to relatively widely separated cortical regions (studied extensively in rodents; see Ref. 19) and in some cases single central-thalamic neurons project diffusely to both the frontal cortex and striatum.[20] A quantitative study of the connectivity pattern of the entire cat thalamocortical system[21] found that the main cell populations of the central thalamus (anterior and posterior intralaminar nuclei groups) were unique in projecting into the center of a multidimensional cluster analysis, providing the shortest path distance among several different groupings of cortical and thalamic regions identified by the analysis. In this analysis the anterior intralaminar group (CeL, CeM, Pc nuclei that undergo the first sign

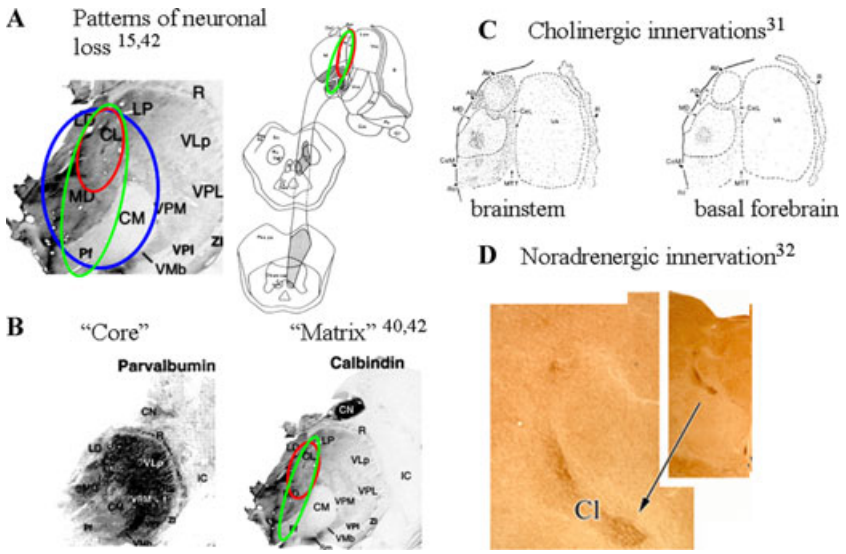

Figure 1. Overlap of CT neuronal population loss in global disorders of consciousness, calbindin expression, and innervation by "arousal systems." (**A**) Overlapping regions of neuronal loss in the central thalamus are seen after diffuse brain injuries (left image adapted from Jennett *et al.*[15] and Munkle *et al.*[42]) and focal brain injuries producing disorders of consciousness (right image adapted from Castaigne[11]). *Red circle* shows areas of neuronal loss seen in patients with severe brain injuries recovering to a level of moderate disability, *green* and *blue circles* indicate enlarging regions of cell loss observed with progressively worsening outcomes of severe disability and minimally conscious state (*green circle*) or permanent VS (*blue circle*).[15] The right figure (adapted from Castaigne *et al.*[11]) indicates common ischemic-stroke pattern associated with acute coma and severe disability if including bilateral involvement of midbrain and thalamus. (**B**) Two sections of the human thalamus from Munkle *et al.*[42] stained for the calcium-binding proteins calbindin or parvalbumin. *Right figure* shows overlap of *red* and *green circles* from part (A) with regions of the central thalamus expressing calbindin proteins. (see text and Ref. 40). (**C**) Overlap of brainstem and basal forebrain cholinergic innervations within the human central thalamus [central lateral (CeL); central medial (CeM), and surrounding association regions]. (Adapted from Heckers *et al.*[31]) (**D**) Noradrenergic innervation in the primate CeL nucleus. (Adapted from Vogt *et al.*[32]; in color in *Annals* online.)

of cell loss after diffuse injury associated with moderate disability) projected closer to the center of the other clusters. The posterior intralaminar group showed closer association to motor and limbic systems, but also showed projection into the center of a surface composed of other pairings of thalamocortical connections.

Thus, the neurons in the central thalamus are positioned by their connectivity patterns to integrate effects of injuries across the cerebrum and cell loss across a wide range of cerebral territories. While permanent VS is associated with overwhelming thalamic cell loss in both hemispheres,[13] in a small study that compared patients with severe disability to those remaining in VS at death, half of the severely disabled patients did not show significant cell loss in the thalamus.[15] This group included some of the most severely disabled patients, who recovered only to the first level of behavioral responses above VS, that is, the minimally conscious state (MCS).[22] These observations suggest that in a subset of MCS patients, deafferentation injuries may be insufficient to cause neuronal death, although they are likely associated with significant reduction in excitatory input. The reduction of input to the central thalamus may play a key role in the functional limitations in such patients, as discussed later in this chapter.[23,24]

The Central Thalamus and Forebrain Arousal Regulation

The importance of the unique vulnerability of the central thalamus to deafferentation in the setting of severe brain injury lies in its key role in forebrain arousal regulation. A detailed consideration of the contributions of the central thalamus to arousal-regulation mechanisms is beyond the scope of this review (see Ref. 25); here we focus on two related aspects of the role of central thalamus that suggest its use as a target for DBS in the severely injured brain: (1) the central thalamus appears to have an intermediate role in forebrain arousal, receiving monosynaptic connections ascending from the brain stem and basal forebrain "arousal systems" and descending connections from the mesial frontal cortex,[26] and (2) CT neurons appear to grade their activity across varying levels of vigilance and in response to cognitive load and stressors, suggesting a role in regulation of the overall level of cerebral activation.[28–30] Collectively, these anatomical and functional specializations suggest that neuronal activity within the central thalamus may contribute to a general phenomenon of behavioral fluctuations seen after severe brain injuries. That is, a partially deafferented and underactive central thalamus may be more likely to fail to maintain adequate forebrain arousal levels or respond with short-term patterns of activation required to carry out even relatively limited cognitive functions.

The central thalamus is broadly innervated by both the brain stem and basal forebrain arousal systems[26,31–34] (Figs. 1C 1D, and 2). Ascending inputs to the anterior intralaminar nuclei (CeL, CeM, paracentralis [Pc]) and adjacent paralaminar regions of thalamic-association nuclei (median dorsalis, ventralis anterior/lateral) make them particularly well positioned to play a role in arousal regulation. These regions receive the heaviest thalamic innervation from brainstem cholinergic neuronal populations as well as contributions from cholinergic populations originating in the basal forebrain[31,33,35] (Fig. 1C, and blue circle in Fig. 2). These areas of the central thalamus also receive at least two other important sources of ascending inputs, one arising from the glutamatergic components of the arousal system (green circle, Fig. 2) in the parabrachical nucleus, and another important monosynaptic excitatory pathway from the mesencephalic reticular formation.[36,37] In addition to these inputs, a heavy innervation from both the noradrenergic afferents from the locus ceruleus (red circles, Fig. 2) and serotoninergic afferents (yellow circle, Fig. 2) from the medial raphe[26,32,38,39] projects to both the anterior and posterior intralaminar nuclei. The neuronal populations within these regions of the central thalamus that are heavily innervated by the arousal systems express a calcium-binding protein, calbindin D_{28K} (white oval, Fig. 2)[40] This expression pattern identifies them as part of a class of thalamic neurons ("matrix" cells) that project to supragranular cortical layers across relatively wide cortical territories. Matrix cells synapse in layer I on the apical dendrites of pyramidal cells whose cell bodies are located in

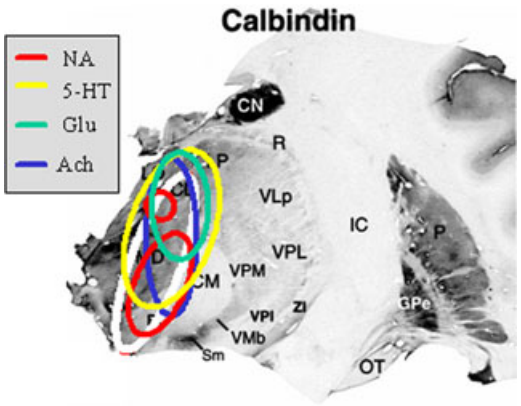

Figure 2. Overlapping innervations of central thalamus from "arousal systems." The overlap of arousal system innervations is diagrammed within the central thalamus in relation to areas of calbindin (a calcium-binding protein) expression neurons (*white oval*). A convergence of cholinergic (*blue oval*), noradrenergic (*red ovals*), serotoninergic (*yellow oval*), and glutamatergic (*green oval*) innervations is seen within the areas targeted for central thalamic deep-brain electrical stimulation (CT/DBS). (Figure background element adapted from Munkle *et al.*[42]; in color in *Annals* online).

layers II–III and layer V.[40] In both humans[41,42] and nonhuman primates,[43] intralaminar subdivisions of the thalamus (anterior intralaminar nuclei and Pf nucleus) show a predominance of matrix neurons. In contrast, the centromedian nucleus exclusively shows a different calcium-binding protein (parvalbumin) staining profile. The matrix neurons are proposed to act collectively as a functional system that organizes global patterns of corticothalamic synchronization.[40]

Consistent with the broad cortical projections from the central thalamus and their strong modulation by the arousal systems, human imaging studies demonstrate selective activation of the central thalamus for tasks that either require a short-term shift of attention,[28] sustained cognitive demands of high vigilance,[29] or memory holds over extended time periods.[44] Specific activation of both the anterior (CeL, Pc) and posterior intralaminar nuclei (CeM–Pf complex) occurs in conjunction with mesencephalic reticular neurons during the short-term shifting of attention component of a forewarned reaction-time task.[28] Studies of sustained vigilance show covariation of activity within the region of the anterior intralaminar nuclei and the anterior cingulate cortex (ACC), as well as the pontomesecephalon.[29] Like the central thalamus, the ACC is recruited by a wide variety of cognitive demands[45] and grades its activity with increasing cognitive load.[46] The ACC may drive the central thalamus when increased cortical activation is required in response to demands on effort.

Marked fluctuations of behavioral response are the sine qua non of recovery from direct injuries to the central thalamus with both unilateral[47,48] or bilateral lesions.[49,50] Moreover, these behavioral fluctuations bear a very close resemblance to the fluctuations seen in patients and animals with frontal-lobe lesions.[51] This resemblance reflects the close anatomical and functional relationships of the central thalamus and frontal lobe both through direct corticothalamic connections (including supplementary motor, anterior cingulate, premotor, and prefrontal cortex)[19,27] and indirectly through the frontostriatal loop systems (cortico–striatopallidal–thalamocortical).[19,52,53] The strong link between behavioral fluctuations following CT and frontal-lobe injuries is supported by rodent behavioral studies that show quantitative and qualitative similarity of the deficits produced by anterior intralaminar system lesions and wide excision of frontal-cortical regions.[54,55]

Central Thalamic Deep-Brain Stimulation for Impaired Consciousness following Severe Brain Injury

Earlier investigations (see Ref. 56 for review) considered the hypothesis that electrical stimulation of the thalamus might restore conscious wakefulness to severely brain-injured patients. Initial studies focused on comatose patients and the related group of patients who showed alternating periods of eye opening and eye closure but no evidence of consciousness, now recognized as the key diagnostic features of VS as later defined by Fred Plum and Bryan Jennett in 1972.[57] Experimental studies by Moruzzi and Magoun in 1949[58] had demonstrated that low-frequency, large-amplitude voltage tracings seen in the EEG of cats under anesthesia could be changed to a "desychronized" pattern of low-amplitude fast activity similar to that seen in wakefulness by stimulating either the midbrain reticular formation or central thalamus. Based on these experimental observations, several case reports of human clinical studies subsequently described efforts to apply thalamic stimulation (and other targets to comatose and vegetative patients without clinical success).[56]

Following these earlier case studies, Medtronic, Inc. (Minneapolis, Minnesota, USA) undertook a multicenter trial involving ~50 patients, including the well-known patient Terri Schiavo who had remained in a postanoxic VS for 6 months at the time of the

study.[59–63] Patients had electrodes placed in the centromedian nucleus (the component of the posterior intralaminar nuclei that does not contain calbindin staining neurons). Although EEG frequency shifts and metabolic changes were observed (in some patients cerebral metabolic rates increased to 300% of resting values),[62] these physiological effects did not correlate with sustained clinical recovery that could be linked to DBS.[63,64] A small group of patients with traumatic brain injuries who were noted to improve had received their DBS implants early in their clinical course (within 3–6 months), and had already shown transition to the MCS.[63] Importantly, spontaneous recovery of patients remaining in MCS at 3–6 months is associated with functional outcomes better than severe disability in a significant proportion of patients.[4]

The negative results of thalamic DBS studies in VS patients can be considered in light of both the anticipated underlying cerebral substrate remaining in the patients studied and the rationale underlying these earlier studies. As reviewed earlier in this chapter, patients remaining in the VS for three months after an anoxic brain injury or more than a year after traumatic brain injury typically show overwhelming neuronal death in the thalamus, and stimulation of this structure is unlikely to be effective, even if there is a relative preservation of other cerebral structures. Moreover, the scientific rationale in these studies, inspired by the earlier Moruzzi and Magoun EEG studies,[58] aimed to restore the wakeful state per se. It is important to recognize that the underlying cause of low-frequency, large-amplitude EEG in chronic VS patients has a distinct biophysical meaning compared to the similar changes seen in the EEG of intact human or animal brains under anesthesia. While both situations reflect passive inhibitory effects of the withdrawal of excitatory synaptic activity[65,66] in VS patients, this is a consequence of (and a proxy for) widespread cerebral deafferentation. The lack of clinical improvement and findings of desychronization of background EEG with DBS in some of these VS patients, moreover, suggests that a gross recovery of the normal spectral features of the EEG is not a sufficient marker for potential functional recovery in the severely injured brain and other measurements will be more important.[67,68]

Patients within the category of MCS are the first group of severely brain-injured patients who may retain sufficient anatomical and functional cortical sparing to support evidence of cognition. The pathological observations reviewed earlier demonstrate that at least some of these patients do not show widespread neuronal death within either the thalamus or cortex and yet remain at a very low functional level.[15] In such patients, the central thalamus thus provides a potential substrate for greater integrative cerebral function. Although the central thalamus is presumably significantly deafferented in these patients compared to a normal healthy subject, if these neurons remain intact, their function may modulated by electrical stimulation. This premise is further supported by the large shifts in cerebral metabolic rates seen even in chronic VS patients during DBS independent of behavioral modulation.[62] In support of the idea that some MCS patients retain a capacity for greater integrative cerebral function, several studies have demonstrated preservation of large-scale functional cerebral networks in MCS patients.[24,69–72] In these MCS patients, who retain functionally connected, but chronically down-regulated, forebrain networks (due primarily to deafferentation and loss of neuronal volume and connectivity), a different set of scientific rationales for CT stimulation can be presented. This rationale focuses on supporting cognitive function in conscious but cognitively impaired patients and is outlined in the following sections.

Proposed Circuit Mechanisms for Use of Central Thalamic Stimulation in the Severely Injured Brain

In conscious patients with severe brain injuries, the underlying hypothesis for use of

TABLE 1. Brief Outline of the Rationale for Stimulation of the Anterior Intralaminar Thalamic Nuclei in Severe Brain Injury

1. The pathophysiologic mechanisms of severe brain injury selectively impair function within the central thalamus.
   a. Functional impairment of the central thalamus is the direct result of anatomical disconnection and neuronal dysfunction following traumatic brain injury that produces a global down-regulation of cerebral metabolism (a proxy for decreased neuronal firing rates) in the human forebrain.
   b. The specific embedding of CT neurons within the cortico–striatopallidal–thalamocortical system makes them them vulnerable to the background level of synaptic activity across the corticothalamic system.
2. Activation of the central thalamus with deep-brain electrical stimulus (DBS) following severe brain injury may facilitate behavioral and cognitive processing by approximating the effects of a normal outflow of impulses from neurons within the central thalamus that appear to regulate broad network activation of connected cortical, basal ganglia, and thalamic networks.
3. The anatomical specializations of the intralaminar nuclei are critically involved in the integration of long-range cortico–cortical and cortico–striatopallidal–thalamocortical networks.
4. Maintaining activation from the central thalamus may produce lasting changes in the behavioral response profile of patients and animals.

CT/DBS to facilitate behavioral responsiveness is framed by a specific set of physiological rationales (summarized in Table 1). As diagrammed in Figure 3, CT/DBS may act through four interrelated mechanisms that are based on current models of the functional role of neurons in the central thalamus. The primary expected effect of CT/DBS is depolarization of target neurons in the cortex (particularly regions of frontal and prefrontal cortex) and striatum through activation of the excitatory glutamatergic connections from the central thalamus (Fig. 3). CT/DBS can be expected to be more effective in driving activity in cortical and striatal neurons than the systemic application of traditional neuromodulators such as dopaminergic and cholinergic agents. On the one hand, the marked clinical impact of bilateral[47,48] or unilateral[49,50] lesions in the stimulated regions of the central thalamus demonstrates that, collectively, these projections have considerable synaptic weight in the human brain. Functionally disabling them in the aggregate leads to acute coma and enduring cognitive impairments, as reviewed earlier in this chapter and elsewhere.[7] CT neurons typically are driven to firing threshold by a convergence of inputs from the different neuromodulatory systems and direct cortical and mesencephalic excitatory neurotransmission and are therefore sensitive to overall levels of cerebral background synaptic activity. Although under normal physiological conditions such large groups of neurons would presumably not be synchronously active, a volume of both cell bodies and fibers of passage comparable to the size of a typical ischemic lesion in these regions will be activated within the volume of activation produced by DBS electrodes.[104] The addition of a single drug or even multiple neuromodulators would be unlikely to drive the output of a similarly large volume of CT neurons at rates even approximating the high-frequency ($\sim$>100 Hz) firing rates expected with CT/DBS. In addition, glutamate is the main excitatory neurotransmitter, and CT/DBS may be expected to lead to strong excitatory potentials in many of the postsynaptic cortical and striatal neurons.

Thus, it is proposed that providing a severely deafferented brain with a broad, albeit partial and abnormally patterned, restoration of excitatory drive to cortical and striatal neurons may have significant network impact. Increasing the level of membrane depolarization can be expected to promote marked changes in the firing pattern of some cortical and striatal neurons.[73,74] In the intact brain, maintaining

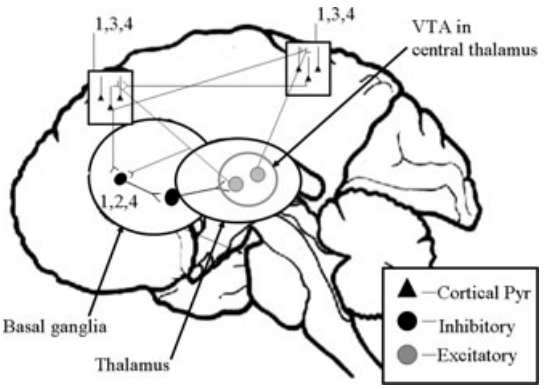

Figure 3. Possible mechanisms of action of central thalamus DBS in the injured brain. (1) Depolarization of deafferented neuronal populations that are passively inhibited or exhibit reduced firing rates and low metabolic rates due to decreased synaptic background activity resulting from widespread neuronal loss or dysfunction across the cerebrum following a severe brain injury. (2) Synchronization and coordination of long-range cortico–cortical connections resulting from specific laminar innervation pattern of intralaminar/paralaminar calbindin (a calcium-binding protein) staining thalamic relay cells.[10,40,83,85,89] (3) Dual action promoting sufficiently high synaptic background firing rates of medium spiny neurons (MSNs) within the striatum impacting the intrinsic striatopallidal microcircuit.[80] CT inputs to frontal and prefrontal-cortical neurons activate cortical columns leading to increased corticostriatal outflow. In parallel, direct thalamostriatal activation from central thalamus provides similar activation. Neurons within the central lateral (CeL) nucleus of the central thalamus have axons with diffuse branching in the striatum that also travel to frontal-cortical regions.[20] These neurons appear to make contact on dendritic spines of the MSNs.[81] (4) Possible promotion of frequency-dependent plasticity within synaptic contacts in apical dendrites of cortical neurons and striatal neurons.[90,93,94] VTA, volume of tissue activation.

a cortical neuron near its firing threshold is an active process; without the typical incoming barrage of synaptic activity, cortical neurons remain 10–30 mV below their threshold for firing an action potential.[75] Moreover, the synaptic background activity primarily determines membrane voltage and firing modes of cortical neurons that may significantly shift their patterns of firing and sharply increase firing rates as they are further depolarized.[73] In anesthetized intact cats,[76] electrical stimulation of the pontine cholinergic projections to the central thalamus increases the intrinsic excitability of cortical neurons by depolarizing their membrane potentials (presumably with a large contribution from thalamocortical afferents driven by the stimulation). This increased excitability is characterized as an "activated state" similar to the "UP state" seen in spontaneous slow-wave sleep epochs observed in cortical and striatal neurons that reflects a balanced pattern of recurrent excitatory and inhibitory local-network activity.[65,77–79]

Depolarization of striatal neurons by CT/DBS in a damaged, deafferented brain may play an even more important role as the medium spiny striatal neurons (MSNs) depend on high levels of corticostriatal and thalamostriatal inputs to maintain firing at all due to a high threshold UP state.[80] Anterior intralaminar projections from the CeL nucleus make contact with dendritic spines of the MSNs, suggesting that they act as drivers of the MSNs'[81] inhibition of the globus pallidus interna; in the absence of MSN output tonic pallidal inhibition of the thalamus will remain unopposed. This active inhibition of the thalamus likely combines in the severely injured brain with the strong passive inhibition (disfacilitation) of thalamic neurons due to the relative depletion of excitatory synaptic contacts following cerebral injury.[66] This mechanism has been suggested to play a role in partially reversible anterior forebrain hypometabolism seen after many types of severe brain injuries.[25,82]

Another potentially important mechanism of action for CT/DBS is facilitation of long-range cortico–cortical interactions that is proposed as one of the functional roles for CT neurons.[83] Afferents from the central thalamus project in a laminar-specific pattern within the cerebral cortex that appears to facilitate coactivation of supragranular and infragranular cortical regions driving overall increases in cortical column activity and facilitating mechanisms of long-term

potentiation.[84–87] Coactivation of the supragranular and infragranular layers has been proposed as a coincidence-detection mechanism,[85,88,89] and has received experimental support from intracellular recording studies.[90] The wide point-to-point connections of the nuclei within the central thalamus[19] would allow coactivation across large cerebral territories in a damaged brain with CT/DBS and may enable increased integration of synaptic activity linking cortical regions.[10] This mechanism is consistent with the hypothesis of increasing the probability and time duration of the cortical activity similar to the UP state with CT/DBS, and is consistent with experimental findings of brainstem stimulation in intact brains.[76,79] Recent studies demonstrate that prolonged sensory stimulation similarly increases UP-state activity,[75] providing a model for the activity seen in extracellular recordings from cortical neurons during memory delays or periods of sustained attention (that are often associated with increased spectral power in the 20–80-Hz range (see Ref. 78 for review). Such prolonged stimulation is associated with broad changes in cortical neuronal responsiveness to sensory stimuli, including widening the dynamic range of elicited responses, increasing output gain, and more tightly linking neuronal activity to measured behaviors.[75] In the aggregate, through broad depolarization of cortico–cortical and striatal targets of the projecting thalamic neurons, CT/DBS might be expected to similarly influence both patterns of large-scale circuit function and the detailed response properties of individual neurons across many neuronal populations.

Finally, although this potential mechanism of action is the most speculative, there is some evidence that repeated exposure to CT/DBS may have a slow accumulating effect in addition to immediate effects of turning stimulation ON or OFF.[91,92] In rodents, three days of exposure to CT/DBS at frequencies of 100 Hz for 30 minutes/day showed accumulating effects of behavioral facilitation on a simple object-recognition memory task.[91] Whether such behavioral effects depend on high-frequency stimulation is unknown. However, the presumed targets of CT/DBS, the dendritic arbors of neurons within Layers I–III and Layer V that may be activated in Layer I via CT synapses there,[83,85,91] have high-frequency thresholds (100 Hz and 130 Hz, respectively; see Refs. 90 and 93) for different forms of dendritic electrogenesis (backpropagating action potentials and dendritic action potentials) that could play a role in triggering mechanisms of synaptic plasticity or neuronal growth. Recent studies have shown that release of brain-derived neurotrophic factor occurs with spontaneous backpropagating action potentials providing one specific mechanism for such activity-dependent synaptic plasticity.[94]

Clinical Results of a Single-Subject Study

A recent single-subject study provides the first evidence that some very severely brain-injured humans may benefit from CT/DBS.[92] A 38-year-old man who had remained in MCS for 6 years following a severe traumatic brain injury was enrolled in a study of DBS in the anterior intralaminar nuclei. The patient had sustained a severe closed-head injury following blunt trauma to the right frontal lobe that produced bilateral hemorrhages surrounding the brain and deep coma (see Ref. 92). The patient had remained in VS until approximately 3 months after injury, when the first evidence of clear behaviors in response to sensory stimulation were identified, placing the patient in the MCS.[22] Over a time period of more than 2 years following injury the patient did not advance past MCS with a best behavioral response of inconsistent command following using eye movements. The patient was enrolled into the DBS study 4 years later after remaining in a skilled nursing facility where no change in behavioral baseline occurred Once in the DBS study a 4-month quantitative behavioral assessment was completed, with ongoing therapy

beginning at the time of enrollment (Fig. 5A). At 4 months the DBS electrodes were placed, followed by a 2-month period, with the electrodes remaining OFF to reassess the patient's postsurgical behavioral baseline (which did not change). Two subsequent phases of evaluation of DBS effects were carried out: (1) a 5-month titration phase of testing tolerance to DBS and assessment of varying stimulation parameters, and duration of stimulation, and subsequently; and (2) a 6-month double-blind alternating crossover study.

Bilateral DBS electrodes were implanted in the anterior intralaminar thalamic nuclei (CeL nucleus and adjacent paralaminar regions of the thalamus). Figure 5B shows the placement of the electrodes in situ (adapted from Ref. 92). Figure 5C organizes the results of a 6-month double-blind alternating crossover study and comparison of prestimulation baselines of performance, reflecting the overall impact of DBS compared to approximately 6 months of rehabilitation efforts without concurrent DBS. The patient was evaluated according to three subscales of a primary outcome measure, the Coma Recovery Scale Revised (CRS-R), a validated psychometric tool used in patients with disorders of consciousness and three tailored secondary measures developed during the titration trial. The overall findings indicate significantly improved behavioral responsiveness in this patient, as seen in the comparison of prestimulation frequencies of highest-level behavioral response in the six categories shown. All six measures showed a marked change from prestimulation baselines, with five of the six measurements showing higher-level behaviors than seen prior to stimulation, whether the electrodes were ON or OFF. Three measures showed a statistically significant dependence on electrical brain stimulation during the six-month crossover trial, as indicated by increasing the frequency of specific cognitively mediated behaviors of attentive responsiveness measured across examination items (a top score for the CRS arousal scale is achieved for no more than three nonresponses to an examiner across an assessment period) and functional limb control (demonstration of purposeful movements such as combing and drinking, see description in supplementary material for Ref. 92) and recovery of oral feeding (chewing, swallowing, and completing meals compared to tube feeding) during periods in which DBS was ON as compared with periods in which it was OFF. The marked improvements during periods during the crossover trial when the DBS electrodes were OFF compared to the prestimulation baselines indicates a carryover effect of changes that occurred after exposure to DBS during the titration period. The evidence in this single-case study for both reproducible and sustained acute effects of DBS, as well as more enduring and slowly accumulating effects, suggest that biological mechanisms on multiple timescales play a role in the alteration of behavioral responses seen. Detailed logistic regression modeling of these behavioral data that include the time course of stimulation history and behavioral observations demonstrates statistical linkage between the observed functional improvements and recent stimulation history for both the crossover data and effects seen during the titration phase.[92]

Moreover, a detailed state-space analysis of the same data indicates intermediate time courses for declines in responsiveness during some DBS OFF transitions,[95] suggesting further consideration of parameter adjustment such as the duty cycle (which remained at half-day for this study).

Although the present findings are limited to a single human subject, they provide many hints and leads to follow that appear consistent with the proposed meso-and microcircuit mechanisms suggested earlier in this chapter. The carryover of clinical improvements from the 5-month titration period into the OFF DBS phases of the crossover trial is supportive of a two timescale model of CT/DBS effects with implications for the potential role of synaptic plasticity and normal learning and memory processes,[91] or other mechanisms that could account for slow processes, including structural

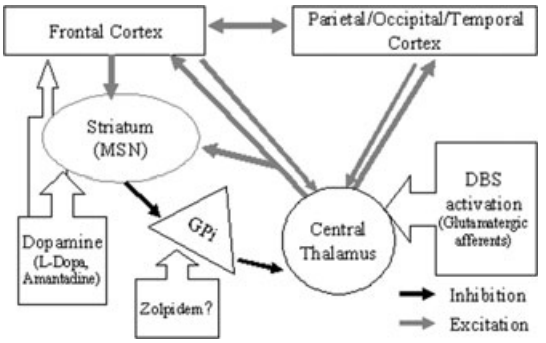

Figure 4. Schematic circuit mechanism linking central thalamic deep-brain electrical stimulation (CT/DBS) and pharmacologic activation in severe brain injuries. Medium spiny neurons (MSN), of the striatum; globus pallida interna (GPi). (See text for further interpretation.)

alterations.[96] Cortical-evoked potentials from the electrode contacts used to generate the volume of tissue activation in this study demonstrate a frontotemporal and central predominance of activation[92] consistent with the large mesocircuit model shown in Figures 3 and 4. The evident driving of these cortical populations with CT/DBS is also broadly consistent with the notion of overall depolarization playing a key role in the effects. One important implication of this model is that observed behavioral effects might be further potentiated with traditional neuromodulators, even if prior applications of such agents did not result in significant clinical effects. Since the overall level of background synaptic activity may strongly influence both meso- and microcircuit-level responses, CT/DBS may allow for a qualitatively different effect of traditional pharmacologic neuromodulation in the same patient. Anecdotal observations in this patient after the blinded trial noted further improvements in verbal fluency coincident with introduction of the mixed action agent amantadine. This drug's increased effect may have been a result of interaction with a more active brain through its dopaminergic action on frontal-/prefrontal-cortical systems and the striatum.[97]

Limitations and Ethical Considerations

Several limitations can be foreseen even if CT/DBS can be developed as a method for partial restoration of function in the severely injured brain. The technique is limited by several inherently nonphysiological aspects of the spatiotemporal pattern of its effects. The large volume of activation produced by clinically effective electric fields using DBS[104] necessarily activates large groups of fiber pathways that normally would not be synchronously active with a constant monotonic firing rate for hours a day. The broad spatial spread of activation is likely to create a mix of effects and trade-offs, as seen in other applications. For example, Leentjens and colleagues.[98] reported a remarkable patient treated with DBS for parkinsonism where parameter settings could not separate an ambulatory mobile state from the adverse effect of mania. This patient could remain akinetic or ambulatory, but manic. Related to this general problem of anticipated trade-off of effects are the additional complications of accounting for the role of carryover effects in study designs and the vast parameter space that must be searched for potential effects. In addition, the large variance in location, distribution, type, and duration of brain injury among individual patients presents significant challenges for clinical trials.

These limitations of the nonphysiologic spatial spread of activation may be mitigated to some extent under the assumptions of the mechanism of action for CT/DBS, as proposed earlier in this chapter. Continuous stimulation in a damaged brain with many cerebral networks that are poorly active or quiescent may be the best way to widely facilitate depolarization across many cortical regions with point-to-point connections and throughout the striatum. By holding a roughly constant level of additional depolarization, it may be possible to avoid impeding internal circuit mechanisms in the target regions (adding excitatory postsynaptic potentials, but not undermining local

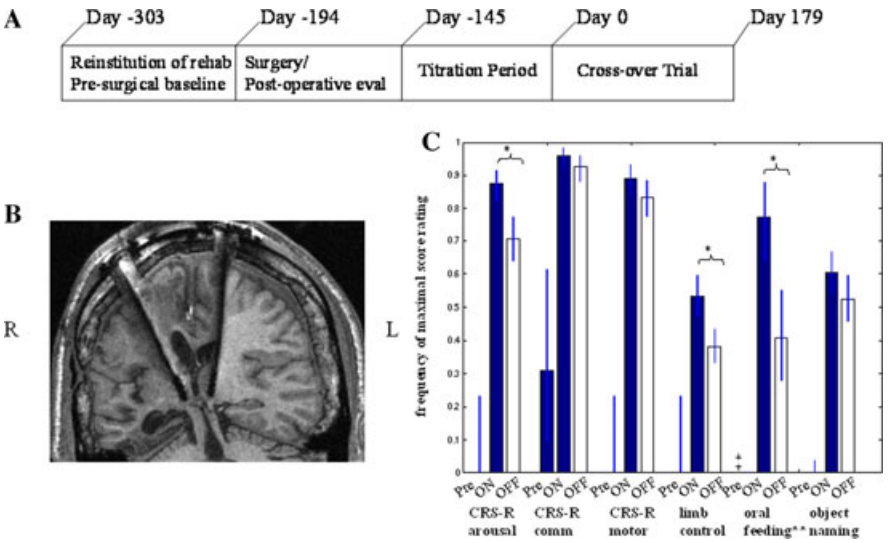

Figure 5. Central thalamic deep-brain electrical stimulation (CT/DBS) in the minimally conscious state. (**A**) Study time line. (**B**) Electrode-lead placements within central thalamus of patient's right (R) and left (L) hemispheres displayed in T1-weighted MRI coronal image. (**C**) Comparison of presurgical baselines and DBS ON and DBS OFF periods during a six crossover trial of CT/DBS in a patient with severe traumatic brain injury (see text). (Figure elements adapted with permission from Schiff *et al.*[92]).

circuit processes). From this point of view, it is also important to note that all nodes within the circuit diagrams of Figures 3 and 4 are not topologically or functionally equivalent. The central thalamus is the only node that allows placing a volume of activation for simultaneous direct monosynaptic activation of wide cortico–cortical and striatal territories. Although different points within this circuit likely could be electrically activated with DBS, or white-matter bundles connecting them, these alternatives appear to have additional significant limitations. For example, stimulation of isolated white-matter tracts undercutting individual cortical regions to facilitate cortico–cortical interactions may not drive cortical columns effectively as these cortico–cortical fibers are weaker initiators of cortical UP states than thalamocortical afferents.[99] The fanning out of the thalamocortical fibers near their cortical targets would present significant difficulties in achieving a similarly broad activation of distant cortical fields and the striatum through stimulation at this distal point. In addition, targeting small fiber bundles in the diffusely injured brain may be both difficult and possibly more likely to generate trade-offs of unwanted pathway activation. In structurally intact human and cat brains, stimulation of white-matter tracts projecting into the central thalamus has been used to activate cortical projection areas.[100,101] However, in the structurally damaged, deafferented, and depopulated brain, it may not be possible to rely on transmission of effects across more than the synapses directly activated by the artificial triggering of action potentials in axons exposed to the time-varying electric field generated of the DBS electrode.

The most immediate and important limitation, however, is that the generalizability of the results reviewed earlier is completely unknown, and developing an understanding by which patients might respond to this approach (if others do) will require significant further investigation. The marked variation of cerebral substrates after a severe brain injury will undoubtedly determine whether a clinically meaningful effect could be predicted. Moreover, as this research moves forward, parallel concerns about the

type of effects produced, if any, and stratifying the potential risks to subjects will require consideration of ethical proportionality and the goals of care.[102,103] At present the potential effect sizes are unknown, and better understanding of what determines any effect and its potential size will be required to calibrate the proportionality of chronic device implantation against any anticipated potential clinical benefits.

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Conflicts of Interest

The paper describes work that was, in part, funded by a company, IntElect Medical, Inc., in which Cornell University has part ownership; through the licensing of technology, the author is a listed Cornell inventor and may benefit in the future from commercialization of intellectual property owned by Cornell. The author acts as a consultant to IntElect Medical, Inc.

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