Deep brain stimulation and cognition: moving from animal to patient

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Purpose of review

Brain electrical stimulation has been proposed as a strategy to improve chronically impaired cognitive function. This brief review places a small number of recent studies into a broader historical context and identifies important challenges for further development of this area of research.

Recent findings

Behavioral improvements following severe brain injury with central thalamic deep brain stimulation were observed in experimental studies conducted in rodents and a report on a single human. These findings suggest that this technique warrants further study as a method to modulate cognitive function in the setting of acquired brain injury.

Summary

This area of research offers the promise of new avenues to engage patients with nonprogressive brain injuries who, at present, have rather limited therapeutic options. These efforts, however, will require careful attention to issues of research and clinical ethics and study design.

Keywords

arousal regulation, central thalamus, consciousness, consent in decisional incapacity, intralaminar thalamic nuclei, minimally conscious state

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Abbreviations

DBS deep brain stimulation
MCS minimally conscious state
MRF midbrain reticular formation

1350-7540

Introduction

Historically, deep brain stimulation (DBS) in the thalamus, upper brainstem, and allied targets has been advanced as a method by which to restore consciousness to chronically unconscious patients following severe brain injuries, with limited evidence of effects. Although DBS is an increasingly used mode of treatment for neuropsychiatric disorders, its underlying mechanisms of action in these applications are not well characterized [1•,2•]. Recent proposals have considered the application of central thalamic DBS to improve cognitive function in conscious patients with severe cognitive disabilities. These efforts are closely linked to both the basic neurophysiologic functions of the DBS targets in forebrain arousal regulation mechanisms and the underlying pathology of chronically impaired cognitive function following severe brain injury.

In this review we briefly outline the clinical and scientific foundations underpinning a recent study that demonstrated behavioral improvements with central thalamic stimulation in a single human subject who had remained in a minimally conscious state (MCS) for 6 years following a severe traumatic brain injury. These experimental and clinical data support further research to develop central thalamic stimulation as an investigational therapeutic method. Such development, however, will require stringent efforts to develop patient selection criteria, study design, and ethical frameworks to ensure that this line of enquiry remains aimed at achievable and desirable clinical goals.

Early experimental studies of deep brain stimulation and forebrain arousal

The modern history of brain stimulation and arousal of the forebrain begins with the studies conducted by Moruzzi and Magoun [3], who demonstrated that electrical stimulation of the brainstem reticular formation and midline thalamus could produce desynchronization of the electroencephalogram, similar to that seen in wakeful states. Based on these and other related experimental findings the concept of an ascending reticular activating system arose, with an essential role for the midbrain and intralaminar regions of the thalamus. A precise anatomic demonstration of a pathway from the midbrain reticular formation (MRF) to the intralaminar nuclei of the thalamus, as suggested by the original studies conducted by Moruzzi and Magoun, was identified three decades

later by Steriade and Glenn [4] using electroanatomical and single-unit recording methods. In a remarkable set of early behavioral experiments, Fuster [5] demonstrated that direct electrical stimulation of the MRF improved behavioral responsiveness and perceptual awareness in conscious monkeys, reducing reaction times and increasing detection of near threshold stimuli.

More recently, human imaging studies have shown that activation of this pathway between MRF and intralaminar nuclei of the thalamus is associated with increasing levels of attentional focus during simple reaction time tasks [6]. At present, however, the nuclei within the central thalamus are considered to play a more intermediate role in arousal state control, with a primary role of activation assigned to brainstem monoaminergic and cholinergic neuronal groups and neurons within the basal forebrain [7]. Importantly, inputs from the brainstem and basal forebrain arousal system converge strongly on the intralaminar and surrounding regions of the central thalamus [8], suggesting that these neurons can be recruited through many types of arousal.

Deep brain stimulation in chronically unconscious patients

Following these early experimental observations, clinical investigators in the late 1960s and 1970s began to consider electrical stimulation of the brainstem (tegmental midbrain), thalamus (posterior intralaminar nuclei–centromedian parafasicularis complex), and basal ganglia (globus pallidus interna) for restoration of arousal and consciousness in chronically unconscious patients [9] (additional references are available in other reports [10–12]). Most patients included in these initial studies had remained in conditions consistent with either near brain death or vegetative state following severe traumatic brain injury. Although eye opening and some fragmentary movements were generally observed with electrical stimulation, consistent with an arousal effect, no examples of recovery of sustained interactive behavior were noted; neither were formal behavioral assessments conducted to link DBS to clinical improvement. In a study of a single individual, conducted by Sturm *et al.* [9], electrical stimulation of the rostral thalamus was applied in a patient with focal injuries in the midbrain and thalamus following a posterior circulation stroke. The patient was described to be in 'some kind of unconsciousness which was neither a manifest coma nor a typical apallic syndrome [an older term for vegetative state]'. In this patient, electrical stimulation reportedly produced brief recovery of simple command following, but it became ineffective over a few weeks of application.

Following on from these early reports, a multicenter study was initiated in the late 1980s by Medtronic Inc. (Minneapolis, Minnesota, USA), involving neurosurgeons in France, Japan, and the USA (further references available in the reports by Cohadon [10], Tsubokawa *et al.* [11] and Hosobuchi and Yingling [12]), in which DBS was applied to the centromedian thalamus and cervical spinal cord in a group of about 50 patients who were in the vegetative state. It was as part of this series of studies that the most famous patient in this cohort, Terri Schiavo, was implanted with a deep brain stimulator in the posterior intralaminar nuclei of the right thalamus without effect [12].

Despite clear, clinically judged increases in arousal and physiologic responses to brain stimulation in many patients, including changing of the frequency content of the electroencephalogram and increases in cerebral metabolic rates measured using positron emission tomography, substantive clinical improvements were not identified in the vegetative state patients treated with DBS. A small number of patients with traumatic brain injury (studies included anoxic, traumatic, and other etiologies) were reported to exhibit significant improvement, but all of these patients were studied within the known time frames for spontaneous recovery (all prior to 6 months). This makes these observations uninterpretable, given that the studies were carried out without blinding, without formal behavioral assessment of linkage of DBS to behavioral changes, or with blocked periods of withdrawal of stimulation. More recently it has been acknowledged that the patients did not fulfill the criteria for vegetative state [13] at the time of initiation of DBS; in retrospect, the patients were judged to have exhibited evidence of behavioral responsiveness consistent with MCS [14]. MCS patients have a longer time frame for significant functional recovery [15], making spontaneous recovery even more likely in these cases.

The general failure of DBS when applied to vegetative state patients can be understood within the context of the patients' underlying pathology and the rationale for these studies. Although vegetative state may be a transient condition, patients remaining in vegetative state until death have shown consistent neuropathology demonstrating widespread death of thalamic and cortical (typically less injured) neurons [16]. The application of DBS to patients with overwhelming brain injuries was motivated by the concept that DBS might support an overall state change (such as restoration of desynchronized patterns from the background of anesthesia-induced slow waves, as seen in the experiments conducted by Moruzzi and Magoun [3]), with the hope being that stimulation would restore a wakeful brain state. The majority of patients studied, like Schiavo as revealed at autopsy [17], had suffered widespread cerebral injury, and activation of such widely disconnected and damaged neuronal tissue simply could not have restored integrative function. Although some neuroimaging studies have demonstrated preserved

cerebral integrative function in patients fulfilling criteria for vegetative state [18], these are clearly exceptional cases [19]. Moreover, further recovery within known time frames for vegetative state has occurred in each of these cases. Thus, the application of DBS to vegetative state patients in general does not appear to be supported by available data. Importantly, recovery mechanisms from vegetative state and MCS are poorly understood and currently judged only by time after injury [20]. Therefore, the risks for injury to critical structures within the central thalamus with implantation of DBS electrodes must be mitigated by initiation of studies only after spontaneous recovery is statistically unlikely and formal assessments demonstrate a flat behavioral baseline (see Ethics, below).

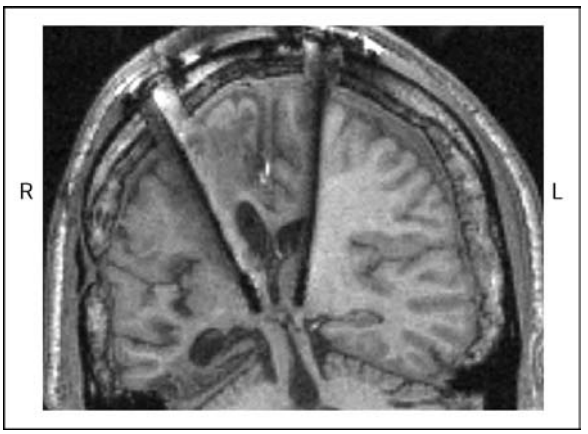
Deep brain stimulation for impaired cognitive function in conscious patients

Schiff and colleagues [21–23] first proposed a systematic approach to the application of DBS techniques in conscious patients with chronically impaired cognitive function. This strategy considered the basis of patient selection, emphasizing clinical evidence of consciousness within the wakeful state, evidence of fluctuations in behavioral performance, and the specificity of connections between components of the central thalamus and cerebral cortex, basal ganglia, and other subcortical structures. In contrast to the previous human neurosurgical studies discussed above [10–12], which targeted the centromedian nucleus of the thalamic posterior intralaminar system and spinal cord, greater emphasis is placed on the anterior components of the intralaminar system. These neurons collect more afferents from the brainstem arousal systems [8] and are the principal thalamic targets of the midbrain reticular projection [4]. These anterior intralaminar neurons have strong connections to medial frontal cortical systems that regulate arousal level [23] and exhibit increased concentration of calbindin staining neurons that project most strongly to supragranular cortical regions [24], allowing for a parallel role in cerebral activation comparable to that of projections from the brainstem arousal systems [25]. The neurons within human centromedian nucleus *per se* are exclusively parvalbumin staining [26] and project mainly to the basal ganglia [27].

In a recent report, following on from these proposals and experimental studies in nonhuman primates [28] and rodents [29••], Schiff *et al.* [30••] reported findings from a study of DBS electrodes implanted bilaterally into the central thalamus as part of a pilot clinical trial in a 38-year-old male who remained in a MCS for 6 years following a severe traumatic brain injury. Although the patient was unable to communicate reliably, prior characterization of brain function using functional magnetic resonance imaging demonstrated preservation of bi-hemispheric large-scale cerebral language networks [31]. Positron emission tomography revealed that cerebral metabolism during wakefulness was markedly depressed. The DBS electrodes targeted the anterior intralaminar thalamic nuclei and adjacent paralaminar regions of thalamic association nuclei. A 6-month double-blind alternating crossover study showed that bilateral DBS of the central thalamus improved behavioral responsiveness in this patient, increasing the frequency of specific cognitively mediated behaviors (primary outcome measures) and functional limb control and oral feeding (secondary outcome measures) during periods in which DBS was on as compared with periods in which it was off (Fig. 1). Detailed logistic regression modeling of the behavioral data demonstrated statistical linkage between the observed functional improvements and recent stimulation history. The investigators interpreted the observed effects of DBS as evidence of partial functional restoration of frontal cortical systems involved in arousal regulation and behavioral drive. Direct activation of neocortical and basal ganglia neurons via stimulation of the central thalamus was proposed as compensating for a loss of arousal regulation that is normally controlled by the frontal lobe in the intact brain and was supported by the central thalamic regions targeted. These findings provide the first evidence that DBS can promote significant late functional recovery from severe traumatic brain injury and they provide motivation for further research.

Importantly, in this study the rationale for applying DBS is different in focusing on MCS patients with relatively widely preserved brain structure and clear evidence of interactive behaviour, with elements of language function (command following, verbalization, or inconsistent communication). DBS in this patient group may improve arousal regulation of functionally connected but inconsistently active cerebral networks that are present in some

Figure 1 Electrode lead placements in central thalamus of minimally conscious state



Electrode lead placements within central thalamus of patient's right (R) and left (L) hemispheres displayed in T1-weighted magnetic resonance coronal image. Reproduced with permission from Schiff *et al.* [30••].

MCS patients and are expected to be absent in permanent vegetative state. For such MCS patients, restoration of reliable communication or response initiation and persistence may have functional significance.

Another important observation in this study was the demonstration of carry-over effects, with a shifting baseline of function in the DBS off period arising after initiation of DBS and in comparison with a 6-month pre-stimulation baseline period that remained unchanging. This observation can be compared with recent rodent studies of continuous unilateral electrical stimulation of the central lateral nucleus using comparable stimulation parameters, which also demonstrated carry-over effects of DBS [28]. In these studies behavioral facilitation of object recognition memory and upregulation of memory-related immediate early genes were demonstrated using the same stimulation parameters. The findings suggest a possible mechanism for the observed carry-over effects in the human study. Future experimental designs must anticipate persistent DBS effects after discontinuation of stimulation. In the study reported by Schiff *et al.* [30••], enough evidence of decay in response was observed to support the continued use of a crossover design, but the findings suggest the use of shorter periods of stimulation titration and uniform collection of data outside the crossover period.

Ethics

Developing DBS for severely brain-injured patients to improve cognitive function will require an evolving responsive and responsible research ethic, attentive to concerns about proportionate goals of care and protection of vulnerable research subjects [32]. In a series of examinations of the ethical principles surrounding this work, Fins and colleagues [32–35] developed a central theme of balancing nonmaleficence and distributive justice – avoiding harm to vulnerable individuals while providing access to a study intended to assess whether DBS might therapeutically restore cognitive function. Addressing the challenge of surrogate authorization for patients who lack decisional capacity for consent, those authors asserted that decisional incapacity should not be a criterion for categorical exclusion from research participation when the object of inquiry (here a disorder of consciousness) is the etiology of the individual's inability to provide autonomous consent. Study authorization, in the trial under consideration, was addressed by monitored and staged surrogate authorizations, and the inclusion of a provision to obtain subject consent should decisional capacity be restored [35].

In addition to ethical considerations aimed at the individual patient, broader social considerations will have an impact on the development of these investigational therapies. Importantly, disanalogies with psychosurgery and the therapeutic nihilism historically directed toward individuals with disorders of consciousness must be considered when attempting to understand the slow progress of work in this underserved clinical population [36••,37].

In the study reported by Schiff *et al.* [30••], the patient's recovered ability to interact with others in a meaningful manner was cited by family members as the most important change observed during the trial. Restoration of functional communication also provides an opportunity for more detailed clinical assessment and permits the patient to assume a more active role in treatment because personal preferences and feedback can be conveyed to care givers. This may take the form of patient assent, which, in the context of decisional incapacity, is a step toward restoration of autonomous decision making and consent. Identification of patient surrogate and care giver goals should be the focus of future research in the articulation of neuropalliative care frameworks [31]. The response to DBS is likely to be highly variable and limited in scope; therefore, a neuropalliative ethic of care must be developed to establish proportionate goals of care and help families to balance the potential for improvement against associated burdens in light of the patient's previously articulated preferences [32].

Current limitations and cautions

Beyond the need to establish ethically informed investigative and therapeutic research goals, there are several important limitations that impede rapid advance of research in this area. Among the most important, there are few available scientifically vetted outcome measures developed for patients with marked cognitive impairment following brain injury. The Coma Recovery Scale Revised [38] is the most carefully studied, but its functional range is insufficient to quantify the degree of cognitive improvement for patients recovering past the minimally conscious state who retain significant chronic cognitive disability. More precise evaluation of cognitive, motor and emotional capacities will be needed to assess quantitatively the impact of potentially therapeutic interventions. In addition, such metrics are required to develop selection criteria to categorize patients appropriately and develop formalized risk stratification approaches when considering possible interventions in this diverse population. Furthermore, as these efforts progress it will be essential to foster informed public and transparent discourse among all stakeholders in order to generate the societal consensus necessary for this line of inquiry to proceed.

Conclusion

Recent animal studies and the report in a single human subject reviewed above suggest that the application of DBS for modulation of cognitive function and behavioral responsiveness in patients with nonprogressive brain injuries may be possible but will require careful and systematic development. In particular, this area of

research will require careful assessment of patients and study designs that balance the scientific questions against appropriate and proportionate goals of intervention. Ethical frameworks have been proposed to navigate the future evolution of this scientific work.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 740).

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