Ann. N.Y. Acad. Sci. ISSN 0077-8923

ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Issue: *Brain Stimulation in Neurology and Psychiatry*

Moving toward a generalizable application of central thalamic deep brain stimulation for support of forebrain arousal regulation in the severely injured brain

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This review considers the challenges ahead for developing a generalizable strategy for the use of central thalamic deep brain stimulation (CT/DBS) to support arousal regulation mechanisms in the severely injured brain. Historical efforts to apply CT/DBS to patients with severe brain injuries and a proof-of-concept result from a single-subject study are discussed. Circuit and cellular mechanisms underlying the recovery of consciousness are considered for their relevance to the application of CT/DBS, to improve consciousness and cognition in nonprogressive brain injuries. Finally, directions for development, and testing of generalizable criteria for CT/DBS are suggested, which aim to identify neuronal substrates and behavioral profiles that may optimally benefit from support of arousal regulation mechanisms.

Keywords: mesocircuit; microcircuit; medium spiny neuron; consciousness; intralaminar thalamus

Overview

This paper focuses on the potential role for central thalamic deep brain stimulation (CT/DBS) in facilitating recovery of consciousness and cognition after severe brain injuries. Beginning with an overview of historical antecedents and a detailed review of an initial proof-of-concept study, CT/DBS is discussed in the context of proposed circuit and cellular mechanisms underlying recovery of consciousness after severe brain injury. These considerations are then used to frame what can be anticipated as the natural next steps necessary to move toward developing a generalizable set of selection criteria for applications of CT/DBS.

Historical precedents

Several clinical investigations, spanning the late 1960s to the late 1980s, began to explore electrical stimulation of the tegmental midbrain, posterior intralaminar nuclei–centromedian parafasicularis complex, and globus pallidus interna for restoration of arousal and consciousness in chronically unconscious patients.[1–7] Most of the patients evaluated fulfilled the diagnostic criteria for vegetative state (VS) following severe traumatic or anoxic brain injuries. Behavioral arousal accompanied all reported instances of electrical stimulation in these studies, typically eye opening, changes in cardiopulmonary function, and, in some reports, observations of fragmentary movements. None of these studies provided formal behavioral assessments to link DBS to any sustained clinical improvements. In a multicenter study involving investigators in France, Japan, and the United States, DBS in the posterior intralaminar thalamus and cervical spinal cord applied to a group of ∼50 patients in the vegetative state resulted in no evidence of DBS-related benefit.[4–6] Recently, Yamamoto *et al.*[8] presented data from a large group of patients (∼100) who did not receive DBS treatments but were evaluated at the time (in the 1980s) for one arm of this clinical trial; comparing these patients and the DBS treatment group, they claimed to identify an overall difference in outcome (i.e., none of the untreated patients recovered from vegetative state), demonstrating the efficacy of DBS.

doi: 10.1111/j.1749-6632.2012.06712.x

Ann. N.Y. Acad. Sci. 1265 (2012) 56–68

There are two problems with drawing an inference of effect in these earlier studies. On the one hand, all of the patients treated with DBS reported by Yamamoto *et al.*[8] received their electrode implantations well within the known time frames for spontaneous recovery from VS and minimally conscious state (MCS) (all prior to six months after injury). Based on the MultiSociety Task Force (MSTF)[9] study, including data from 434 adults in VS, patients remaining in VS three months after traumatic brain injury showed a 35% rate of recovery of consciousness at one year; in addition, 16% of VS patients recovered independent function at one year. Both sets of outcomes are significantly better than those achieved in any of the DBS-treated VS cases reported or those in the proposed *post hoc* untreated control group (in the study by Yamamoto *et al.*). Moreover, even considering more chronically impaired patients, based on the MSTF data approximately 20% of patients remaining in VS after traumatic brain injury at 6 months recover consciousness, at least at the level of MCS,[10] and ∼25% of these VS patients reach independence after one year. The *post hoc* nonimplanted control group, introduced 20 years after the original study by Yamamoto *et al.*,[8] showed no examples of further recovery in any of the VS patients, suggesting that a significant sampling bias existed in the inclusion of patients—three to six months after injury for implantation, and thus an inappropriateness of using this population as a control group for the VS patients receiving DBS. A significant problem, however, is that the group of patients reported by Yamamoto *et al.*,[8] to have made the most considerable gains from DBS, were earlier reclassified by the investigators as fulfilling clinical criteria for MCS.[11] This is a major confound, as the majority (>80%) of patients remaining in MCS at three to six months after injury will emerge spontaneously,[12,13] with some demonstrating no disability, as measured by the Disability Rating Scale. Carrying out a controlled study to account for this baseline recovery would be daunting and well beyond the methods employed in the these early clinical trials; the recent demonstration of effect of amantadine on VS and MCS patients within this time frame indicates the sufficient size of sampled patient and control populations and the data collection methods needed to establish a link to any intervention at this early stage of recovery.[14]

Finally, several recent studies provide clear evidence that some patients remaining in VS or MCS for at least one year continue to have spontaneous recovery. A prospective study of 50 VS patients with anoxic, traumatic, and hemorrhagic vascular injuries showed that 20% of them spontaneously recovered responsiveness after one year.[15] Recent studies have also shown that (1) more than half of the surviving patients who remain in MCS at one year emerged from MCS over a two to five year time period after injury,[16] and that (2) in a large study (∼400 patients) of initially VS or MCS patients, cognitive improvements continue over two to five years and include a significant percentage of good outcomes, including independent function (21%) and vocational readiness (∼20%).[17] Thus, in light of these statistics, no inference about the efficacy of DBS can be drawn from these earlier studies, which did not link DBS to measured behavioral changes. Importantly, the available data, which include prospective cohort studies, indicate that carefully controlled clinical trials and reporting requirements are essential when proposing a highly invasive experimental intervention such as CT/DBS. This is particularly important for structurally brain-injured patients, so that the scientific foundations can be further developed and adverse event profiles can be carefully and systematically collated.[18]

Proof-of-concept study: measurements and observations

However, as noted previously, several prior studies have employed deep brain stimulation methods to severely brain injured patients (reviewed in Refs. 19 and 20), these studies neither provide evidence for statistical linkage of effects of DBS to changes in measured behavior, nor mechanism-based guidance on the development of such an application. Findings from a single-subject study of CT/DBS provided the first evidence that some severely brain-injured patients in MCS may benefit from central thalamic DBS.[21] The study reported the results of CT/DBS in a 38-year-old man who had remained in MCS for six years following a severe traumatic brain injury. The patient had sustained a severe closed head injury that included bilateral subdural hemorrhages, a right frontal lobe contusion, and an initial clinical rating of 3 on the Glasgow Coma Scale. The patient remained in VS for ∼three months after injury and initially

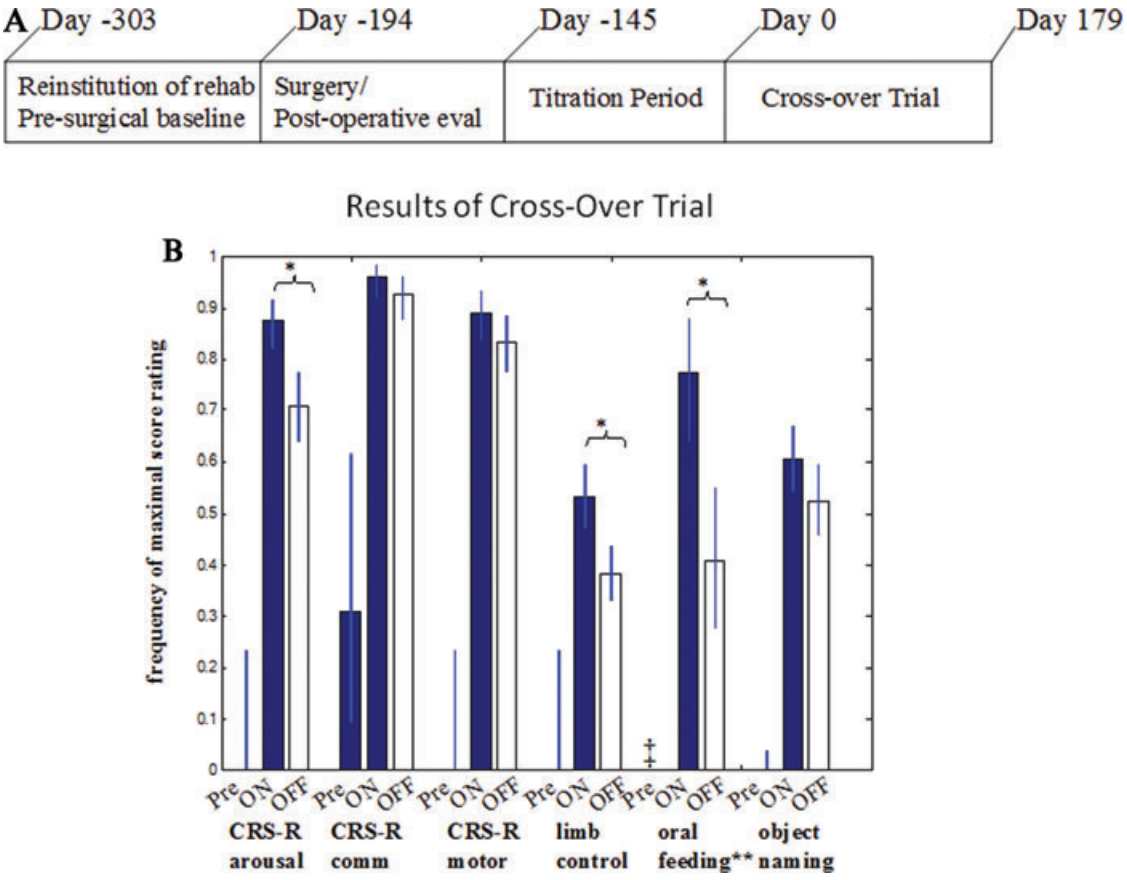

Figure 1. Single-subject study of central thalamic DBS in the minimally conscious state. (A) Study timeline. (B) Comparison of presurgical baselines and DBS ON and DBS OFF periods during a six-month cross over trial of central thalamic DBS in a patient with severe traumatic brain injury (see text). Figure elements adapted from Ref. 21, with permission.

demonstrated nonreflexive responsive behaviors to sensory stimulation, consistent with MCS (see Ref. 10). Further recovery past MCS did not occur over the ensuing four years, and at the time of enrollment in the clinical trial the patient showed inconsistent command-following, using eye movements as their highest level of behavior, with generation of saccadic eye movements in response to commands, indicating answers by direction of eye movement at ∼30% accuracy when asked simple situational questions. At the time of enrollment in the DBS study, a four-month quantitative behavioral assessment and ongoing rehabilitation therapies began, which demonstrated that no intervening change in behavioral ratings had occurred over prior four-year period, or during the months of newly instituted rehabilitation upon trial enrollment. CT/DBS electrodes were placed bilaterally in the central thalami, targeting the central lateral nucleus of each hemisphere. A two-month period followed, with the electrodes remaining OFF to reassess the patient's postsurgical behavioral baseline, which revealed no behavioral changes associated with the placement of the electrodes. The time-frame of two months OFF stimulation postsurgery reflected a control for known gene expression effects observed following electrode placements for 14–30 days.[22,23] A five-month titration phase began after this two-month OFF period, with testing of tolerance to different DBS parameters and duration of stimulation. Following the titration period, a six-month double-blind alternating crossover study began, with data collection of preselected (prior to surgery) primary outcome measures and secondary outcome measures developed during the five-month titration period (see Fig. 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. Figure 1B organizes the results of a six-month double-blind alternating crossover study. As seen, all six outcome measures demonstrated significantly improvement, comparing the prestimulation baselines with either ON and OFF periods of the cross over study. With the exception of the oral feeding scale, all measures specifically captured cognitively mediated behaviors, including identifying and distinguishing simultaneously presented items (for example, working memory and sustained attention), expressed verbal fluency and semantic retrieval, controlled sensorimotor integration, and communication.[21] The marked change in level of function, from prestimulation to OFF DBS measurements at the start of the cross over phase of the trial, reflected the overall effect of five months of exposure to DBS during the titration phase. This can be directly compared with a flat baseline of no change, compared with the starting point of data collection for these prior to the ∼six months of rehabilitation efforts alone before the start of the titration period.[21] Three additional secondary behavioral scales developed during the five-month titration period, when new behaviors linked to DBS were noted, also showed significant difference from prestimulation baselines (see supplementary material in Ref. 21). Three of these measures (marked in Fig. 1B with an asterisk) showed a statistically significant dependence on CT/DBS during the cross over trial. The highest level score for the CRS-R–arousal subscale (one of the primary measures) was achieved for showing no more than 3 nonresponses to an examiner's questions across an assessment period. The observed improvement in this score reflected an increase in cognitively mediated behaviors that require elements of executive function. Consistent ceiling performance on the CRS-R scale only appeared with exposure to DBS, and this measure remained strongly modulated during the cross over trial. In addition to the effect on the CRS-R–arousal subscale, strong ON versus OFF modulation occurred for both the functional limb control measure, which quantified purposeful movements (e.g., combing, drinking), and an oral-feeding scale (see supplementary material in Ref. 21). In addition to providing the only statistically rigorous evidence for a CT/DBS effect on cognitive function, this report[21] emanated from a larger study that, importantly, focused on a different patient population[24] not comparable with patients evaluated in the earlier studies discussed previously; the patient discussed previously, for example, began the study near the ceiling of the CSR-R, with an average score of 19–20, reflecting intermittent communication and consistent command-following.[21] This behavioral profile is the boundary of emergence from MCS,[10] and is distinct from the reported behavioral profiles in other studies.

In addition to providing clear statistical evidence for blocked ON-versus-OFF effects of CT/DBS in the previous subject, detailed subsequent analyses have allowed temporal aspects of OFF and ON effects to be examined. Smith *et al.*[25] developed a Bayesian state-space model that allows for trial-to-trial variability to be assessed, as well as a full assessment of multinomial behavioral data, such as obtained from the CRS-R measurements and the supplementary oral-feeding scale. Application of the state-space analysis demonstrated an intermediate time course for declines in the patient's oral feeding ability during two of the DBS OFF transitions that occurred after ∼two weeks of OFF DBS. During the last two weeks of the first and third DBS OFF periods, the patient showed degradation the ability to chew and swallow food, with periods of inability to swallow food placed in the mouth or remaining unarousable at meal times. This decline recapitulated the subject's baseline status prior to DBS exposure, during which the patient had required feedings via a percutaneous gastrotomy tube over the six-year postinjury course (see supplementary material in Ref. 21). These observations provide evidence for both dynamic "wash-out" and "build-up" processes associated with CT/DBS. The presence of slow variations in CT/DBS effects is important and provides a context for some observations made in the immediate postoperative period that did not correlate with changes at that time in preselected outcome measures. Among the more interesting observations were significant increases in the frequency of maximal limb control scale (see supplementary material in Ref. 21) and a shift in resting basal heart rate and reflex bradycardia with direction of attention.[26] The variations in temporal effects of CT/DBS, however, underscore the problems of using a cross over trial design without the availability of dense behavioral sampling over very long time periods.

Importantly, the generalizability of these findings from a single-subject remains unknown. Of three patients studied under the original trial design,[24] only the one subject reported (in Ref. 21) demonstrated significant effects in the double-blind six-month cross over period. What is clear from the published literature reviewed previously is that simply applying CT/DBS to the severely injured brain, broadly across etiologies of VS/MCS and arbitrary patterns of structural injury, will, on average, have no meaningful, or even detectable, effect. Thus, attention is drawn to the careful consideration of the path to finding generalizable selection criteria for CT/DBS in the injured brain.

Considering the available published literature in the aggregate, two factors appear to be essential for developing future criteria for generalizability: (1) evidence of sufficiently preserved internal dynamical structure in the brain to support measureable elements of cognitively mediated behavior, and (2) preservation of recruitable neuronal populations across anterior forebrain structures connected to the central thalamus and linked to the process of arousal regulation. On the one hand, 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 qualifying for classification at the boundary of MCS (reviewed in Ref. 20), despite claims to the contrary (Yamamoto *et al.*[8]). Moreover, even behavioral evidence of command-following or higher-integrative functions does not guarantee a statistically significant or clinically meaningful response to CT/DBS.[24]

Mesocircuit, microcircuit, and cellular level mechanisms underpinning the rationale for CT/DBS in the severely injured brain

To obtain insights into possible generalizable mechanisms underlying a response to CT/DBS, we first consider general mechanisms at the "circuit" and cellular level underlying recovery of consciousness after severe brain injury. Figure 2 organizes observations supporting the role of an anterior forebrain mesocircuit in the recovery of consciousness, and its effect on cortical microcircuits and neuronal cell types. Alterations of function across this mesocircuit are proposed as a common mechanism arising across severe brain injuries, as a direct consequence of global decreases of excitatory neurotransmission resulting from multifocal neuronal loss and disconnection.[27–29] Positioned at the center of this mesocircuit model, the central thalamus is particularly vulnerable to deafferentation and subsequent disfacilitation[30] of neurons in the setting of severe injuries.[31] The nuclei of the central thalamus are placed to have a considerable effect on function across the anterior forebrain (reviewed in Refs. 20 and 32). These neurons exhibit parallel changes in spontaneous and evoked firing patterns, increasing their responsiveness during the transition to wakefulness and in the awake state.[33] The central lateral-paracentral neurons are tonically facilitated in both wakeful and REM states, and receive inputs from the nucleus cuneiformis and central tegmental field of the mesencephalic reticular formation.[34] In addition, these central thalamic cell populations receive input from all brainstem "arousal" system components, as well as the basal forebrain (reviewed in Refs. 35 and 36). The primary result of down-regulation of central thalamic neuronal activity may be to effectively produce a broad decrease in background synaptic activity and excitatory neurotransmission across the forebrain, as thalamocortical projections are demonstrated to produce disproportionately strong activation of local cortical populations.[37] 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. Refs. 38 and 39)

The basic anatomical relationships and functional signs represented in the mesocircuit considerations presented in Figure 2 follow the standard Albin-Young-Penny[40] and Delong[41] model of cortico–striatopallidal–thalamocortical loops. This model has been criticized for emphasizing "one-dimensional push-pull" dynamics and a strong hierarchical feed-foward sequential processing model.[42] Whereas the Albin/Delong model undoubtedly fails to capture dynamics intrinsic to these complex neuronal networks, feed-forward architectures are increasingly realized as powerful computing structures,[43] and physiological measurements provide support that central thalamus and frontal cortical regions may participate in such network computations.[44] However, this familiar schematic model may have its most direct application to the brain with severe, multifocal injuries in which, as noted

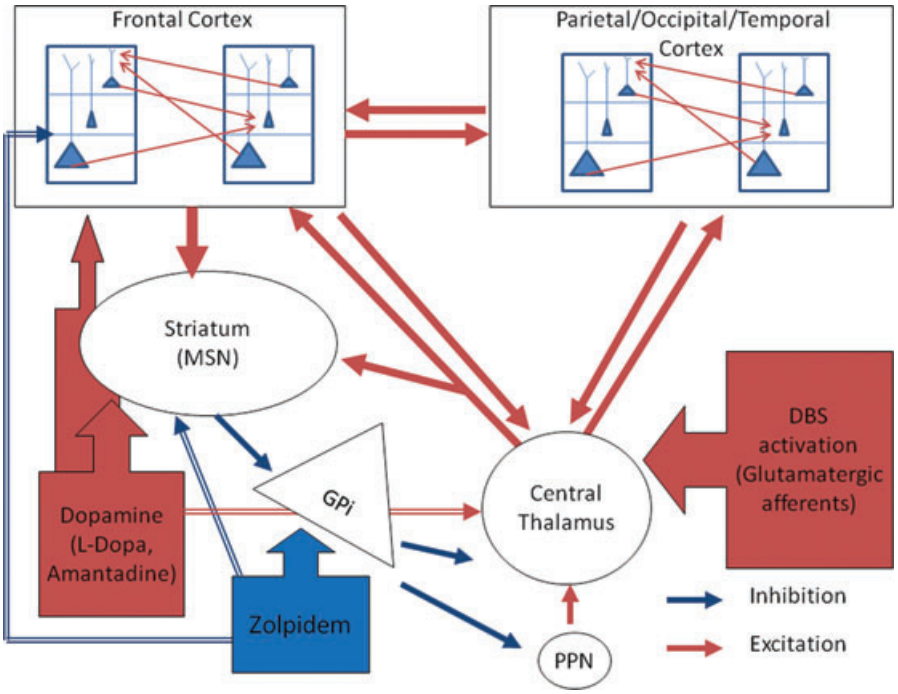

Figure 2. Mesocircuit model placing CT/DBS in the context of mechanisms underlying spontaneous and medication induced recovery of consciousness. A mesocircuit model organizing mechanisms underlying recovery of consciousness after severe brain injury.[28] Diffuse disfacilitation[30] across frontal cortical, central thalamic, and striatal neurons arises from severe structural brain injuries. In particular, reduction of thalamocortical and thalamostriatal outflow following deafferentation and loss of neurons in central thalamus[31] withdraws important afferent drive to the medium spiny neurons (MSNs) of striatum that may then fail to reach firing threshold because of their requirement for high levels of synaptic background activity.[45] Loss of active inhibition from the striatum allows neurons of the globus pallidus interna (GPi) to tonically fire and provide an 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.[78] Amantadine,[14] L-DOPA,[57,58] and zolpidem[60] may reverse these conditions of marked down-regulation of anterior forebrain activity across frontal cortices, striatum, and central thalamus acting at different locations with the mesocircuit.[28] Collectively, restoration of thalamocortical and thalamostriatal outflow will depolarize neocortical neurons and facilitate long-range cortico-cortical, corticothalamic, and corticostriatal outflow. CT/DBS can be considered as a final common pathway aggregating these effects and partial remediating the effects of strong deafferentation of these neurons in severe brain injuries.

previously, widespread deafferentation arises secondary either to disruption of white matter connections (as in diffuse axonal injury) or multifocal neuronal death (as, for example, in ischemic-hypoxic injuries, encephalitis, or multifocal infarction following vasospasm). Considered in the context of the limiting case of significantly degraded long-range connections associated with severe brain injuries, a marked withdrawal of excitation across cerebral structures can be expected, as most long-range projections in the brain are excitatory, though they drive both inhibitory and excitatory neuronal populations.[39] The most significant circuit level consequence of such a broad withdrawal of excitatory input across the forebrain may arise within the striatum in the medium spiny neurons (MSN), the output cell of the striatum.[45] MSNs have high threshold UP states that keeps them below their firing threshold without high levels of spontaneous background synaptic activity arising from excitatory corticostriatal and thalamostriatal inputs.[45] Thus, MSN output could be shut down by withdrawal of direct excitatory striatal projections from neurons within the central thalamus, namely, the central lateral and parafasicularis nuclei,[46,47] and through down-regulation of the frontocortical regions that provide the main corticostriatal input.[48,49] MSNs have a key role in maintaining activity in the anterior forebrain

through their inhibitory projections to the globus pallidus interna, which in turn provides powerful inhibition of pallido-recipient regions of the central thalamus.[50]

The projections from the central thalamus heavily innervate the prefrontal and frontal cortex—particularly mesial frontal cortices of supplementary motor area and anterior cingulate[51] that provide broad, feed-forward activating projections to the prefrontal and frontal cortices[52] and have, in some instances, a joint thalamostriatal projection back to the MSNs.[53] The anterior cingulate cortex likely plays an essential role as it receives strong innervation from the central lateral nucleus and provides very diffuse regulatory input across large territories of the rostral striatum.[46] Collectively, the neurons within the mesial frontal cortices, rostral striatum, and central thalamus form the core of a forebrain arousal regulation system. The driving of frontal cortical regions by CT/DBS is supported by known functional anatomical relationships of the central thalamic projections to frontal cortex (Fig. 3B, Ref. 54). Gating of overall background firing rates of cortex and thalamus is likely a direct effect of activity in the distributed forebrain arousal regulation systems, including central thalamus, mesial frontal, anterior cingulate cortex, supplementary motor area, and subgenual cingulate cortex (see Ref. 55). Recent demonstrations using optogenetic techniques show that direct increases of thalamic firing rates can mimic endogeneous changes in overall activity, changes that are not principally driven by afferent input but rather reflect changes within the corticothalamic systems.[56] A direct physiological correlate of activation across the anterior forebrain in the CT/DBS single-subject study is demonstrated by patterns of cortical-evoked potentials this subject's EEG (Fig 3B and supplementary material in Ref. 21) when generated from a contact used in the effective stimulation protocol.

Several pharmacological manipulations known to be effective in some severely brain-injured patients strongly modulate activity across the anterior forebrain mesocircuit. Amantadine, a mixed dopaminergic agonist and NMDA antagonist, is the first drug shown to be generally effective across the class of disorders of consciousness following severe traumatic brain injury.[14] Amantadine likely facilitates MSN outflow, as well as direct cortical activation. L-DOPA may have a similar effect on the striatum, but it also has a direct effect on the central thalamus.[57,58] Mair and Hembrook[59] carried out a series of experiments using local pharmacological manipulations within the central thalamus and established evidence of inverted U-type modulations of behavioral performance consistent with the Yerkes–Dodson Law with orexin and an inverse GABA agonist (FG-7142), supporting a primary effect on arousal regulation.[32,59] Zolpidem, an alpha 1 subtype selective positive allosteric modulator of the GABA-A receptor, produces paradoxical behavioral improvements in some severely brain-injured patients.[60] Binding of zolpidem to the globus pallidus interna and neocortex within the anterior forebrain mesocircuit has been proposed to release pallidal inhibition of the pallido-recipient thalamus and release of thalamocortical outflow, as its underlying paradoxical effect.[27–29]

Although the striatal MSN cell type may play a critical role in recovery of consciousness in the regime of marked deafferentation and very low global background synaptic activity, it is the functional variation of distributed neocortical neurons that likely plays the key role across the entire spectrum of clinical outcomes following severe brain injuries. The range and subtlety of normal corticocortical and corticothalamic activity is impressively large[39,61,62] and allows for many potential functional variations after multifocal cerebral injuries, even if large-scale mesocircuit-level dynamics are grossly restored. In intact cerebral systems, massive corticothalamic excitation, present in wakeful states,[39,61,62] plays the dominant role in driving thalamic and striatal neurons of the anterior forebrain mesocircuit. Recent detailed neurophysiological recordings in the songbird make this point clearly, demonstrating that neurons in the vocal portion of pallido-recipient thalamus have baseline firing rates of ~100 Hz and phasic activations near ~400 Hz that are principally driven by corticothalamic inputs.[50] These same studies also demonstrate that pallidal inhibition is quite strong and capable of suppressing thalamic firing completely, but only briefly, in the context of the normal, awake state of massive background synaptic activity. The pathological conditions present in the severely injured brain create a very different scenario in which deafferentation may be so severe that central thalamic neurons are silent (for example, as observed for the majority of sampled neurons during the CT/DBS

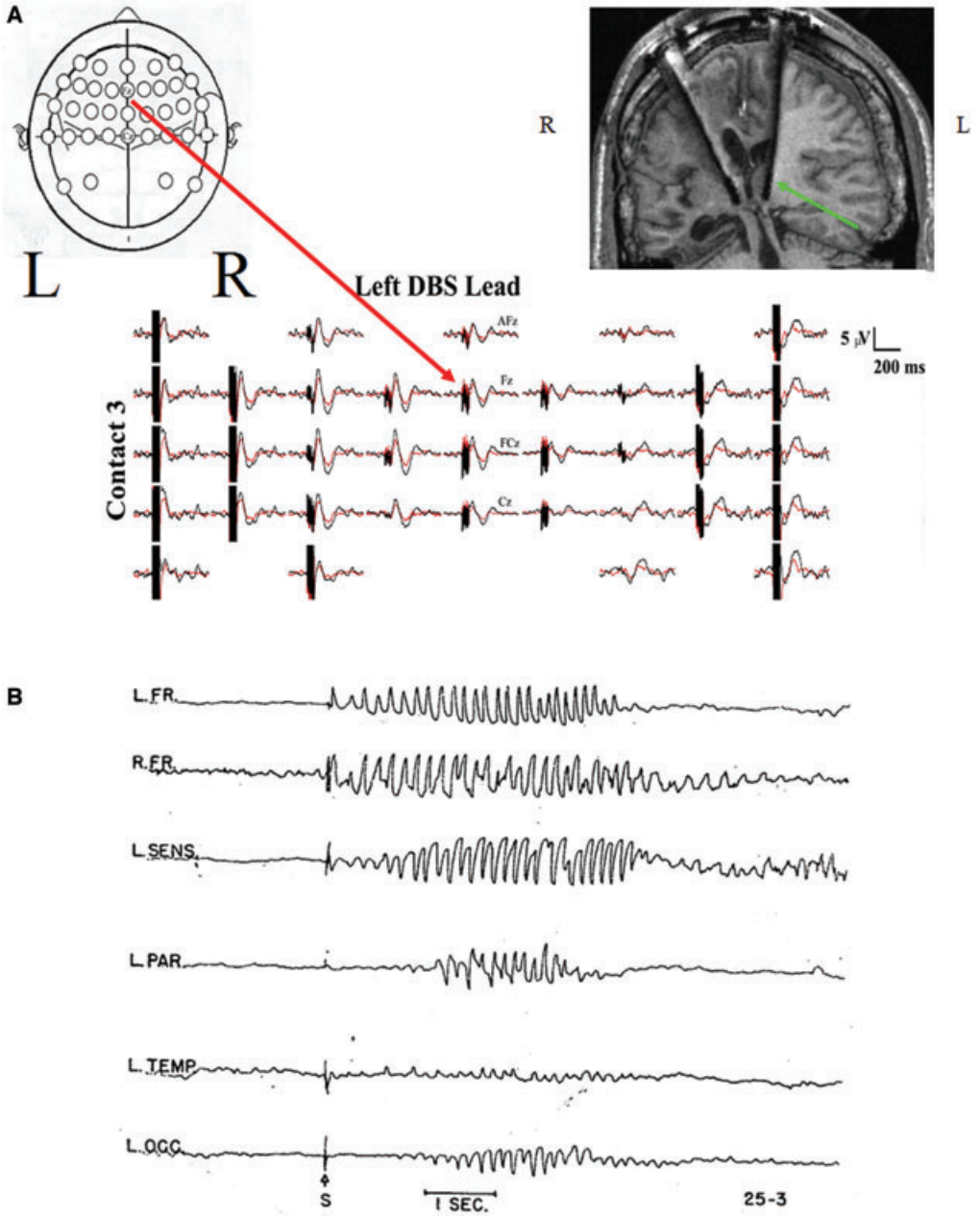

Figure 3. Central thalamic DBS evoked potentials in the minimally conscious state. (A) Figure shows cortical evoked potentials recorded from left DBS electrode in single-subject study of Figure 1 (Ref. 21). Averaged waveforms of the evoked potentials are shown; a 250-ms baseline is shown prior to the 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 following the offset of stimulation. Two waveforms are shown for each recording site, 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 inset shows electrode lead placements within central thalamus of patient's right (R) and left (L) hemispheres displayed in T1 weighted MRI coronal image. Figure elements adapted from Ref. 21, with permission. (B) Image shows classical pattern of bihemispheric EEG activation with spindle bursts seen in six different cortical areas in response to a single shock in the centromedian-parafasicularis nucleus of the cat under pentobarbital anesthesia; modified from Jasper.[54]

placement in the patient discussed previously[21] and two other patients in this study[24]).

Targeting high frequency DBS firing rates with an aim to facilitate restoration of the normal network and cellular integrative processes may be a common underlying mechanism across applications of DBS. Montgomery[42] has proposed that high frequency ~140 Hz oscillations between the motor cortex and ventral lateral thalamus provide a fundamental base frequency for more complex and combinatorial oscillatory activity patterns arising across the motor systems when enacting behaviors. Effective DBS frequencies for modulation of Parkinson's disease are near this frequency and proposed to support the normalization of this base oscillation through both circuit resonance mechanisms and addition of background spiking activity within the distributed cortico–striatopallidal–thalamocortical loop systems.[42,63] This appealing hypothesis has strong conceptual links to the possible mechanisms underlying the response to CT/DBS for chronically impaired consciousness after severe brain injuries.

The effect of CT/DBS on the canonical cortical microcircuit and its feedback and feed-forward connectivity has been proposed to play an essential role in observed behavioral facilitation.[20,64,66] Specifically, the central thalamus appears to play a key role in supporting long-range excitatory cortico-cortical activity linked to cognitive processes.[66] High-frequency CT/DBS stimulation may play a specific role in facilitating these cortico-cortical interactions by affecting integration of synaptic activity within the dendritic arbor of Layer II-III and Layer V cortical pyramid cells.[66–69] These neurons have high-frequency thresholds (100 Hz and 130 Hz, respectively) for the elicitation of back-propagating and dendritic action potentials associated with release of growth factors and synaptic modification.[69] In the CT/DBS subject reported in Ref. 21, stimulation frequencies up to 250 Hz appeared to have similar effects when contact geometry and voltage were held constant during both bedside testing (up to 250 Hz) and in extended multiday and week testing (70 Hz, 100 Hz, 130 Hz) (see supplementary material in Ref. 21). The selection of 100 Hz as the fixed frequency for testing combined evidence from empirical behavioral testing, considerations of preserving battery life, and an inference that higher frequency stimulation would be more effective in driving neocortical neurons based on independent physiological measurements of increased cortical gene expression with 100 Hz compared with 50 Hz stimulation of the rat central lateral nucleus.[70]

Finally, and perhaps most importantly, CT/DBS has been demonstrated to support endogeneous arousal regulation processes within normal wakeful states that aid initiation, maintenance, and effort adjustments underlying ongoing behavior.[59,70] The most compelling evidence to date of the selective contribution of CT/DBS to arousal regulation, as framed operationally in this way, comes from experiments in rodents. Mair and Hembrook[59] demonstrated that phasic stimulation of the central lateral nucleus in rodents produced behavioral improvements in a delayed match-to-position task when stimulation occurred during memory delays and retrieval periods, but not other periods of the trained behavior. Importantly, these effects did not rely on time into the task *per se,* as stretching of delay period or retrieval periods retained facilitatory effects of initial stimulation of equal time duration, indicating that the CT/DBS, in fact, supported specific neuronal processing. While clinical applications that employ continuous stimulation clearly aggregate effects over such specific aspects of behaviors, the observation is salient for considering the matching of the CT/DBS technique to patients with nonprogressive brain injuries, in terms of preferable neuronal substrates, behavioral profiles, and goals of the intervention.

Summary of rationale

Table 1 summarizes the points elaborated previously. The range of applications for CT/DBS as a clinical tool will also likely form an inverted "U," beginning with patients such as the single-subject reviewed previously, in whom broad down-regulation of metabolism indexes low background synaptic activity and results in chronically impaired integrative function.[71] On the other limb of the "U" curve are patients in whom consideration of risk/benefit would be proportionate to comparable uses of DBS in clinical neuroscience.[72] At present, the functional range and physiological profile of such patients is undefined. Conceptually appropriate subjects would be those for whom specific support of arousal regulation systems in aid of facilitating executive functions, such as sustained attention,[25,65,73] working memory, or memory retrieval,[59,70] would allow passing a threshold of clinically meaningful

Table 1. Mesocircuit, microcircuit, and cellular-level mechanisms underpinning the rationale of CT/DBS in the severely injured brain

1. Induce reversal of abnormal "circuit" level dynamics resulting from broadly reduced background synaptic activity across corticothalamic and cortico-striatopallidal-thalamocortical systems (cf. Refs. 21–21)
2. Produce a shift of level of synaptic input to severely deafferented neurons across neocortex, striatum, and other components of thalamus
   a. Alteration of quality of neuronal firing patterns of neocortical pyramidal cells that show marked sensitivity to small differences in level of depolarization of neuronal membrane; engage local network activity generated changes in neuronal responsiveness across wide cortical territories (cf. Refs. 39, 61, and 62)
   b. Restoration of sufficient excitatory drive to striatal medium spiny neurons to bring membrane potentials to a sufficiently depolarized level to allow firing of the neurons (cf. Ref. 45)
3. Produce changes within local neocortical microcircuits facilitating long-range cortico-cortical processing (cf. Refs. 64 and 66)
4. Most critically, exert a behaviorally specific effect on arousal regulation mechanisms by providing selective support to neuronal populations engaged in adaptive allocation of cognitive resources, including attentive behavior, and working memory during ongoing behaviors (cf. Refs. 59 and 70)

effect.[20,64] The first two mechanisms listed in Table 1 would likely play a greater role in patients with very severe structural injuries, as in the patient in Ref. 21. If CT/DBS were effective in subjects in whom baseline patterns of activity across the forebrain are relatively normal, more subtle changes related to patterns of neuronal interaction within and across local microcircuits and influences on global behavioral variables related to executive function would be anticipated as seen in experimental studies of normal animals.[20,70]

Moving toward generalizable selection criteria for CT/DBS

Observations of late spontaneous recovery occurring over years following severe brain injury have now been established in several studies, not just in outlier cases (e.g., see Ref. 74) but as a phenomenon present, on average, across large patient populations with mixed etiologies of injury.[15–17] These findings suggest that while many neurons may survive severe structural brain injury, their functional activity may remain markedly down-regulated for long periods of time. Thus, living neurons in the severely injured brain may chronically function on the low end of their effective dynamic range as a direct consequence of deafferentation produced by structural brain injuries. The most likely primary mechanism underlying this dynamical deficit, as outlined previously, is the broad withdrawal of excitatory synapses from long-range cortico-cortical and thalamocortical connections, and a consequently reduced global means of excitatory neurotransmission. Maintenance of these conditions over time may be associated with down-regulation of AMPA receptor cycling[75] and other cellular and synaptic processes, combining to reduce postsynaptic depolarization events in the neurons.[39] Collectively, such mechanisms may result in neurons being held in low frequency firing patterns, reducing the dynamic range of large groups of neurons in the forebrain via large-scale circuit mechanisms that keep these neurons relatively hyperpolarized or effectively switched off as a result of basic connectivity and functional sign properties conferred by their roles in normal brain function, and ultimately producing a broad reduction in background synaptic activity across the anterior forebrain.

Considering that these very general considerations apply broadly to spontaneous recovery, to drug-induced recoveries after brain injury, and to demonstrations of the effect of CT/DBS in clinical and experimental studies, a critical question is when would CT/DBS likely be an effective and an ethically proportionate[76] experimental intervention? The first conclusion is that nonprogressive brain injuries *per se* should be the context for consideration of CT/DBS for support of arousal regulation, as the underlying biological problems at the mesocircuit, microcircuit, and cellular level share more in common than the differences in the etiological mechanisms may provide variance. The strongest inference from the this review is that common circuit mechanisms will play a key role across all variations of severe brain injury, when considering subjects who had normally developed, intact human

brains prior to onset of an ictal event that produced their nonprogressive injuries. But beyond looking broadly across the variations of structural brain injury, the twin considerations of sufficient neuronal substrate and goals of a CT/DBS intervention remain open and quite challenging questions to be addressed in rigorous clinical trials.[24]

Based on this review, it is reasonable to propose that CT/DBS will achieve clinical efficacy in the context when at least two conditions are satisfied: (1) sufficiently large neuronal populations across the anterior forebrain mesocircuit can be recruited into functional states promoting behaviorally significant improvements in cognitive function, and (2) there exists a matching of the specific interventions to opportunities that can be predicted to be within the range of capabilities of an individual subject, i.e., sustained verbal communication or cognitive behaviors in patients with evidence of intermittent or partially retained capacities. Another essential component of the application of CT/DBS is 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. At present, no data guide a strong expectation of such necessary and sufficient conditions. In addition, optimization of the preferred location of stimulation within the central thalamus is another important next step. The central thalamus is a large structure that when intact provides many possible neuronal populations and sets limits of available coverage of these substructures. While ultimately an empirical question, basic considerations from anatomy and physiology in the intact mammalian brain draw close attention to the central lateral intralaminar nucleus and adjacent paralaminar components of the median dorsalis and ventralis anterior/lateralis regions of the central thalamus.[33,34,36] Isolation of a general and optimal CT/DBS target most likely can only be identified with precision in experimental models in intact animals (cf. Refs. 73 and 77). Extreme variations of thalamic connectivity and structural brain injuries in clinical subjects can be expected to limit meaningful refinement or interpretation of an optimal CT/DBS target.

Clearly, demonstration of effective CT/DBS will be the gold standard for any future set of generalizable criteria. There are many leads to follow and as reviewed previously, these experimental and clinical data points suggest that the hard work needed to make further progress will be worth the effort.

Acknowledgments

This paper was initially presented as a lecture at the 91th Annual Meeting for the Association for Research on Nervous and Mental Disease (ARNMD) on November 30, 2012. The support of the NIH-NINDS and NICHD are gratefully acknowledged.

Conflicts of interest

The author is a listed inventor on deep brain stimulation technology patents owned by Cornell University.

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