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Deep Brain Stimulation, Neuroethics, and the Minimally Conscious State

Moving Beyond Proof of Principle

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We briefly review the motivation, ethical framing, and results of a recent single-subject study of central thalamic deep brain stimulation (DBS) in a patient remaining in the chronic minimally conscious state (MCS). In the study, a severely brain-injured human subject showed behavioral improvements in attentive responsiveness, limb control, recovery of oral feeding, and spoken language following central thalamic DBS.[1] These findings are placed into the context of, and contrasted with, prior efforts applying thalamic brain stimulation to patients in the vegetative state (VS). Efforts to develop DBS for recovery of function in the setting of disorders of consciousness must meet several challenges presented by the expected wide variance of underlying brain injuries and need to carefully identify potential goals of therapeutic intervention. Although the study involved only a single subject, the results demonstrate a causal relationship between brain stimulation and cognitive recovery. The generalizability of these findings is completely unknown and the complexity of the problem will require careful and systematic research to move forward.

It is increasingly recognized that patients with very limited behavioral repertoires may have significantly greater cognitive capacities than recognized. The clinical condition termed the *minimally conscious state* operationally characterizes specific observable behaviors that indicate some level of awareness and environmental responsiveness in severely brain-injured patients who cannot reliably communicate.[2]

Several observations suggest that some patients in MCS retain a sufficiently preserved cerebral substrate to warrant consideration of neuropalliative interventions aimed at restoring limited but nonetheless important functional capacities[3]; such observations include evidence of large-scale cerebral network responses in some patients in MCS[4-7] and rare examples of late spontaneous recovery of communication in some patients.[8] It is expected that as neuroimaging techniques evolve it will be possible to better identify patients with greater underlying capacity to restore function. These measurements will naturally raise the scientific question of whether it is possible to achieve greater functional recovery and pose the ethical dilemma of whether such a recovery might lead to greater awareness of one's deficits, future challenges, and attendant emotional consequences.[9]

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RATIONALE

The rationale for DBS in the central thalamus as a potential strategy begins with a consideration of both the underlying functional role that the central thalamus plays in the human brain and its unique vulnerability to multifocal brain injuries. The central thalamus has a role in several mechanisms of impaired forebrain function following severe injuries.[10]

Neurons within the central thalamus (anterior and posterior intralaminar nuclei and the paralaminar portions of related thalamic association nuclei) share

specific anatomical and physiological specializations that support their key role in elementary cognitive functions of sustained attention; working memory; and motor preparation.[11-15] The central thalamus is interposed between brainstem and basal forebrain "arousal systems" that control overall levels of corticothalamic activity and frontal cortical supervisory attentional systems. The latter organizes both goal-directed behavior and adjustments of vigilance level or alertness.[16] The central thalamus is recruited under conditions of cognitive demand, increasing its activity when normal human subjects attempt to maintain behavioral performance in the setting of fatigue, illness, sleep deprivation, or increasing task difficulty.[13,17,18] Several anatomical specializations of the central thalamus help explain its key role in regulation of effort and arousal level during wakefulness. Among them are its broad point-to-point connectivity across wide cerebral cortical areas,[19] strong efference into the frontal corticostriato-pallidal-thalamocortical loop systems,[20,21] and specialized innervation of the cerebral cortex that emphasizes a uniquely modulatory role.[22-25] The broad connectivity and functional role of the central thalamus accounts for the significant impact of lesions restricted to this region[26,27] as well as its unique vulnerability to deafferentation in the setting of nonselective brain injuries such as diffuse axonal injury.[28,29]

These findings can be understood in part as a simple consequence of geometry. The central thalamus has broad, multifocal connections within the forebrain that are positioned to integrate the impact of deafferentation across many different cortical regions and other cerebral structures.

Given the functional role of the central thalamus and its particular vulnerability to multifocal brain injuries, a team of investigators from Weill Cornell Medical College, the JFK Johnson Rehabilitation Institute, and the Cleveland Clinic sought to determine whether central thalamic DBS might be effective in patients in MCS by partially substituting for the top-down regulation of arousal and attention normally provided by mesial frontal cortical regions that operate in conjunction with the brainstem and basal forebrain arousal systems.[1]

SINGLE-SUBJECT STUDY OF DBS IN MCS

In a first subject studied as part of a pilot clinical trial, central thalamic DBS electrodes were implanted in a 38-year-old man who remained in MCS for 6 years following severe traumatic brain injury.[1] The patient had sustained a closed head injury following blunt trauma to the right frontal lobe that produced bilateral subdural hematomas (right > left) with significant mass effect and subfalcine and central herniation (with loss of right pupillary response). The patient had an initial Glasgow Coma Scale score of 3 and remained in a VS until approximately 3 months after injury when the first clear-cut behavioral signs of conscious awareness (ie, visual pursuit and simple command following) were identified, placing the patient in MCS.[2] The subject remained in a comprehensive rehabilitation program more than 2 years following injury but did not emerge from MCS and was subsequently transferred to a skilled nursing facility. The highest level of cognitive responsiveness observed during this time was inconsistent command following using eye movements. On enrollment into the DBS study at more than 6 years postinjury, no improvement in neurobehavioral function was observed based on standardized behavioral assessments conducted over that period.

Bilateral DBS electrodes were surgically implanted in the anterior intralaminar thalamic nuclei targeting the central lateral nucleus and adjacent paralaminar regions of thalamic association nuclei.[1] The **Figure** shows the results of a 6-month double-blind alternating crossover study that demonstrated improved behavioral responsiveness indicated by significant increases in level of arousal, functional limb movements, and oral feeding during periods in which DBS was on as compared with periods in which it was off. The frequency of the highest scores obtained on selected subscales of the JFK Coma Recovery Scale–Revised (CRS-R),[30] the primary outcome measure, are displayed in the Figure. The CRS-R is a standardized neurobehavioral rating scale comprising 6 subscales designed to assess auditory, visual, motor, oromotor/verbal, communication, and arousal functions in patients with disorders of consciousness. Subscale items are organized hierarchically in that the lowest-scoring items represent reflexive activity while the highest-scoring items reflect cognitively mediated behaviors. Psychometric studies of the CRS-R have established adequate reliability, validity, and diagnostic sensitivity/specificity.[30-32] Three secondary outcome measures were also developed to determine the effects of DBS on expressive speech, upper extremity limb control, and swallowing ability.

Comparison of the frequency of the highest scores observed during the crossover trial with the prestimulation baseline period demonstrated behavioral improvements on all 6 measures after exposure to DBS. However, only 3 measures (CRS-R arousal, oral feeding, and limb control ratings) showed statistically significant dependence in on vs off DBS periods. The highly significant comparison of scores obtained during the off DBS condition of the crossover phase with those from the prestimulation baseline period demonstrated a carryover effect of changes attributable to prior DBS exposure from the titration period that began 50 days after surgery.[1] The main effects of DBS modulation for this subject were on response consistency (ie, maximum score on the CRS-R arousal subscale), recovery of swallowing (top score on the oral feeding rating subscale as shown in the Figure), and frequency of functional limb movements (see "Limb Control" measure description in the supplementary material for Schiff et al[1]). The combination of both reproducible and sustained short-term effects of DBS alongside more enduring and slowly accumulating carryover effects suggests that study designs to assess the effects of central thalamic DBS will require careful consideration of multiple time scales.

COMPARISON WITH EARLIER STUDIES

Several prior studies have assessed electrical stimulation of the posterior components of the central thalamus (posterior intralaminar nuclei–centromedian parafascicularis complex), basal ganglia (globus pallidus interna), and midbrain as a method of restoring pat-

terned arousal and consciousness in chronically unconscious patients in prolonged coma or VS (mostly in the VS by current classification methods.)[33]

The most recent large series of subjects was completed in the early 1990s in a group of about 50 patients in VS. Unilateral DBS electrodes placed either in the centromedian thalamus or dorsal columns of the cervical spinal cord failed to demonstrate clinical improvements linked to DBS.[34-36] The majority of the patients in these studies had had traumatic brain injuries, although other etiologies, including anoxic encephalopathy, were included (notably, Terri Schiavo was included in this trial). The majority of patients in this trial were shown to have an acute behavioral arousal response with DBS associated with consistent physiological responses, including desynchronization of the electroencephalogram and increased cerebral metabolic rates measured by positron emission tomography.[37] Two investigative groups involved in the trial reported that a small number of patients with traumatic brain injury showed significant functional improvement, including recovery of independence.[34,35] However, these patients received DBS at 3 to 6 months postinjury, which is well within the window for spontaneous recovery from traumatic VS. Moreover, it has been recently reported by one group that the few patients in their cohort who improved did not meet international diagnostic criteria for VS but had shown evidence of nonreflexive behavior consistent with the MCS, further increasing the likelihood that spontaneous recovery accounted for at least some of the behavioral changes reported. Recent prospective studies of patients in MCS demonstrate that significant spontaneous recovery may occur after 1 year.[38] Thus, it is essential that formal assessment of DBS interventions in patients with disorders of consciousness include careful diagnostic evaluations, structured data collection, and blinding procedures to allow statistical linkage of behavioral changes, if any, to DBS exposure.[16]

Importantly, our approach to studying the effects of DBS is different in that it targets patients in MCS with relatively widely preserved brain structure and clear evidence of interactive behavior, specifically requiring elements of language function (ie, command following, verbalization, or inconsistent communication). Deep brain stimulation in this patient group may improve arousal regulation of functionally connected but inconsistently active cerebral networks that are present in some patients in MCS and are expected to be absent in permanent VS. For patients in MCS, restoration of reliable communication or response initiation and persistence may have functional significance.

SCIENTIFIC OPPORTUNITIES

An important observation in this study was the large difference in behavioral performance noted between the DBS off period (arising from carryover effects of the titration phase) and the 6-month prestimulation baseline period. This observation can be compared with recent rodent studies of continuous unilateral electrical stimulation of the central lateral nucleus using comparable stimulation parameters that also showed carryover effects of DBS.[39]

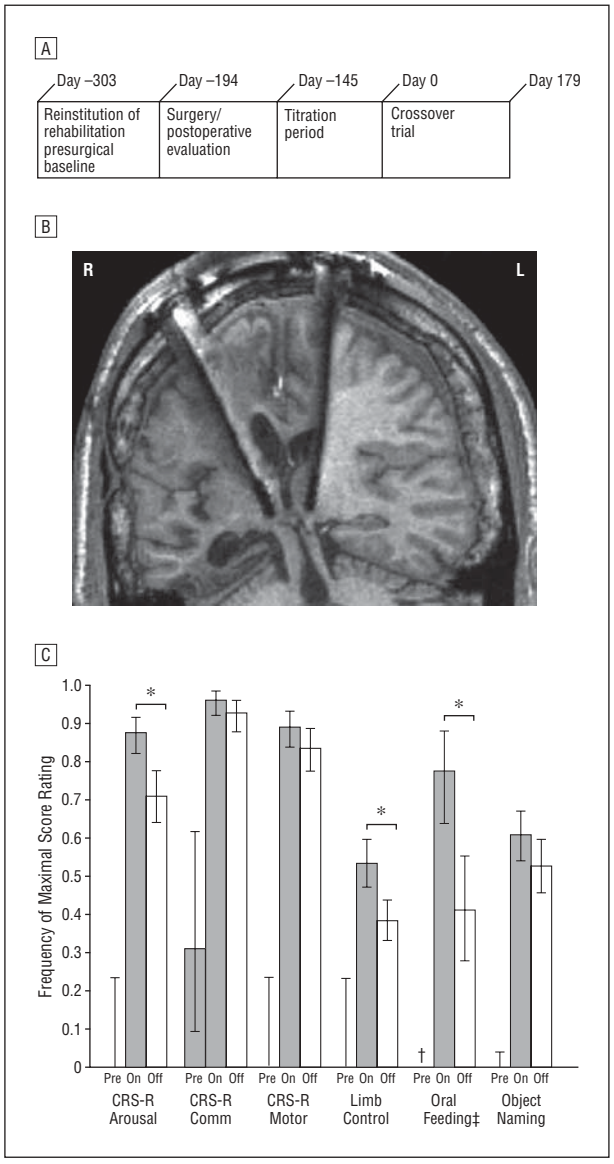

Figure. Study timeline, electrode lead placements, and comparison of presurgical baseline and deep brain stimulation (DBS) on and off periods. A, Study timeline. B, Electrode lead placements in the right (R) and left (L) hemispheres of the central thalamus of a patient in a minimally conscious state displayed in a T1-weighted magnetic resonance coronal image. C, Comparison of presurgical baseline (pre) 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. Presurgical baseline and crossover trial observations are displayed with 95% confidence intervals for binomial distributions with *n* observations for 3 primary behavioral outcome measures on the Coma Recovery Scale–Revised (CRS-R) subscales measuring attentive responsiveness (arousal) (n=185 off, 189 on); communication (comm) (n=185 off, 189 on); and motor function (motor) (n=185 off, 189 on) and secondary measures of limb control (n=336 off, 261 on); oral feeding (n=54 off, 53 on); and object naming (n=206 off, 235 on). *Significant differences in on vs off periods for CRS-R arousal, limb control, and oral feeding measures at $P<.001$ established by Pearson χ^2 (2-tailed). †No pre data were available because the patient was fed by gastrostomy tube feedings prior to the state of recovery of oral feeding function during the trial. ‡Unlike the other categories in the Figure, the y-axis values for this group of measurements reflect a combination of the 2 highest scores on the rating scale that both reflect functional oral feeding, not just the top score on the rating scale, as in the other categories. Figure elements adapted from Schiff et al[1] with permission.

In these studies, behavioral facilitation of object recognition memory and upregulation of memory-related immediate early genes were demonstrated using the same

stimulation parameters. These findings suggest a possible mechanism for the observed carryover effects in our human subject study. Future experimental designs must anticipate persistent DBS effects after discontinuation of stimulation. In the Schiff et al study,[1] there was sufficient evidence of decay in response to support the continued use of a crossover design, although shorter periods of stimulation titration and uniform collection of data outside of the crossover period may minimize the impact of this confound.

It is hoped that DBS manipulation of arousal and motivational drive may be able to be linked to facilitate existing cognitive rehabilitation interventions that have been shown to effectively remediate residual functional impairments.[40] The effects of these two interventions might be synergistic, with DBS supporting a more reactive cerebral substrate that could allow cognitive rehabilitation to reestablish previously learned patterns of behavior and build compensatory strategies to substitute for impaired neurologic systems. Animal studies showing the additive benefit of traditional rehabilitative treatments (eg, physical therapy) alongside neuropharmacologic interventions provide a historical precedent for such combined therapies.[41]

CHALLENGES AND LIMITATIONS

A clear limitation of this study is that it is a result obtained in a single subject. Although it is possible to draw statistically rigorous conclusions in an "n-of-1" context,[42] it is also impossible to know whether these outcomes are generalizeable. Lest we conclude prematurely that this proof of principle constitutes a validated therapy, we should pause and avoid fostering a therapeutic misconception and reflect on the challenges that will need to be overcome through subsequent inquiry.

One major barrier is diagnostic and concerns the syndromic heterogeneity and variance of subjects who might benefit from DBS. Risk stratification of potential recipients of DBS is limited by our current inability to estimate cerebral function based on bedside examination. Dissemination of this technology will depend on both its validation as well as an enhanced ability to cultivate diagnostic and prognostic measures using noninvasive tools to risk-stratify subjects for inclusion in future clinical trials. Behavioral metrics like the CRS-R will need to undergo further study to establish sensitivity and specificity in well-defined patient groups and to maximize positive and negative predictive value.

Identification of potential subjects is further compromised by the lack of reliable epidemiologic data about the incidence, prevalence, and natural history of disorders of consciousness.[43] These public health data coupled with diagnostic and prognostic information are essential to engage in assessment, as are safety data about these devices and operative procedures. Such risk stratification is especially important given the decisional incapacity of potential subjects and the ethical and regulatory burdens posed by surrogate decision making. These questions of proportionality take on a greater ethical valence when higher-functioning subjects are considered as putative candidates for this intervention: their potential benefit may be associated with a greater risk of sustaining harm and losing retained function.

ETHICAL IMPLICATIONS

Lewis Thomas famously coined the phrase "halfway technology" to describe interventions that ameliorated but did not eliminate a condition.[44] Should additional cases duplicate the effects seen in our initial subject, DBS for MCS would become a halfway technology, improving cognitive and physical function while leaving patients severely disabled, still burdened with significant impairment.

As a halfway technology, it is fair to ask whether DBS for MCS represents an improvement over the patient's premorbid condition. On the one hand, the subject can now interact meaningfully with his family, eat by mouth, and execute movements essential for self-care activities. With intake by mouth, he has regained lost weight. No longer dependent on feeding by gastrostomy tube, he can enjoy the act of eating. His mobility decreases the risk of deep vein thrombosis and eliminates the risks of prophylactic anticoagulation. Most importantly, his newfound ability to communicate with others has allowed him to make his needs known and to interact with his family. This is clearly a benefit perceived by his parents and caregivers, if not by him as well.

Already he has been able to voice preferences when asked whether he wants to continue with a physical therapy session. His responses, while seemingly routine, are in fact demonstrative of a restitution of elements of his decision-making capacity. While they remain at the level of assent, and do not reach the level of formal consent, this degree of improvement is ethically noteworthy. In our view, this progress is a further validation of the philosophical and regulatory arguments mustered to use a surrogate decision maker, the patient's legally authorized representative, to authorize enrollment in this protocol approved by 3 institutional review boards and granted an investigational new device exemption by the Food and Drug Administration.[1,9,45-51] By asserting such a role for surrogate authorization, given the subject's inability to provide consent because of his disorder of consciousness, we have been able to restore a modicum of personal agency and patient self-determination. This degree of autonomy has allowed him a degree of newfound control over his environment and facilitated engagement with others, an outcome we take as a moral good.

But with these improvements comes the possibility of concurrent burdens.[9] While progress in digestion and mobility seem unimpeachable goods, the cognitive improvements seen might raise the question of whether increased awareness of self, others, and the environment represent a patient-centered benefit.

It is conceivable that improvements in cognitive function could lead to a heightened awareness of a situation to which the patient had previously been unaware, stripping away a protective veneer that spared him knowledge of the severity of his injury and its associated burdens. If an ability to perceive these challenges antedated an capability to cope with them, then the progress afforded by DBS in MCS could represent a net liability. This situation, however, is by no means unique to patients re-

covering from MCS. Rather, this paradox of recovery is commonly encountered by many severely brain-injured patients who must come to terms with the gradual realization of a "new self."[3]

These speculations, however, assume that the patient in MCS would forever remain permanently unaware of his or her predicament, an assumption that is called into question by evidence that higher levels of awareness may be present with very little bedside evidence in patients with disorders of consciousness.[52] These and other data[5] suggest a reservoir of retained cognitive potential that may or may not be engaged in higher-level processing. While not dispositive of thought or emotion, these findings suggest that patients in MCS retain the physiological substrate necessary for cognitive tasks at much higher levels than might be demonstrated by overt behaviors on clinical examination.

This potential discordance between thought and action, in our view, alters the burdens to benefits ratio of DBS in MCS. Its therapeutic potential becomes proportionate because neuromodulation fosters functional communication and provides the patient in MCS with an expressive vector to the outside world. As such, DBS in MCS may be a response to the affective and cognitive isolation that may be experienced by patients in MCS. And yet an ethical tautology remains: determining the burdens and benefits of the cognitive effects of DBS remains difficult because, absent an ability to communicate effectively, we remain blinded to the patient's inner state of mind and thoughts, if he had thoughts, prior to implantation of his thalamic stimulators.

We believe this question, this "mystery of the mind," to echo Penfield's phrase, is a patient-centered question that warrants a pragmatic clinical response.[53,54] We emphasize this point about responsiveness because the reaction to the publication of our work has sometimes implied that our intervention has somehow created this problem space and not been an attempt to respond to a pressing clinical need.

Reasonable people will disagree about whether life on the cusp of consciousness is a life that is worth living and articulate preferences to forgo life-sustaining therapies in an advance directive for this state of decisional incapacity. Nonetheless, it is inappropriate to categorically exclude patients who are currently in this state from access to medical advances.[55] While knowledge of a dire clinical outcome might have altered a family's prior decisions about emergent care, or prompted a decision to withhold or withdraw life-sustaining therapy, a post hoc analysis applied to a patient's current state of health is a recipe for clinical neglect.[56]

Our primary ethical motivation was a justice ethic,[9,45] to overcome the societal neglect syndrome that has plagued this population[47] and to be responsive to their needs by advancing a therapeutic hypothesis that might mitigate their burdens. Our trial did not create the condition we seek to create. That is a consequence of acute surgical and neuroprotective measures that save lives that heretofore would have been lost, albeit with diminished states of consciousness.

If validated by replication in other subjects, our efforts will be viewed as a first, initial step in mitigating the chronic care burdens experienced by these patients and their families by harnessing the underactivated but remaining neural networks that undergird cognitive function and consciousness.

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