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Recovery of consciousness after severe brain injury: The role of arousal regulation mechanisms and some speculation on the heart-brain interface

ABSTRACT

Recovery of consciousness after severe brain injury involves reconstitution of brain arousal mechanisms and cerebral integrative function. This review discusses several aspects of neuroanatomy and neuropathology relevant to the process of recovery. Particular emphasis is placed on the role of the anterior forebrain and circuit mechanisms linking the frontal lobe, striatum, and central thalamus. The article concludes with some observations on the heart-brain interface and future research directions in the context of recovery from severe brain injury.

WHY WE NEED TO UNDERSTAND MECHANISMS OF RECOVERY AFTER SEVERE BRAIN INJURY

The problem of recovery of consciousness after severe brain injury is one that easily captures the imagination of both the lay public and the professional. Puzzling reports continue to arise of late recovery of speech, language, memory, and other higher cognitive functions in rare patients, yet a scientific framework for the systematic assessment of these phenomena has been lacking.[1–3] Some of these cases provide intriguing hints to the possible role of various medications (such as dopaminergic, serotoninergic, and noradrenergic agents) as well as spontaneous changes in brain function arising over time. As discussed below, the varying levels of recovery following coma seen after multifocal traumatic or nontraumatic brain injuries may share some common underlying mechanisms at the "circuit" level. Severe brain injuries producing coma have many causes (see Posner et al[4] for a comprehensive review), but careful review reveals an overlap of structural pathologies and functional disturbances isolated to specific cerebral structures across several clinical syndromes grouped under the framework of "disorders of consciousness,"[5] with an emphasis on the role of particular substructures. Perhaps most important is a consideration of the pathologic, anatomic, and pathophysiologic role of the anterior forebrain, particularly the relationships of the brainstem and basal forebrain arousal systems, the central thalamus, and frontostriatal pathways, as reviewed below.

Figure 1 indexes neurologic disorders of consciousness on a two-dimensional grid that highlights the independence of the degree of impairment of cognitive function and motor function that may be encountered in a patient. In the bottom left corner of the figure, coma and vegetative state are both considered unconscious brain states as judged by the bedside behavioral examination in the context of appropriate neurologic history. In both coma and vegetative state, patients do not demonstrate responses to environmental stimuli or initiate goal-directed behaviors. Comatose patients also show no state variation and usually remain close-eyed. In vegetative state, an observable cycling of irregular periods of eye opening and eye closure is evident, but this cyclical variation in behavioral state does not correlate with identifiable electroencephalographic features of either sleep or normal wakefulness.[6] To the right of vegetative state in the figure is the minimally conscious state.[7] Patients in minimally conscious state show unequivocal but inconsistent evidence of awareness of self or the environment through a wide range of behavioral response patterns that can be elicited by bedside examination.[8] Patients may track objects with their eyes, exhibit stereotyped automatic motor behaviors, follow simple commands with small motor movements, or intermittently communicate through verbal or gestural means. The functional boundary indicating emergence from minimally conscious state is the demonstration of reliable verbal or gestural communication. Operationalizing this level of function is a topic of current research, as even simple "yes" versus "no" communication can be unreliable in brain-injured patients who recover past the level of minimally conscious state.[9]

The large gray box in **Figure 1** indicates the disquietingly high degree of uncertainty in assessing cognitive

Dr. Schiff reported that he is a listed inventor on patents for deep brain stimulation in the central thalamus for cognitive neuromodulation issued to Cornell University and licensed to IntElect Medical, Inc., a start-up company formed by Cleveland Clinic and Cornell University. He is also a paid consultant and advisor to IntElect Medical, Inc. Published research described in this article received partial support from IntElect Medical, Inc.

doi:10.3949/ccjm.77.s3.05

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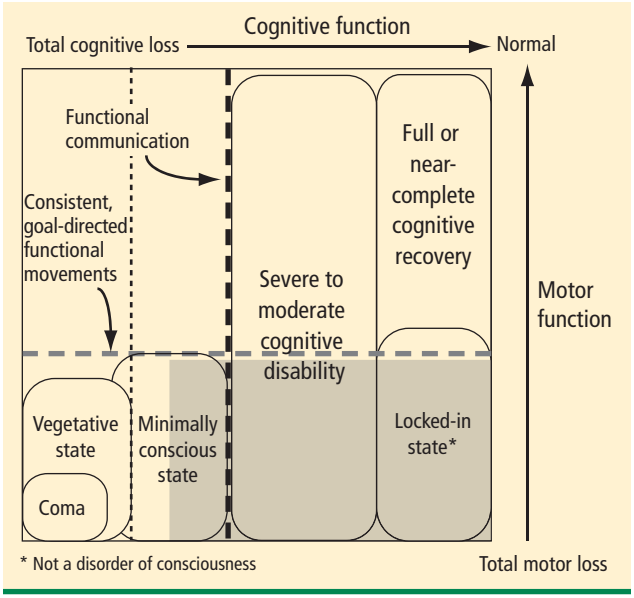

FIGURE 1. Correspondence of cognitive and motor impairment across outcomes following severe brain injuries. Impairment ranges from coma and vegetative state to minimally conscious state to locked-in state, which is not a disorder of consciousness. The gray box shows the large region of diagnostic uncertainty in establishing the true cognitive level of patients who behaviorally cannot reliably signal through controlled goal-directed movements (horizontal dashed line).

level in some patients who lack controllable motor output channels. The locked-in state (bottom right corner of figure) defines patients who retain total preservation of cognitive function but otherwise may appear no different from those in deep coma. Although locked-in state often arises in the context of neurologic injuries that selectively damage motor output pathways distal from their cortical origins or that slowly reduce primary motor neuron function, this syndrome and closely similar conditions arise in patients with complex brain injuries. Such patients likely retain full or nearly normal consciousness but unfortunately are unable to produce consistent goal-directed movements that allow for communication. In principle, such patients could retain significant cognitive capacity near the normal range of cognitive function yet be indistinguishable from patients in minimally conscious state.

ROLE OF THE CENTRAL THALAMUS IN SEVERE BRAIN INJURIES

Recent studies have yielded evidence for common anatomic pathologies following severe injuries associated with vegetative state[10] and minimally conscious state[11] as well as pathologies underlying severe to moderate cognitive disability.[12] Autopsy studies of patients remaining in vegetative state at the time of death have identified widespread neuronal death throughout the thalamus as the common finding following either anoxia or diffuse axonal injury that produces widespread disruption of white matter connections.[10] The severe bilateral thalamic damage after either trauma or anoxia seen in permanent vegetative state is not, however, invariably associated with diffuse neocortical neuronal cell death. This is particularly true of traumatic brain injury, in which only approximately 10% of brains at autopsy show widespread neocortical cell death.[10] Specific subnuclei of the thalamus show the greatest neuronal cell loss following global and multifocal cerebral injuries produced by traumatic brain injuries.[13] In particular, the central thalamic nuclei (intralaminar nuclei and related paralaminar nuclei) demonstrate progressive neuronal loss following severe traumatic brain injuries,[13] and there is some evidence that a similar pattern might be identified in hypoxic-ischemic injuries.[14]

Progressively severe disability grades with neuronal loss along a rostrocaudal axis: the anterior intralaminar and surrounding regions initially show volume loss associated with moderate disability, while neuronal loss in the ventral and lateral nuclei of the central thalamus (posterior intralaminar group) appears with worsening disability associated with minimally conscious state and vegetative state.[13] This progressive and relatively specific involvement of the nuclei of the central thalamus likely results from the unique geometry of these neurons, which have wide point-to-point connectivity across the cerebral hemisphere.[15,16] The marked neuronal volume loss in these cells is likely due to their integration of the effects of neuronal cell death across large cerebral territories after diffuse trauma, hypoxia, and other nonselective severe brain injuries.

Importantly, however, focal bilateral injuries to these regions of the central thalamus are also associated with global disorders of consciousness (coma, vegetative state, and minimally conscious state).[5,17] This observation indicates that these neurons also play a causal role in the production of disorders of consciousness. Abrupt injuries of the central thalamus on both sides of the brain are associated with acute coma, reflecting these cells' key contribution to normal mechanisms of arousal regulation (reviewed by Schiff[18]). The central thalamus receives ascending projections from the brainstem/basal forebrain "arousal systems" that control the activity of many cortical and thalamic neurons during the sleep-wake cycle. Importantly, the central thalamus is strongly innervated by the cholinergic, serotoninergic, and noradrenergic afferents of the brainstem arousal systems (see Schiff[18] for review). These same neurons also are innervated by descending projections from frontal cortical regions supporting "executive" functions that underlie goal-directed behaviors. Collectively, these ascending and descending influences on the central thalamus appear to modulate the level of arousal associated with generalized alertness and variations in cognitive effort, stress, sleep deprivation, and other variables affecting the wakeful state.[15,18–22]

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Neuroimaging and electrophysiologic studies offer further evidence that the anatomic specializations of the central thalamus play an important role in regulating brain activation during attentive wakefulness. The central thalamus shows selective activation in normal subjects performing tasks requiring a short-term shift of attention,[19,23] sustained cognitive demands of high vigilance,[22] or memory holds over extended time periods.[23,24] Central thalamic activation associated with varying levels of vigilance correlates with global cerebral blood flow[19] and specifically covaries within the anterior cingulate cortex and pontomesencephalon.[22] Brain activity in the anterior cingulate cortex grades with increasing cognitive load and is recruited by a wide range of cognitive tasks, apparently reciprocally increasing activity along with the central thalamus in response to increasing demands of cognitive effort.[20,22]

CIRCUIT MECHANISMS UNDERLYING RECOVERY AFTER SEVERE BRAIN INJURY

In addition to the studies reviewed above providing evidence for the role of specific disconnection of neurons within the central thalamus in disorders of consciousness, **Figure 2** illustrates a key vulnerability of the anterior forebrain in the setting of the widespread deafferentation and neuronal cell loss seen with severe brain injuries. This vulnerability places the role of the central thalamus in a wider context. A "mesocircuit"-level[25] model has been proposed that suggests that functional alterations across very large connected neuronal populations of the anterior forebrain may arise primarily as a result of global reductions of excitatory neurotransmission.[26,27] The majority of etiologies associated with coma and related disorders of consciousness diagrammed in **Figure 1** effectively produce a broad decrease in background synaptic activity and excitatory neurotransmission (eg, diffuse axonal injury, anoxia, hypoxia-ischemia, cerebral vasospasm with strokes; see Posner et al[4] for review).

In addition to the wide point-to-point connections of the central thalamus with the cerebral cortex (predominantly connections to frontal and prefrontal cortices; see Van der Werf et al,[15] Groenewegen and Berendse,[28] Morel et al[29]), these neurons have important projections to the striatum that return via projections from the globus pallidus.[30] These projections from the central thalamus (both central lateral nucleus and parafascicularis nucleus) diffusely innervate the striatum and project onto the medium spiny neurons (MSNs), the output neuron of structure.[31] Because the specific thalamostriatal projections from these central thalamic neurons use glutamate transmitters with a high probability of synaptic release,[32] they likely also have a strong role in modulating background activity in the striatum.

The MSNs represent an important point of vulnerability in this anterior forebrain mesocircuit, as they have

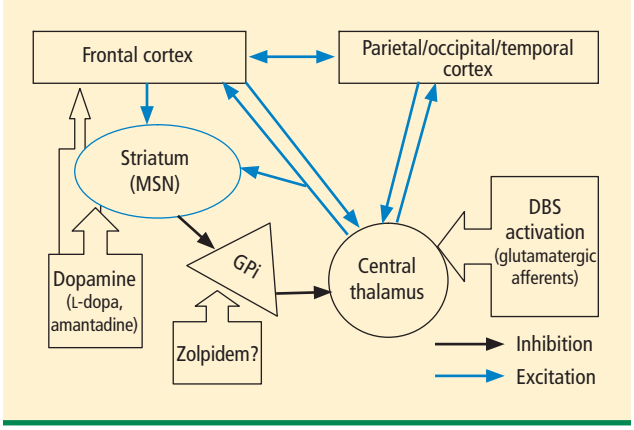

FIGURE 2. Proposed "mesocircuit"[25] linking behavioral fluctuations following severe brain injuries and improvements in response to interventions. The model focuses on the modulatory role of the anterior forebrain in overall corticothalamic dynamics. The anterior forebrain (frontal/prefrontal cortical-striatopallidal thalamocortical loop system) is particularly vulnerable to large-scale dysfunction following multifocal brain injuries that produce widespread deafferentation or neuronal cell loss. At least two mechanisms related to this mesocircuit appear to play a key role after severe injuries: (1) the high demands of striatum output neurons for background activity and dopaminergic innervations and (2) the anatomic connections and physiologic specializations of the thalamocortical projections from the central thalamus. These central thalamic neurons have a potent activating role strongly driving both cortical and striatal neurons and wide point-to-point connections that make them more sensitive reporters of global neuronal loss than other thalamic nuclei. Withdrawal of thalamocortical transmission from the central thalamus is known to associate with coma and other disorders of consciousness (see Schiff and Plum[5]). The thalamostriatal projection from the central thalamus contacts the medium spiny neurons (MSNs) of the striatum, forming axodendritic (centromedian[32]) or axospinous (central lateral, parafascicular[31]) synapses. The MSNs, in turn, send inhibitory projections to the globus pallidus interna (GPi); without MSN output, the GPi tonically inhibits the central thalamus.[33] Thus, a suppression of MSN output resulting from a loss of dopaminergic modulation or marked reduction in background synaptic activity can potentially catalyze a shutdown of the anterior forebrain. The mesocircuit model economically accounts for several clinical observations and aspects of normal physiology (see text for further discussion). (DBS = deep brain stimulation)

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a key role in maintaining activity in the anterior forebrain through their inhibitory projections to the globus pallidus interna, which in turn inhibits the central thalamus.[33] MSNs have instrinsic cell membrane properties that keep them below their firing threshold unless a high level of spontaneous background synaptic activity arising from excitatory corticostriatal and thalamostriatal inputs is present in concert with sufficient concentrations of the neurotransmitter dopamine.[33] In the setting of diffuse deafferentation or neuronal loss following severe brain injury of any type, it is expected that background

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excitatory synaptic activity is considerably reduced. Under these circumstances, a broad withdrawal of direct excitatory striatal projections from the central thalamus and corticostriatal inputs is likely to cause MSN output to shut down. Observations of regional changes in brain metabolism following severe brain injuries, specific responses to pharmacologic and electrophysiologic interventions in brain-injured subjects, and normal variations in brain state are all consistent with this mesocircuit model (see Schiff[26] for comprehensive review). Similarly, a consistent pattern of selective metabolic downregulation within the anterior forebrain has been shown to specifically grade with severity of behavioral impairment following diffuse axonal injury,[34] and application of dopaminergic agents in such patients often will produce behavioral facilitation.[35,36] These medications may facilitate the output of the MSNs and directly modulate mesial frontal cortical neurons, possibly restoring anterior forebrain activity within the loop connections of the frontal cortex, striatum, pallidum, and central thalamus.

This model provides context for understanding another paradoxical observation—ie, the association of the sedative zolpidem (Ambien), a nonbenzodiazepine hypnotic that potentiates $GABA_A$ receptors, with behavioral improvement of alertness and interactive behavior in severely brain-injured patients.[37–41] Zolpidem's primary direct action in patient responders, as originally proposed by Schiff and Posner,[27] may be upon on the globus pallidus interna, producing a release of tonic inhibition of the central thalamus in the setting of a broad reduction in background excitatory neurotransmission (as seen, for example, following diffuse hypoxic-ischemic injury) and leading to a shutdown of the inhibitory projection of the MSNs. The $GABA_A$ alpha-1 subunit is expressed in large quantity in the globus pallidus interna, and experimental studies support this mechanism of action.[42]

SINGLE-SUBJECT STUDY OF CENTRAL THALAMIC STIMULATION IN MINIMALLY CONSCIOUS STATE

A further implication of the mesocircuit model is that direct activation of the central thalamus is expected to be the causal step in reactivating a downregulated anterior forebrain system, suggesting that direct modulation of the central thalamus might facilitate behavioral responsiveness in some patients with severe brain injuries. A recent study offers evidence that direct electrical stimulation of the central thalamus can produce behavioral facilitation.

In this single-subject study of central thalamic deep brain stimulation (DBS), a 38-year-old man remained in minimally conscious state for 6 years following a severe closed head injury following blunt trauma to the right frontal lobe.[43] After 3 months in a vegetative state, the patient exhibited the first evidence of clear behaviors in response to sensory stimulation consistent with minimally conscious state and advanced to eventually demonstrating a best behavioral response of inconsistent command-following and communication using eye movements. This behavioral level remained unchanged at the start of the DBS study 4 years later, as confirmed by evaluation with the Coma Recovery Scale–Revised (CRS-R), a formal behavioral assessment tool.

The patient entered into a study of central thalamic DBS according to the timeline in **Figure 3A**. An initial 4-month quantitative behavioral assessment was completed prior to placement of the DBS electrodes, which were implanted bilaterally in the anterior intralaminar thalamic nuclei (central lateral nucleus and adjacent paralaminar regions of the thalamus; **Figure 3B**). Following electrode placement and brief contact-by-contact testing of the electrodes, 2 months of behavioral testing was conducted with the electrodes remaining off to reassess the patient's postsurgical behavioral baseline, which had not changed as a result of electrode placement. Two subsequent phases of the study focused on evaluation of DBS effects. A 5-month titration phase focused on establishing tolerance of DBS and evaluating several combinations of different electrical stimulation parameters (contact geometry, frequency, intensity) as well as the duration of the stimulation period. Following this titration phase, the patient entered a 6-month double-blind alternating crossover study. Through all phases of the study, the patient received standard rehabilitation efforts amounting to 3 hours a day, 4 days per week.[43]

Figure 3C summarizes results of the alternating crossover study and compares the prestimulation baseline assessments of various behaviors with the "on" versus "off" testing of the DBS electrodes during the crossover phase. The results demonstrate the overall impact of DBS compared with approximately 6 months of ongoing rehabilitation efforts in the absence of DBS exposure. Overall the findings show marked improvement in behavioral responsiveness compared with prestimulation frequencies of the highest-level behavioral response across six categories. The primary outcome assessments were prospectively chosen from subscales of the CRS-R, which is a well-validated psychometric tool used in patients with disorders of consciousness. CRS-R subscale items that had shown variation during the presurgical baseline assessment were chosen prospectively as the primary outcome measures. Notably, the CRS-R oral motor subscale was not chosen because no variation in this measure had been identified during the baseline assessment period. In addition, an object-naming scale and two other tailored secondary measures were developed later, during the titration phase, as the patient's behavior changed, and were calibrated to be tested using these secondary measurement scales. All six measures showed marked change from prestimulation baseline levels, with five of the six measures showing

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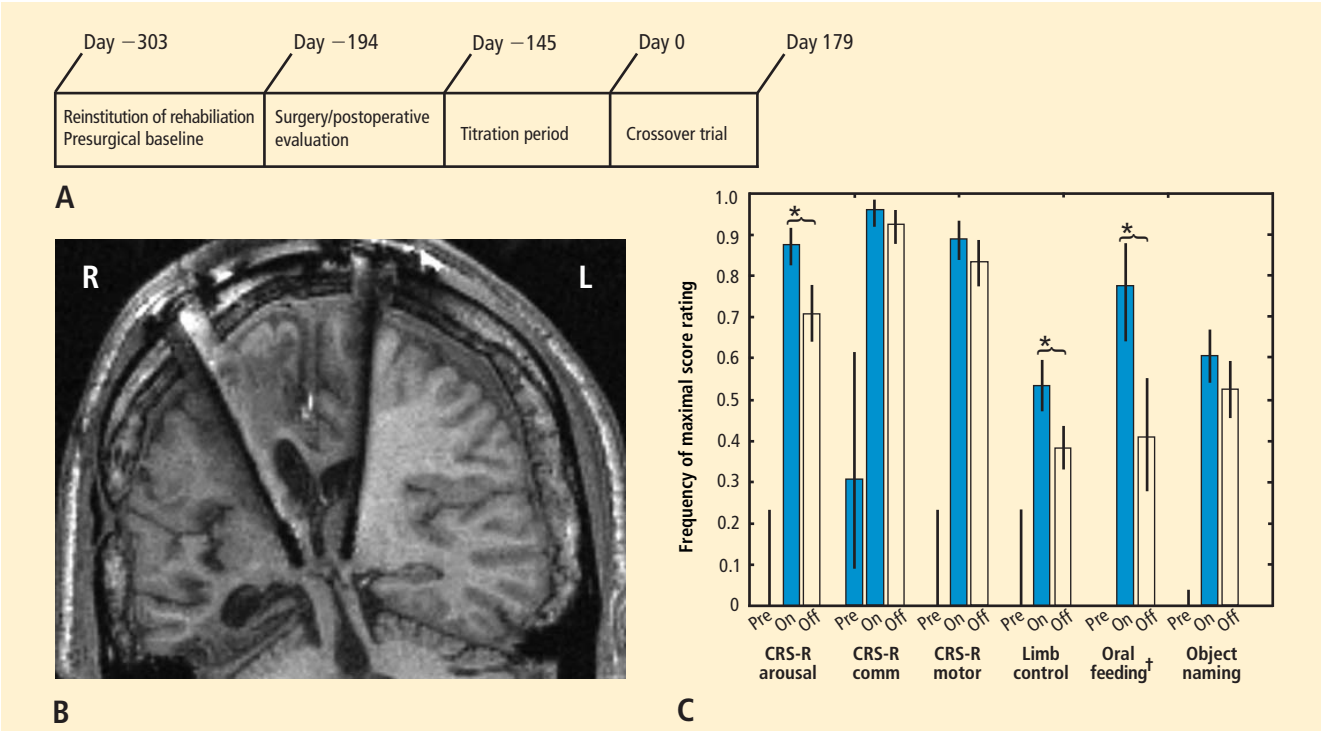

FIGURE 3. Overview of a 6-month alternating crossover study of central thalamic deep brain stimulation (DBS) in a patient in minimally conscious state following severe traumatic brain injury.[43] **(A)** Study timeline. **(B)** Electrode lead placements within central thalamus of patient's right (R) and left (L) hemispheres displayed in T1-weighted coronal magnetic resonance image. **(C)** The patient's responsiveness on six cognitive and functional measures at presurgical baseline ("Pre") and during periods when DBS was on ("On") and off ("Off") during the crossover phase. Responsiveness measures are shown with 95% confidence intervals (whiskers). Asterisks denote measures for which there were statistically significant differences between DBS "on" versus "off" periods. Dagger is present after "Oral feeding" to note that oral feeding data were not available before titration (hence no "Pre" value for this measure); also, oral feeding scores 1 and 2 are combined for dichotomy. See text for further explanation (including explanations of outcome measures). Reprinted from Schiff et al.[43]

higher-level behaviors than those seen prior to stimulation, regardless of whether the electrodes were on or off.[43]

As shown in **Figure 3C**, the behaviors captured by secondary measures had never occurred before the titration phase of the study; ie, the patient initially lacked a capacity for object naming, oral feeding, and the complex controlled goal-directed movements captured in the secondary limb movement measure, thus setting a prestimulation baseline frequency of 0 for these measures (see supplementary material in Schiff et al[43]). Three outcome measures—one primary (CRS-R arousal subscale) and two secondary (oral feeding and limb control)—showed statistically significant dependence on DBS during the 6-month period, as indicated by a significantly higher frequency of maximal score rating during "on" versus "off" periods **(Figure 3C)**. The continuation of improvements during the "off" periods of the crossover trial (relative to the prestimulation baseline assessments) showed that the DBS effects produced carryover changes that remained after the extensive exposure to DBS during the titration period (for further analysis of the dynamic of these data, see supplementary material in Schiff et al[43]).

Importantly, these observations are limited to a single human subject and do not provide a guide to their generalizability,[44,45] although they are consistent with the proposed mesocircuit model reviewed above. While the precise mechanism underlying this patient's improved behavioral responsiveness with central thalamic DBS is unknown, it is likely that DBS served to partially reverse the markedly depressed cerebral global metabolism earlier measured in this patient using fluorodeoxyglucose position emission tomography (FDG-PET)[46] and also seen in other patients in minimally conscious state.[47] The depressed cerebral metabolism seen in minimally conscious state likely reflects volume loss of neurons, deafferentation of remaining neurons, and neuronal functional impairments. All of these mechanisms may result in low firing rates of neurons in the neocortex, thalamus, and striatum. The mesocircuit model in **Figure 2** suggests that direct activation of the central thalamus in patients with such chronically downregulated background synaptic activity may produce excitatory output from central

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thalamic neurons that acts to partially normalize firing rates and possibly firing patterns within the cortico-striatopallidal-thalamocortical system.

SPECULATIONS ON THE IMPORTANCE OF HEART-BRAIN RESEARCH IN FUTURE STUDIES OF RECOVERY OF CONSCIOUSNESS

As this conference is focused on the heart-brain interface, it is appropriate to consider the relevance of heart-brain research to the general set of problems reviewed above. In fact, the linkage is quite natural, and classical physiologic psychology research has shown that cerebral arousal regulation is associated with patterned modulation of cardiac rhythm and autonomic function linked to the behavioral state.[48,49] Among the most relevant observations are demonstrations that sustained focused attention is associated with several stereotyped cardiac and autonomic changes, including anticipatory bradycardia,[50,51] pupillary dilatation,[52] and others (eg, galvanic skin response). Neurologic cases have shown that such couplings of effort to reflex bradycardia, pupillary dilatation, and other autonomic markers are altered by focal cerebral lesions in the right frontal lobe[53] and left anterior cingulate cortex.[54]

In the single-subject central thalamic DBS study reviewed above,[43] there were several unpublished observations that are potentially relevant to these mechanisms. During initial bedside testing of the individual DBS electrode contacts in first 2 postoperative days, electrical stimulation above threshold voltages associated with visible arousal response (for details, see supplementary material in Schiff et al[43]) consistently produced marked changes in heart rate and audible modulations of heart rhythm during interactions with the patient. Notably, the patient's basal heart rate rose from a stable level of approximately 50 to 55 beats per minute to approximately 70 to 75 beats per minute—a nearly 50% increase. While increases in blood pressure and heart rate typically accompany arousal, the heart rate change observed here may reflect a marked change in cerebral metabolic rates. Earlier quantitative FDG-PET imaging in this patient revealed a global metabolic rate across the brain of approximately half the normal level.[46] Considering that the brain consumes approximately 23% of the cardiac output,[55] the increased heart rate observed in this setting may reflect an increase in demand in cardiac output, possibly as much as 100%. At the same time that these changes occurred, there was an audible cardiac deceleration noted when the patient was attentionally engaged by the examiner (this occurred without scoreable variation in most of the quantitative neurobehavioral metrics; see supplementary material in Schiff et al[43]). Of note, although the patient had suffered a complex severe brain injury, the right ventral frontal lobe showed the largest structural lesion[46]; injuries to the right hemisphere are associated with loss of such anticipatory changes in heart rate during attentional task performance.[53]

These anecdotal observations suggest that future studies that include measures to track patterns of heart rate variation during recovery of consciousness might provide an indirect index of increasing brain demand for allocation of cardiac output or emergent neural control of mechanisms linking cardiovascular response to attentive behavior. Ongoing coupling of electroencephalographic measures to autonomic and basal cardiac rhythms may be particularly interesting to examine during social interactions,[56] as it is likely that behavioral responsiveness is linked to social stimuli. Emotional reactivity has been proposed as an essential component of arousal per se,[49] and although not formally studied in the DBS trial reviewed above, emotional reengagement seems to be a clear concomitant of the collection of gestural and verbal behavioral improvements operationally tracked using quantitative behavioral scales. Beyond tracking heart-brain interactions as an index of brain recovery, it is possible that the integrity of heart-brain interactions may also be a target for optimization in support of recovery of consciousness after nonprogressive brain injury. Moreover, studies of optimization of cardiac function in severely brain-injured patients may provide insight into the recovery process as well.

Acknowledgments

The author gratefully acknowledges the support of the Charles A. Dana Foundation, the National Institute of Neurological Disorders and Stroke, the National Institute of Child Health and Human Development, and IntElect Medical, Inc.

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