

# Central thalamic deep brain stimulation for support of forebrain arousal regulation in the minimally conscious state

NICHOLAS D. SCHIFF\*

*Department of Neurology and Neuroscience, Weill Cornell Medical College, New York, NY, USA*

## **HISTORICAL EFFORTS TO APPLY THALAMIC BRAIN STIMULATION IN THE SEVERELY INJURED BRAIN PLACED IN A MODERN CONTEXT**

Inspired by the pioneering demonstrations of [Moruzzi and Magoun in 1949](#), which showed that direct electrical stimulation of the midbrain reticular formation or intralaminar thalamus could produce desynchronization of the electroencephalogram in anesthetized cats with intact forebrains, effort began to apply electrical stimulation methods in severe brain injury. Several clinical studies beginning late 1960s and continuing through the late 1980s explored electrical stimulation of the tegmental midbrain, posterior intralaminar nuclei–centromedian parafascicularis complex, and globus pallidus internus for restoration of arousal and consciousness in chronically unconscious patients ([McLardy et al., 1968](#); [Hassler et al., 1969](#); [Cohadon et al., 1985](#); [Tsubokawa et al., 1990](#); [Deliac et al., 1993](#); [Hosobuchi and Yingling, 1993](#)). In these studies, enrollment focused on patients fulfilling the criteria for vegetative state (VS), mostly following severe traumatic or anoxic brain injuries; some of the very early studies ([McLardy et al., 1968](#)) also included patients in prolonged coma with near current criteria for brain death ([Posner et al., 2007](#)). Electrical stimulation of each of these subcortical structures produced evident behavioral arousal with widening of the palpebral fissure and eye opening, increases in heart rate, blood pressure, and, in some reports, fragmentary movements. With one exception, none of these studies reported interactive behavior with immediate onset of stimulation, or collected formal behavioral assessments so that any link of deep brain stimulation (DBS) to sustained clinical improvements

could be established if present. One very interesting and intriguing report in these series ([Sturm et al., 1979](#)), however, described a patient identified by the authors as not fulfilling criteria for VS, who demonstrated immediate changes in interactive behavior, showing command-following with stimulation without a sustained effect.

In the late 1980s, a multicenter study involving investigators from France, Japan, and the USA was undertaken in which the DBS target was the posterior intralaminar thalamus and cervical spinal cord in a group of about 50 patients in VS ([Tsubokawa et al., 1990](#); [Deliac et al., 1993](#); [Hosobuchi and Yingling, 1993](#)). The majority of patients reported in these studies showed no changes in clinical status; a small number of patients who had suffered severe traumatic brain injury were reported by one arm of the study to have shown improvement ([Tsubokawa et al., 1990](#); [Yamamoto and Katayama, 2005](#); [Yamamoto et al., 2010](#)). Collectively, these open-label studies did not employ quantitative behavioral metrics or a statistical structure that allowed assessment of effects of brain stimulation against the strong and well known spontaneous recovery rate after severe traumatic brain injury. Statistics for spontaneous recovery rates starting within the timeframe of 3–6 months using these studies of electrical stimulation in patients with VS are available from the Multi-Society Task Force on Persistent Vegetative State ([MSTF, 1994](#)) study of over 700 patients. Patients remaining in VS at 3 months after traumatic brain injury in the MSTF data demonstrated a 35% rate of recovery of consciousness at 1 year, with 16% of these patients recovering independent function by the 1-year time point. Even at the outer endpoint of enrollment at 6 months postinjury,

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\*Correspondence to: Nicholas D. Schiff, M.D., Jerold B. Katz Professor of Neurology and Neuroscience, Director, Laboratory of Cognitive Neuromodulation, Department of Neurology and Neuroscience, Weill Medical College of Cornell University, New York, NY 10065, USA. Tel: (212) 746 2372, Fax: (212) 746 8532, E-mail: [nds2001@med.cornell.edu](mailto:nds2001@med.cornell.edu)

MSTF data showed that 20% of patients remaining in VS after traumatic brain injury recover consciousness at least at the level of the minimally conscious state (MCS) at 1 year (Giacino et al., 2002), and approximately 25% of these patients even reach an independent level of function at 1 year. Thus, rates of spontaneous recovery within the first year after injury are considerable and must be accounted for in any interventional study carried out within this timeframe. To populate and control such a study sufficiently to account for this rate of baseline recovery is quite daunting. The first, and only, clinical trial to achieve this milestone is the recent demonstration of the impact of amantadine on outcomes of patients in VS and MCS after severe traumatic brain injury (Giacino et al., 2012b). To achieve a sufficient sample size of nearly 200 patients and 200 controls, this study required 11 participating centers and more than 7 years of careful data collection (Giacino et al., 2012b).

Recently, Yamamoto and coworkers (2010) presented data from a large group of about 100 patients in VS who did not receive DBS treatments but were evaluated for one arm of the earlier multicenter clinical trial in the 1980s (Tsubokawa et al., 1990). In a comparison of outcomes in these 100 patients with those in the smaller group of 25 patients implanted with brain stimulators, they found a significant impact of brain stimulation on outcome. Importantly, none of untreated patients recovered from VS. As noted above, this is a significant variance with the expected natural history of the condition. That none of the *post hoc* nonimplanted “control group” showed further recovery suggests that a significant sampling bias is present, and that this group is an inappropriate control for the patients in VS receiving DBS. A larger concern, however, is that the subgroup of patients reported by Yamamoto and colleagues (2010) to have made the most considerable gains from DBS were earlier reclassified by the investigators as actually in MCS at the time of electrode implantation (Yamamoto and Katayama, 2005). This reclassification creates a very significant confound, as statistics for spontaneous emergence from MCS are very different than for VS; the majority (more than 80%) of patients remaining in MCS at 3–6 months after injury emerge spontaneously by 10 months (Giacino and Kalmar, 1997; Lammi et al., 2005), with outcome including no disability at the 1-year time point. Moreover, several recent studies have shown a small, but nonetheless relevant, rate of spontaneous emergence from both VS and MCS after 1 year of remaining in these conditions (Estraneo et al., 2010; Luauté et al., 2010). A large study of patients aggregated across the Model Systems programs for rehabilitation of traumatic brain injury in the USA that

included about 400 patients initially in VS or MCS found that cognitive improvements continued over 2–5 years and included a significant proportion of patients who recovered independent function (21%) and vocational readiness (about 20%). As all patients in both VS and MCS reported by Yamamoto and associates (2010) were implanted well within the known timeframes for spontaneous recovery (all prior to 6 months), no inference regarding the efficacy of DBS can be drawn from these earlier studies that did not link DBS to measured behavioral changes. In fact, rather than demonstrating evidence for the efficacy of DBS, outcomes for patients both VS and MCS reported are, in aggregate, worse than would be expected by the now documented natural history of these conditions.

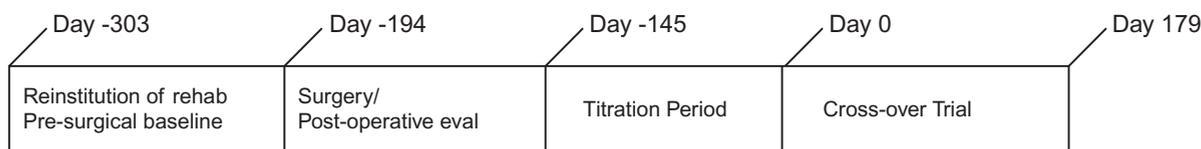
### **PROOF OF CONCEPT IN A SINGLE-SUBJECT STUDY OF CENTRAL THALAMIC DEEP BRAIN STIMULATION**

As reviewed above, several prior studies employed electrical brain stimulation in subcortical structures of severely brain-injured patients in VS or MCS (reviewed by Schiff and Fins, 2007; Shah and Schiff, 2010), but these studies did not ultimately provide evidence for statistical linkage of effects of DBS to any observed changes in behavior or insight into possible mechanisms to guide further development of such applications of DBS. From a historical perspective, a single-subject study of central thalamic deep brain stimulation (CT-DBS) provides the first evidence that some very severely brain-injured patients in MCS may benefit (Schiff et al., 2007). In a single-subject study, as part of a larger feasibility study done under a US Food and Drug Administration Investigational Device Exemption (Giacino et al., 2012a), a 38-year-old man who had remained in MCS for 6 years following a severe traumatic brain injury received bilateral CT-DBS electrodes targeting the central lateral nuclei of the intralaminar nuclear groups of the thalamus. The patient had initially sustained a severe closed head injury with bilateral subdural hemorrhages and a Glasgow Coma Scale score of 3. The patient remained in VS for about 3 months after the injury and then first demonstrated nonreflexive responsive behaviors in response to sensory stimulation consistent with MCS (Giacino et al., 2002). Further recovery did not occur over a 4-year period following discharge from active rehabilitation at 2.5 years after injury, and at the time of enrollment in the clinical trial at 6 years postinjury the patient showed an identical behavioral profile compared with the earlier baseline (only inconsistent command-following using eye

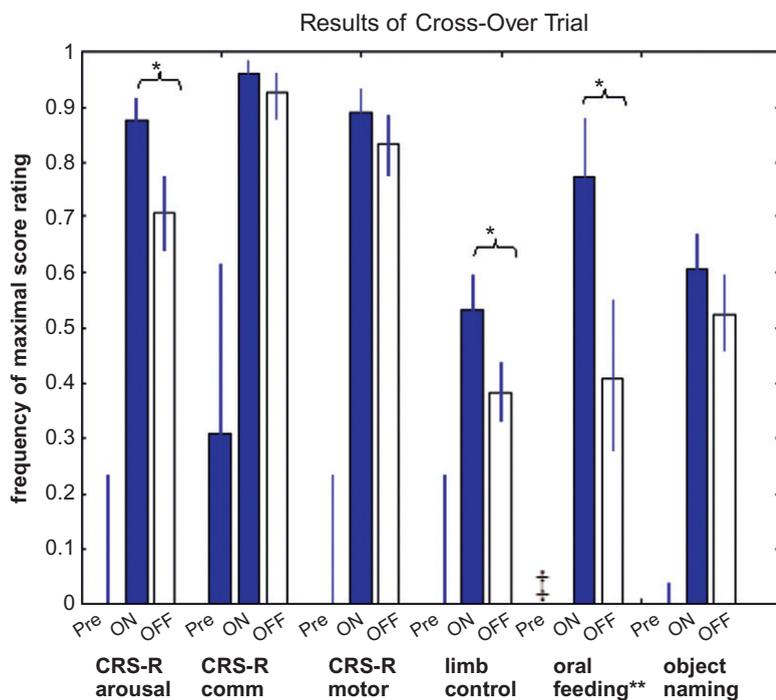
movements as the highest level behavior demonstrated at the bedside). A 4-month quantitative behavioral assessment and ongoing rehabilitation therapies began on study enrollment; no intervening change in behavioral rating occurred as a result of these newly instituted rehabilitation treatments, which continued for a total of 6 months prior to exposure to continuous CT-DBS (4 months before implantation surgery, 2 months after surgery with electrodes remaining OFF). A 5-month titration phase followed the 2-month OFF period during which various DBS parameters and durations of stimulation were applied to evaluate tolerance and effects. Following the titration period, a 6-month double-blind alternating crossover study began using 30-day ON and 30-day OFF periods. A set of preselected primary and secondary outcome measures developed during the 5-month titration period were collected during this 6-month crossover trial (Fig. 24.1A).

The patient was evaluated according to three subscales of the Coma Recovery Scale – Revised (CRS-R)

as the primary outcome measures which are known to reflect independent functional assessments (Giacino et al., 2004). Figure 24.1B displays the results of a 6-month double-blind alternating crossover study; all six measures demonstrated significant improvement when the prestimulation baseline values were compared with either ON and OFF periods of the crossover study. All measures, with the exception of the oral feeding scale, specifically capture cognitively mediated behaviors including test of object recognition and complex command-following, verbal fluency and semantic retrieval, controlled sensorimotor behaviors and verbal or gestural communication (Giacino et al., 2004). The notable difference in functional levels from the prestimulation period to OFF DBS measurements seen at the start of the crossover phase of the trial reflects the overall impact of 5 months of exposure to CT-DBS during the titration period. In each case, these changes can be compared directly to a flat baseline of no change at the end of the 6-month period of rehabilitation



A



B

**Fig. 24.1.** Single-subject study of central thalamic deep brain stimulation (DBS) in the minimally conscious state. (A) Study timeline. (B) Comparison of presurgical baseline values and DBS ON and DBS OFF periods during a 6-month crossover trial of central thalamic DBS in a patient with severe traumatic brain injury. See text for details. (Adapted from Schiff et al., 2007, with permission.)

efforts alone before the start of the titration period (Schiff et al., 2007). Additional secondary behavioral measures developed during the titration period also showed significant difference from prestimulation baseline values (Schiff et al., 2007, supplementary material). Three measures demonstrated a statistically significant dependence on CT-DBS during the crossover trial (marked in Figure 24.1B with an asterisk). One primary outcome measure, the CRS-R arousal subscale, showed statistically significant modulation by CT-DBS. The highest score for this measure is achieved if no more than 3 nonresponses to an examiner's questions are observed across an assessment period. The observed improvement in the CRS-R arousal score thus reflects an increase in cognitively mediated behaviors requiring elements of executive function. Consistent ceiling performance on this subscale only appeared with introduction of CT-DBS, and this functional capacity remained strongly modulated during the crossover trial. Strong ON versus OFF modulation also occurred for both the functional limb control secondary measure, which quantified purposeful movements (e.g., combing, drinking), and an oral feeding scale (Schiff et al., 2007, supplementary material).

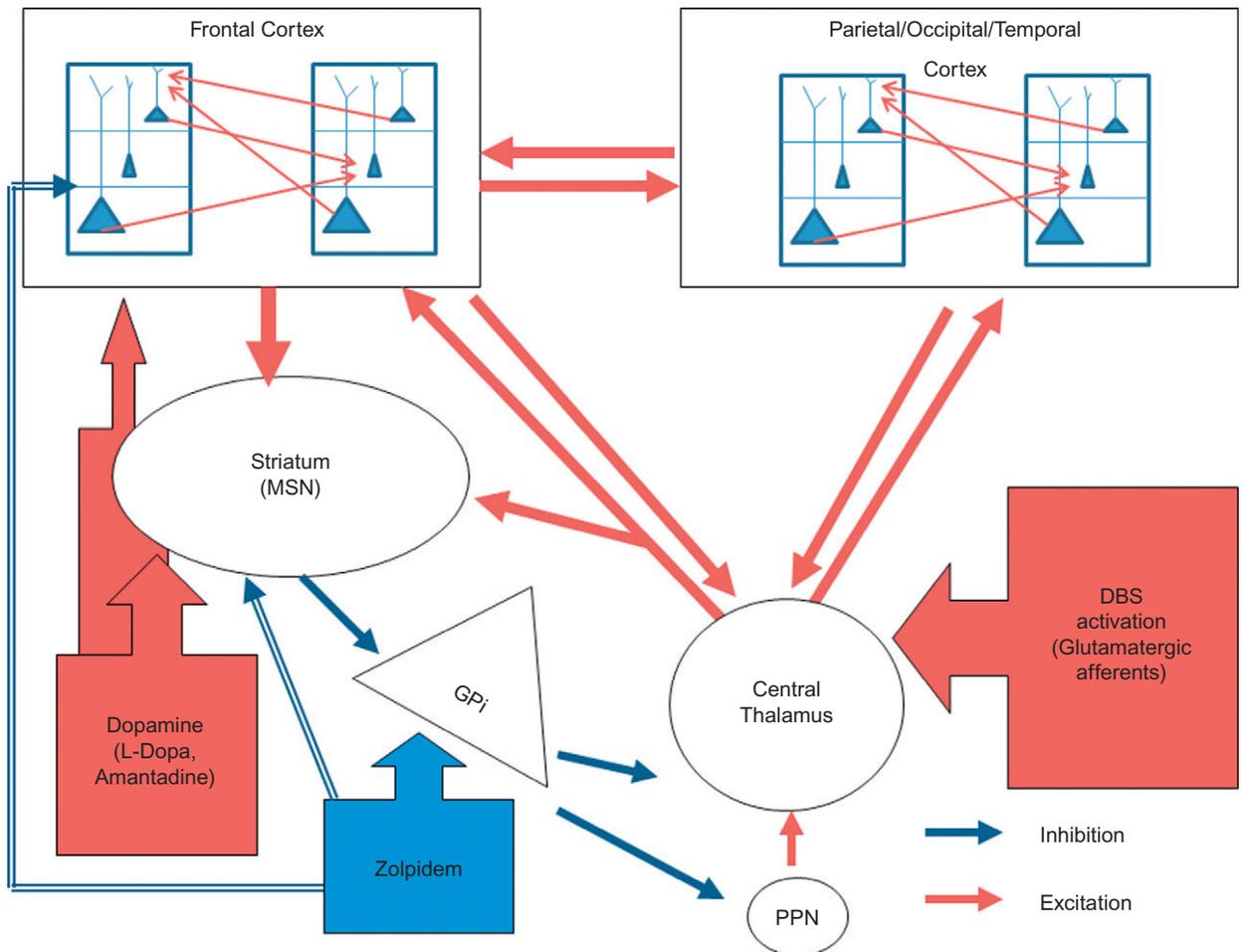
In a historical context, these findings in a single subject remain the only statistically rigorous evidence for an effect of CT-DBS on cognitive function late in the course of severe structural brain injury. Importantly, this study, which emanated from a larger study (Giacino et al., 2012a), focused on a different patient population from that of earlier trials. The patient studied by Schiff et al. (2007) is not comparable to patients in the earlier studies reviewed above in terms of behavioral profile or the chronicity of injury, and in the use of statistical controls to rule out spontaneous recovery or effects of rehabilitation. The patient discussed above began the CT-DBS study with behavioral ratings near the ceiling of the CRS-R, with an average score of 19–20 reflecting intermittent communication and consistent command-following (Schiff et al., 2007). This behavioral profile is near the boundary of emergence from MCS (Giacino et al., 2002) and is quite distinct from the reported behavioral profiles of patients in other studies.

Most importantly, the generalizability of these findings from a single subject is unknown, and developing selection criteria for finding similar response profiles prospectively remains future work. The guidance provided by the above review of the published literature indicates that applying CT-DBS to VS and MCS across patients with widely varying patterns of structural injuries will likely be unsuccessful. Below, the mechanisms underlying of recovery of consciousness are considered in light of a search for generalizable selection criteria for CT-DBS in patients in MCS.

## **NEURONAL MECHANISMS UNDERPINNING THE RATIONALE OF CT-DBS IN THE SEVERELY INJURED BRAIN**

The significant rate of continuing recovery after even very severe brain injury leading to months of function at the level of VS or MCS has an important implication for the development of CT-DBS a potential clinical tool. The implication is that biological mechanisms underlying recovery from severe injury may not initiate or be optimally driven in the absence of structured and supervised interventions over long time periods. As reviewed above, observations of late spontaneous recovery occurring over years following severe brain injury have now been established as general phenomena in patients in MCS (Estraneo et al., 2010; Luauté et al., 2010; Nakase-Richardson et al., 2012), placing outlier cases of late recovery from MCS (e.g., Voss et al., 2006) into a new context as endpoints along an expected continuum. Such continuing recovery of brain function appears to occur on average and across patient populations with widely varying patterns and etiologies of structural brain injury (Estraneo et al., 2010; Luauté et al., 2010; Nakase-Richardson et al., 2012). These findings thus focus attention on generalizable mechanisms underlying recovery of consciousness across varying etiologies (Williams et al., 2009; Schiff, 2010; Drover et al., 2011). The observations indicate that many neurons may survive but remain functionally downregulated for long periods of time following severe injury. As outlined below, the primary mechanism underlying this dynamic deficit is most likely a broad withdrawal of excitatory synapses across long-range corticocortical and thalamocortical connections. As a result of this basic aspect of severe injury, circuit-level mechanisms may additionally act to keep surviving neurons in low-frequency firing patterns, altering their capacity to function within distributed networks underlying large-scale cognitive processes in the brain.

Several clinical and experimental observations support the role of an anterior forebrain mesocircuit in the recovery of consciousness after brain injury (Schiff and Posner, 2007; Schiff, 2010) (Fig. 24.2). Alterations of cellular function in specific neuronal populations across this mesocircuit are proposed as a common mechanism arising across severe brain injuries as a direct consequence of global decreases of excitatory neurotransmission produced by multifocal neuronal and disconnection of white matter connections (Schiff and Posner, 2007; Brown et al., 2010; Schiff, 2010; Laureys and Schiff, 2012). The central thalamus is a key structure within this mesocircuit, based on its wide point-to-point connections across the forebrain (van der Werf et al., 2002) and



**Fig. 24.2.** Mesocircuit model placing central thalamic deep brain stimulation (CT-DBS) in the context of mechanisms underlying spontaneous and medication-induced recovery of consciousness. A “mesocircuit” model organizing mechanisms underlying recovery of consciousness after severe brain injury. Diffuse disfacilitation across frontal, cortical, and striatal neurons broad arises from severe structural brain injury. In particular, reduction of thalamocortical and thalamostriatal outflow following deafferentation and loss of neurons in central thalamus withdraws important afferent drive to the medium spiny neurons (MSNs) of striatum, which may then fail to reach firing threshold because of their requirement for high levels of synaptic background activity (Grillner et al., 2005). Loss of active inhibition from the striatum allows neurons of the globus pallidus internus (GPi) to fire tonically and provide active inhibition to their synaptic targets, including relay neurons of the already strongly disfacilitated central thalamus and possibly also the projection neurons of the pedunculopontine nucleus (PPN) (Williams et al., 2009). Amantadine, L-dopa, and zolpidem may reverse these conditions of marked downregulation of anterior forebrain activity across frontal cortices, striatum, and central thalamus, acting at different locations with the mesocircuit. Collectively, restoration of thalamocortical and thalamostriatal outflow will depolarize neocortical neurons and facilitate long-range corticocortical, corticothalamic, and corticostriatal outflow. CT-DBS can be considered as a final common pathway aggregating these effects and partially remediating the effects of strong deafferentation of these neurons in all severe brain injuries. (Reproduced from Schiff, 2012, with permission of Wiley–Blackwell.)

afferent input from arousal systems in the brainstem, basal forebrain, and cortex (Schiff, 2008). As a result of their unique geometry of connections, the neurons of the central thalamus are also particularly vulnerable to deafferentation and subsequent disfacilitation (Gold and Lauritzen, 2002) in the setting of severe injury (Maxwell et al., 2006). In the intact brain these anatomical features combine with physiological specializations of the neurons themselves to give these structures an essential role in

forebrain arousal regulation, as expressed in the most basic executive function of vigilance (reviewed by Shah and Schiff, 2010; Mair et al., 2011). Central lateral–paracentral neurons, targeted in the single-subject study discussed above, increase their responsiveness during the transition to wakefulness and in the awake state (Glenn and Steriade, 1982) and are tonically facilitated in both wakeful and rapid eye movement (REM) states. In addition, these central thalamic cell

populations receive input from all brainstem “arousal” system components, including the nucleus cuneiformis and central tegmental field of the mesencephalic reticular formation (Steriade and Glenn, 1982) and the basal forebrain (reviewed by Parvizi and Damasio, 2001; Schiff, 2008). Deafferentation of neurons in the central thalamus can be expected to produce broad decreases in global background synaptic activity across the forebrain (Rigas and Castro-Alamancos, 2007). Direct and indirect (via brainstem-projecting neurons) stimulation of central thalamus alters the intracellular properties of cortical neurons, producing high input resistance consistent with broad activation of inhibitory background activity along with balanced excitation (cf. Rudolph et al., 2005; Haider and McCormick, 2009).

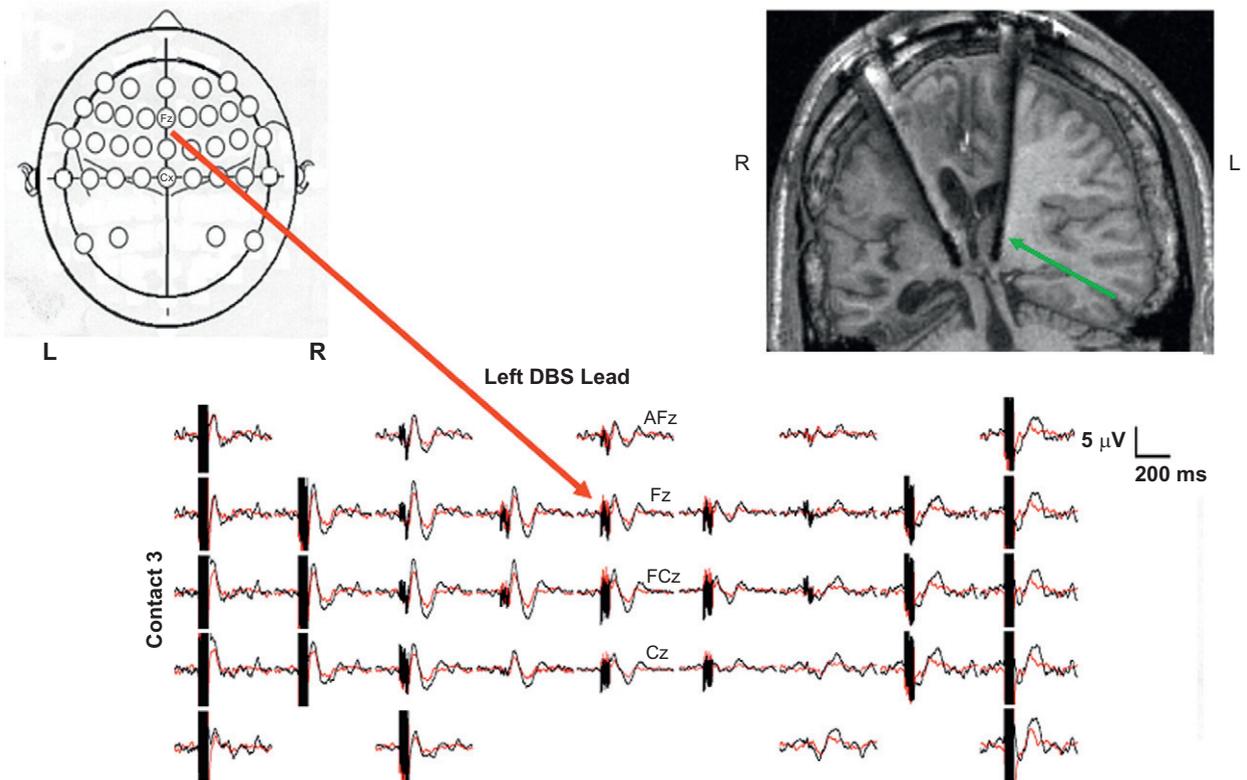
The functional anatomical relationships shown in Figure 24.2 derive from the classical Albin–Young–Penny (Albin et al., 1989) and DeLong (1990) model of corticostriatopallidal–thalamocortical loops. While the strong hierarchical feedforward sequential processing embodied in this model has been reasonably criticized for simplification and failure to capture complex dynamics (Montgomery, 2007), feedforward network architectures have powerful computing advantages (Goldman, 2009). Recent studies using direct *in vivo* physiological measurements provide evidence that central thalamus and frontal cortical regions may participate in such feedforward network configurations (Shah et al., 2010). Moreover, the schematic model likely does capture well the circuit-level problem that may arise with severe multifocal injuries where, as noted above, widespread deafferentation arises secondary to either disruption of white matter connections (as in diffuse axonal injury) or multifocal neuronal death (as in, for example, ischemic–hypoxic injuries, encephalitis, multifocal infarction following vasospasm). Degradation of long-range connections across corticocortical and thalamocortical systems will result a marked withdrawal of excitation across cerebral structures, with the most significant circuit-level consequence likely arising within the striatum in the medium spiny neurons (MSNs). MSNs require high levels of spontaneous background synaptic activity arising from excitatory corticostriatal and thalamostriatal inputs to maintain membranes near their firing thresholds (Grillner et al., 2005). MSN output can, in principle, be shut down by withdrawal of both direct excitatory striatal projections from neurons within the central thalamus and via downregulation of the frontocortical regions that provide the main corticostriatal input (Haber, 2003; Haber et al., 2006).

Projections from the central thalamus heavily innervate the prefrontal and frontal cortex, particularly mesial frontal cortices of supplementary motor area and anterior cingulate (Morel et al., 2005). These medial

frontal regions in turn provide broad, feedforward projections to the prefrontal and frontal cortices (Barbas and Pandya, 1989). The same central thalamic neurons provide a thalamostriatal projection back to the MSNs (Lacey et al., 2007). Considered as a connected cerebral subunit, neurons within the mesial frontal cortices, rostral striatum, and central thalamus form the core of a forebrain arousal regulation system. Preferential activation of the frontal cortical components of this system by CT-DBS is supported by known functional anatomical relationships of the central thalamic projections. A direct physiological demonstration of such a pattern of activation is evident in Figure 24.3, which shows cortical evoked potentials elicited from a CT-DBS electrode contact in the single subject discussed above (Schiff et al., 2007, supplementary material). This activation profile corresponds to one of the contacts used in the effective stimulation protocol.

Both spontaneous recovery and pharmacological manipulations known to be effective in some severely brain-injured patients strongly modulate activity across the anterior forebrain mesocircuit. Figure 24.4 shows fluorodeoxyglucose positron emission tomography (FDG-PET) measurements obtained longitudinally in a patient recovering from a severe traumatic brain injury (Voss et al., 2006). An initial FDG-PET scan obtained at 6 months after injury when the patient remained in MCS showed marked bifrontal and thalamic hypometabolism (see Fig. 24.4A); notable increases in cerebral metabolism were observed at 10 months and correlated with the patient’s emergence from MCS. As seen in Figure 24.4B, mesencephalic, thalamic, and mesial frontal regions showed marked metabolic increases. These changes in anterior forebrain metabolism were further correlated with normalization of resting state networks measured using functional magnetic resonance imaging (fMRI) (Voss et al., 2006). Figure 24.5 shows a group study of quantitative cerebral blood flow in patients in MCS using the arterial spin labeling neuroimaging technique (ASL). As seen in Figure 24.5A, global cerebral flow is reduced in patients in MCS compared with normal controls, and is somewhat further reduced in mesial frontal regions (Liu et al., 2011).

In a single-subject longitudinal study using ASL, changes in blood flow were correlated with emergence from MCS occurring over a 2-year time period and with the use of amantadine (see Fig. 24.5B). Amantadine is a mixed dopaminergic agonist and *N*-methyl-D-aspartic acid (NMDA) antagonist, and is now the first drug shown to be generally effective across both VS and MCS following severe traumatic brain injury in the early course of recovery (Giacino et al., 2012b). Among possible mechanisms, amantadine likely facilitates MSN outflow as well as facilitation of mesial cortical neurons.

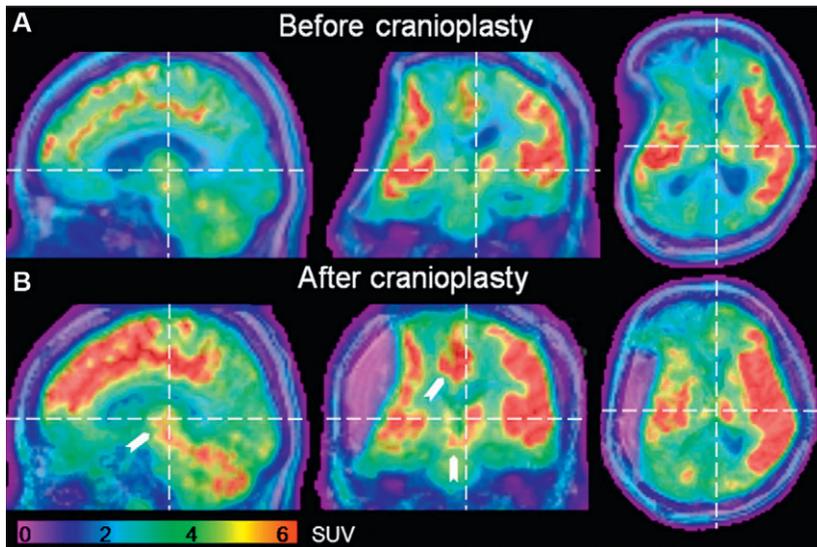


**Fig. 24.3.** Central thalamic deep brain stimulation (DBS) evoked potentials in the minimally conscious state. The figure shows cortical evoked potentials recorded from left DBS electrode in the single-subject study of [Figure 24.1](#). Averaged waveforms of the evoked potentials are shown; a 250-ms baseline is shown prior to the onset of the approximately 100-ms stimulus electrical artifact induced by the stimulus train, followed by a 900-ms window containing the physiological response to the stimulation. Consistent, time-locked changes in EEG pattern are present for as long as 450 ms after the offset of stimulation. Two waveforms are shown for each recording site, with each representing half of the acquired data (first/second half) to demonstrate the neuronal origins of the response as opposed to volume conduction of the electrical field from the electrode cathodes. Bilateral activation is seen with a dominant effect over the ipsilateral (left) hemisphere and frontocentral midline, consistent with activation of frontal cortical regions involved in arousal regulation mechanisms. Magnetic resonance image (MRI) inset shows electrode lead placements within central thalamus of the patient's right (R) and left (L) hemispheres displayed in T1-weighted MRI coronal image. (Adapted from [Schiff et al., 2007](#), with permission.)

L-Dopa may have similar impact on the striatum, but also has a direct effect on the central thalamus ([Rieck et al., 2004](#); [Fridman et al., 2010](#)). In a series of experiments using local pharmacological manipulations within the central thalamus, [Mair and Hembrook \(2008\)](#) established evidence of “inverted U”-type modulations of behavioral performance consistent with Yerkes–Dodson Law, with orexin and an inverse  $\gamma$ -aminobutyric acid (GABA) agonist (FG-7142). Zolpidem, an  $\alpha_1$ -subtype-selective positive allosteric modulator of the GABA-A receptor can induce paradoxical behavioral improvements in some patients in MCS ([Brefel-Courbon et al., 2007](#)). Release of pallidal inhibition of the pallido-recipient thalamus and release of thalamocortical outflow have been proposed to play a key role underlying this paradoxical effect via the binding of zolpidem to the globus pallidus interna and neocortical regions with

the anterior forebrain mesocircuit ([Schiff and Posner, 2007](#); [Brown et al., 2010](#); [Schiff, 2010](#)).

Functional variations of distributed neocortical neurons in the setting of marked cerebral deafferentation are likely to play an even more important role across the entire spectrum of clinical outcomes following severe brain injury. The range and subtlety of normal corticocortical and corticothalamic activity is impressively large, with very modest increases in membrane potential produced by depolarization of only 1 mV giving rise to increases of 3–7 spikes per second in neocortical firing rate ([Steriade et al., 2001](#); [Steriade, 2004](#); [Haider and McCormick, 2009](#)). This sensitivity suggests that restoring the typical variations of approximately 10 mV observed during wakeful states could have marked impact ([Haider and McCormick, 2009](#)). The dynamic range of neocortical neurons and their

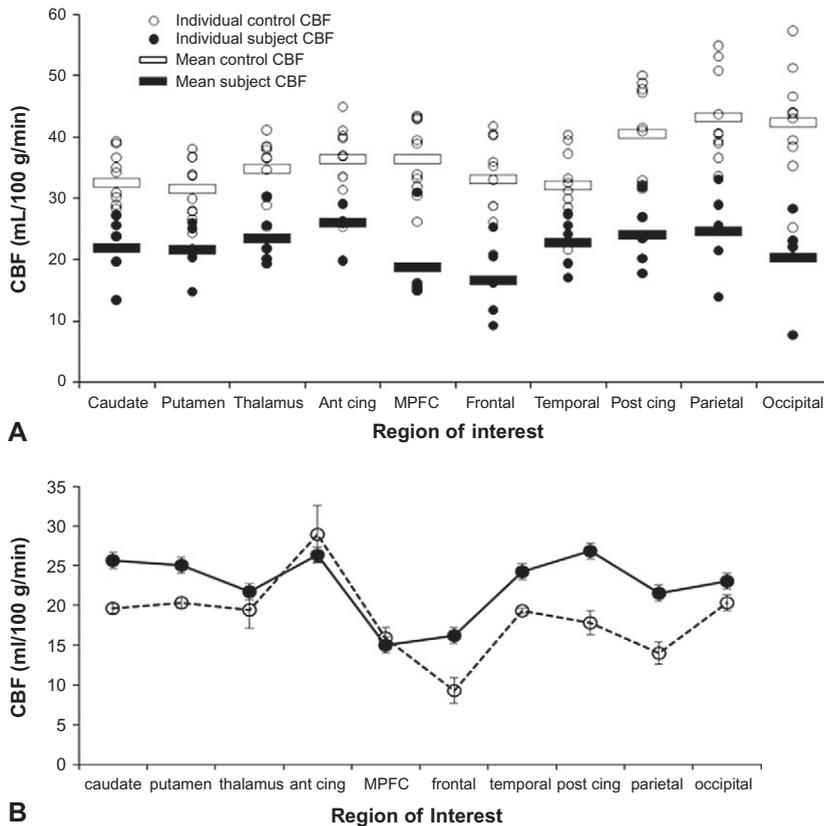


**Fig. 24.4.** Change in anterior forebrain metabolism during spontaneous emergence from a minimally conscious state (MCS), measured by fluorodeoxyglucose positron emission tomography (FDG-PET) in a single subject. Six months prior to the first FDG-PET images (A) the subject demonstrated an examination consistent with MCS, including reliable auditory command-following and intermittent gestural communication. Best total score on the Coma Recovery Scale – Revised (CRS-R) was 14. The second FDG-PET images (B) were obtained 10 months after injury and 2 months after a right-sided cranioplasty. At this time, the patient demonstrated further improvements on examination, including recovery of functional object use, consistent communication, and improved attentional function (best CRS-R total score of 20). At the time of this second evaluation, formal testing indicated emergence from MCS. A marked increase in standard uptake values of FDG is observed after cranioplasty. Mean  $\pm$  sd whole-brain standard uptake values (SUVs) (excluding the cavity at the second time point) increased from  $2.5 \pm 2.0$  to  $3.0 \pm 2.4$  g/mL. Regional changes were observed in left mesial frontal regions and within the upper brainstem and thalamus (arrows). (From Voss et al., 2011, with permission of Elsevier.)

impact on local neuronal microcircuits may be the primary determinant of outcomes following multifocal cerebral injuries, even if large-scale mesocircuit level dynamics are largely restored. In the intact mammalian brain, massive corticothalamic excitation dominates wakeful states (Steriade et al., 2001; Haider and McCormick, 2009) and drives thalamic and striatal neurons of the anterior forebrain mesocircuit. Studies in the songbird demonstrate that neurons in the vocal portion of pallido-recipient thalamus are driven principally by corticothalamic inputs at high rates of 100–400 Hz (Goldberg and Fee, 2012). In the severely injured brain, however, deafferentation may be so severe that central thalamic neurons are largely silent (e.g., as observed in six human thalami of subjects in MCS; Giacino et al., 2012a).

The high baseline corticothalamic activity in the normal awake mammalian brain supports the attempt to use high-frequency DBS firing rates in an effort to facilitate restoration of normal network and cellular integrative following severe traumatic brain injury. In fact, such considerations may be common to the underlying mechanisms of DBS in other settings. Montgomery (2007) proposed that high-frequency (around 140 Hz) oscillations between the motor cortex and ventral lateral thalamus provide a fundamental base frequency

underlying complex oscillatory activity across the normal motor systems, and that effective DBS frequencies for modulation of Parkinson’s disease support the normalization of this base oscillation through both circuit resonance mechanisms and the addition of background spiking activity within the distributed corticostriatopallidal–thalamocortical loop systems (Montgomery, 2007; Montgomery and Gale, 2008). In the context of CT-DBS for MCS, the canonical cortical microcircuit and its feedback and feedforward connectivity have been proposed to play an essential role in observed behavioral facilitation (Schiff and Purpura, 2002; Shah et al., 2009; Shah and Schiff, 2010). Afferents from the central thalamus may support long-range excitatory corticocortical activity linked to cognitive processes (Purpura and Schiff, 1997) and high-frequency CT-DBS stimulation of these afferents may facilitate corticocortical interactions by affecting integration of synaptic activity within the dendritic arbor of layer II–III and layer V cortical pyramid cells (Purpura and Schiff, 1997; Larkum et al., 1999, 2007). In the CT-DBS single-subject study discussed above, stimulation frequencies of up to 250 Hz appeared to have similar effects when contact geometry and voltage were held constant compared with 70-, 100-, and 130-Hz stimulation rates (Schiff et al., 2007, supplementary



**Fig. 24.5.** Arterial spin labeling (ASL) studies in the minimally conscious state (MCS). **(A)** Cerebral blood flow (CBF) pattern for 10 normal controls, ranging from 23.8 to 57.2 mL per 100 g per min. A pattern of relatively increased CBF in posterior structures, including the posterior cingulate (post cing), parietal, and occipital cortices, compared with anterior cortical regions and subcortical structures can be observed. CBF patterns for subjects in MCS showed greater variability and ranged from 7.7 to 33.1 mL per 100 g per min. The majority of subjects demonstrated decreased CBF in the medial prefrontal cortex (MPFC) and midfrontal regions relative to other regions of interest. **(B)** Measurement of ASL sequence in a single subject approximately 13 and 20 months following diffuse hypoxic–ischemic injury from disseminated fat emboli. At 20 months, the patient showed marked improvements in cognition and communication, demonstrating consistently fluent verbal communication. Although the overall amount of CBF increased, a relative decrease in flow was observed in the medial prefrontal and midfrontal regions, with a peak in the anterior cingulate (ant cing) regions. The difference in CBF between times 1 and 2 is greater for most regions than the standard deviation in measurement for any given region. (From Liu et al., 2011.)

material). Selection of 100 Hz as the fixed frequency for testing in this subject balanced considerations of preserving battery life, and an inference drawn from measured evidence of increased cortical gene expression with 100-Hz compared with 50-Hz stimulation of the central lateral nucleus (Shirvankar et al., 2006) that suggested higher frequency stimulation would be more effective in driving neocortical neurons.

Importantly, experimental studies reveal that CT-DBS could support endogenous arousal regulation processes within the wakeful state of normal intact mammalian brains and aid the initiation, maintenance, and effort adjustments underpinning ongoing behavior (Shirvankar et al., 2006; Mair and Hembrook, 2008; Shah et al., 2009; Smith et al., 2009). Perhaps the most compelling evidence for a selective support of specific

neuronal substrates of arousal regulation by CT-DBS comes from the experiments of Mair and Hembrook (2008). These investigators demonstrated that phasic stimulation of the central lateral nucleus in rodents produced behavioral improvements in a delayed match to position task when stimulation was introduced precisely at the start of memory delay and retrieval periods but not during other periods of task. The CT-DBS effects were specific to the phase but not the absolute time elapsed within the phases, demonstrating that CT-DBS exerted effects on neuronal processing related to these specific cognitive processes. Taken together with the discussion above, these observations are of considerable relevance for matching of the CT-DBS technique to patients with nonprogressive brain injuries, as summarized below.

## **DIRECTIONS FOR DEVELOPMENT OF CT/DBS FOR MCS: PREFERABLE NEURONAL SUBSTRATES, BEHAVIORAL PROFILES, AND GOALS OF THE INTERVENTION**

The above discussion of mechanisms underlying the contribution of the central thalamus and its role in supporting activity in the anterior forebrain mesocircuit during recovery of consciousness and cognitive function after brain injury guides an approach to considering the preferable neuronal substrates, behavioral profiles, and goals of the intervention in patients in MCS. At first order, effective CT-DBS should be expected to induce reversal of abnormal “circuit”-level dynamics resulting from broadly reduced background synaptic activity across corticothalamic and corticostriatopallidal–thalamocortical systems in a patient in MCS who could respond (cf. Schiff and Posner, 2007; Brown et al., 2010; Schiff, 2010). The main expected effect of CT-DBS would be to produce a shift of level of synaptic input to severely deafferented neurons across neocortex, striatum, and other components of the thalamus. Among these effects, changing the neuronal firing patterns of neocortical pyramidal cells (which are sensitive to very small differences in the level of depolarization of the neuronal membrane) would be expected both to engage local network activity and to generate changes in neuronal responsiveness across wide cortical territories (cf. Steriade et al., 2001; Haider and McCormick, 2009), and aid long-range corticocortical processing (cf. Purpura and Schiff, 1997; Schiff and Purpura, 2002). Restoration of sufficient excitatory drive to striatal medium spiny neurons to bring membrane potentials to a sufficiently depolarized level to allow firing of these neurons may further facilitate thalamocortical and thalamostriatal outflow with CT-DBS (cf. Grillner et al., 2005). Collectively, CT-DBS could be expected to exert a behaviorally specific effect on arousal regulation mechanisms by providing selective support to neuronal populations engaged in adaptive allocation of cognitive resources (Shirvalkar et al., 2006; Mair and Hembrook, 2008).

Framed from the point of view of this mechanistic rationale, patients in MCS who are more likely to respond to CT-DBS should show evidence of spontaneous capacity to exhibit cognitively mediated behaviors such as command-following and elements of communication (Giardino et al., 2012a). In addition, preservation of recruitable neuronal populations across anterior forebrain structures connected to the central thalamus and linked to the process of arousal regulation are clearly essential. In particular, the presence of an anatomical substrate of a sufficiently large collection of axons from the central thalamus projecting to prefrontal/frontal cortical regions and striatum that can deploy excitatory

neurotransmitters needs methods of quantification and precise parametrization. To date, there is no evidence that CT-DBS produces significant change in the course of patients fulfilling the diagnostic criteria for VS or MCS who do not already exhibit behaviors above the level of nonreflexive movements (the lower boundary for classification within the category of MCS), despite contrary claims as reviewed above. Ultimately, however, only demonstration of effective CT-DBS in well designed and well executed clinical trials will guide development of any future set of generalizable criteria. Hopefully, the above review of experimental and clinical data will help the long process ahead to make further progress.

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