Deep brain stimulation in the management of disorders of consciousness: a review of physiology, previous reports, and ethical considerations

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Patients suffering from disorders of consciousness constitute a population that exists largely outside of the daily practice patterns of neurosurgeons. Historically, treatment has focused on nursing and custodial issues with limited neurosurgical intervention. Recently, however, deep brain stimulation has been explored to restore cognitive and physical function to patients in minimally conscious states. In this article, the authors characterize the physiological mechanisms for the use of deep brain stimulation in persistently vegetative and minimally conscious patients, review published cases and associated ethical concerns, and discuss future directions of this technology. (DOI: 10.3171/2010.4.FOCUS1096)

Key Words • deep brain stimulation • minimally conscious state • persistent vegetative state • thalamus • disorder of consciousness • ethics

The application of deep brain stimulation (DBS) has grown to include a wide variety of clinical situations. A fairly novel and sparsely studied application involves the use of DBS in improving the clinical condition of patients in a persistent vegetative state (PVS) or minimally conscious state (MCS) following traumatic brain injury. Beginning in the 1950s, infrequent reports of the use of DBS for disorders of consciousness had been described. More recently, a widely publicized case of dramatic improvement in a patient in an MCS who was treated with DBS rejuvenated interest in this therapeutic intervention. Still, many factors may ultimately contribute to or confound the possible success of this treatment, including spontaneous recovery, incorrect diagnosis, and the fluctuating baseline consciousness of the patient.

While it is known that a spectrum of consciousness exists from comatose to fully conscious, not until recently has there been a distinction between a PVS and an MCS been established. A PVS is defined as a degree of consciousness after severe brain injury whereby a patient has developed wakefulness with some degree of sleep-wake cycling but without any demonstration of environmental awareness. The patients who fall into this category of consciousness have a functional brainstem and various dispersed “islands” of dysfunctional cortex. In contrast, an MCS represents a more advanced stage of consciousness in which a patient demonstrates an increased awareness of his or her environment via observed, cognitively mediated behaviors but remains inconsistent in his or her communication abilities. On functional brain imaging tests, these patients may have organized cortical functioning despite appearing grossly unconscious. While either state may result from a traumatic brain injury and both have profound functional consequences, differentiating between the two states may be important in determining the possible benefit of DBS therapy.

This review characterizes the physiological mechanisms for the use of DBS in disorders of consciousness, reviews published cases of its use in the literature, the associated ethical concerns, and provides a discussion of the possible future for this application of DBS.

Physiological Basis for DBS in PVS or MCS

Initial theories regarding stimulation of the reticular formation and thalamus as a means of stimulating wakefulness date to early basic science studies conducted in the 1960s elucidating these activating centers. Further

Abbreviations used in this paper: DBS = deep brain stimulation; MCS = minimally conscious state; PVS = persistent vegetative state.
work revealed the role of the intralaminar nuclei in maintaining attention and memory based upon their anatomical neural connections and physiological characteristics. The subsequent discovery of widespread thalamocortical projections then contributed to the understanding of the importance of the central lateral nuclei of the intralaminar nuclei of the thalamus in promoting arousal.

Many thalamic nuclei share important roles in the relay of sensory and motor functions. Biochemical advances have revealed a specific type of thalamic neuron thought to be involved in the more basic function of activating cortical networks. These calbindin-positive staining neurons differ from the standard thalamic relay neurons in that they maintain axonal projections to more diffuse areas of cortex, including portions of the frontal lobe and other areas not traditionally involved in sensory or motor function. Moreover, these neurons synapse in layers of the cortex where relay neurons are typically absent. These special characteristics, combined with the finding that a significant portion of the intralaminar nuclei (nuclei previously believed to be important in the activating system) were composed of such calbindin-positive neurons, helped establish the importance of specific thalamic nuclei in arousal. More recent research has demonstrated that such neural connections between the central lateral nuclei and the cortex are reciprocal and that these nuclei are densely innervated by brainstem arousal systems as well.

Multiple cases have been reported whereby a lesion restricted to these nuclei resulted primarily in disturbances of consciousness and behavior, further confirming the importance of intralaminar nuclei in cognitive arousal and particularly attention and concentration. Patients with specific ischemic infarctions of these nuclei primarily demonstrated disturbances in attention. Subsequent SPECT imaging performed in these patients revealed decreased blood flow to the frontal cortices.

As basic neuroscience research demonstrated the importance of these thalamic nuclei for wakefulness, theories regarding the possibility of stimulating such nuclei to possibly induce an awake state in unconscious patients became increasingly popular. The initial trials involving artificial stimulation of these areas were correspondingly designed and performed in patients with disorders of consciousness. However, a major distinction in the conscious state of the patient was not discovered until much later in the process—namely, the difference between PVS and MCS patients. Schiff et al. suggested that patients most likely to show improvement with DBS therapy are those with relatively preserved areas of essential cortical functioning with damage primarily involving the arousal centers (that is MCS patients rather than PVS patients). These authors reported on a carefully selected study subject in an MCS who showed dramatic improvement with DBS. The positive outcome in this case was hypothesized to relate to the patient’s having had an underlying primary defect in the arousal system while overall cortical function had been preserved. The authors suggested that the central lateral thalamic nuclei of the intralaminar nucleus would be the highest yield targets for stimulation based upon neurophysiological calculation and that MCS patients would be the most likely to benefit. Unfortunately, this conclusion may be confounded by growing evidence of a bias to classify patients as in a PVS, when they may truly be in an MCS.

**Review of Reported Cases**

The earliest published cases of electrical stimulation as a therapy for patients with decreased arousal were conducted in the late 1960s and 1970s. Hassler et al. were the first to report nonspecific behavioral and electroencephalographic arousal after stimulating an unspecified projection system (possibly the rostral ventral thalamic nucleus or intralaminar thalamic nucleus) in a posttraumatic persistently vegetative patient. Although Hassler was unaware of the exact neurophysiological underpinnings of the projection system at the time, it has since been suggested that they likely involved the recently discovered calbindin-positive thalamocortical pathway from the intralaminar nucleus. In 1979, Sturm et al. reported that bipolar stimulation of the nucleus reticularus polaris thalami in a patient with a medial midbrain infarct resulted in improvement in following commands, wakefulness, verbal communication, and an increased oral intake. The patient initially was described as having “some kind of unconsciousness which was neither manifest coma nor a typical apallic [PVS] syndrome.” The patient died 2 months after the implantation of electrodes. Unfortunately, these early cases were confounded by a limited understanding of the differences in the states of impaired consciousness, which have since been shown to alter the prognosis for recovery and outcome. The fact that stimulation was performed within the spontaneous recovery period further limits the conclusions that can be drawn from these early studies. A more recent study suggests that spontaneous recovery in MCS patients can occur up to 1 year following the initial insult.

More recent reported cases of the use of DBS in PVS or MCS patients include reports by Tsubokawa et al. These authors performed therapeutic DBS targeting the mesencephalic reticular formation and nonspecific thalamic nuclei and followed 8 patients in a PVS as a result of severe brain injury (closed head injury, cerebrovascular accident, or anoxia) over 6 months. Improvement in vocal communication and arousal was noted in 4 of the 8 patients. Over the following decade, the same group increased their cohort to a total of 21 patients (including the heavily publicized case of Terri Schiavo), 8 of whom showed improvement in ability to obey verbal commands. Despite the large number of patients in the more recent trials, this study was limited by the timing of DBS therapy within the accepted 1-year time frame of spontaneous recovery. The decision to attempt DBS in patients whose condition was initially diagnosed as a PVS, a cohort that is less likely to benefit from such stimulation than patients in an MCS, may have also limited their findings.

The most recent and widely publicized published case of DBS-based improvement in PVS or MCS patients was reported by Schiff et al. in 2007. In this case, DBS therapy was attempted in a 38-year-old man whose condition was diagnosed as an MCS 6 years after a traumatic
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.. brain injury. Prior to DBS stimulation, the patient demonstrated visual pursuit and intermittently followed simple commands. Following implantation and therapy, the researchers reported improvements in level of arousal (sustained eye opening, head turning to voices), functional limb movements, ability to feed orally, and improvement in the JFK Coma Recovery Scale-Revised score despite a 6-year history of minimal consciousness. The patient was soon able to name objects, move objects with his hands, and feed himself.

A major difference between this case and previous attempts to evaluate DBS in PVS or MCS patients was the patient selection criteria. This patient was in a clearly defined MCS and demonstrated preservation of cortical structure and language function but suffered primarily from inconsistency and loss of arousal. Additionally, he demonstrated improvement outside of the 1-year window whereby the likelihood of spontaneous improvement is low, unlike patients in previous studies. This is an important consideration given that the window of spontaneous recovery, which strongly confounded prior studies, has only recently been described. Moreover, this study was the first to use a widely accepted outcome measure, the JFK Coma Recovery Scale-Revised, to determine the clinical benefit of periods when DBS was turned on. While most previous studies reported subjective outcome improvements such as verbalization, behavioral changes, or limb motion improvements, this was the first to document objective clinical improvement. This report also demonstrated that the bulk of improvement occurred when stimulation was turned on outside of a 50-day postoperative window to minimize any possible residual surgical source of improvement. Additionally, Schiff et al. demonstrated carry-over improvement from prior DBS stimulation periods even after DBS stimulation was turned off.

Despite being based upon only one case, the Schiff et al. report provided much less biased information in the study of DBS for MCS patients. The applicability of this single case however remains difficult to determine. Moreover, the patient chosen for this study was among the higher functioning patients in the MCS state prior to DBS therapy. While the rationale for this decision was that a patient with largely preserved cortical function would be the most likely to recover meaningful function, the gains demonstrated in the case may not be as significant as initially believed given the patient’s high baseline level of functioning.

Ethical Considerations in the Treatment of Disorders of Consciousness

Since being first described approximately 4500 years ago in the Edwin Smith Papyrus, damage to the adult CNS in humans has been regarded as an “ailment which cannot be treated.” This view still seems to be the prevailing one with respect to disorders of consciousness. Despite recent developments in neuroimaging, pharmacology, and neuromodulation, the functional utility of these improvements in the setting of disorders of consciousness remains largely untapped. In a recent editorial, Wijdicks and Rabinstein presented guidelines for meeting with families whose loved ones are comatose, stating, “the attending physician of a patient with a devastating neurologic illness will have to come to terms with the futility of care.” Often, clinicians evaluate brain-injured patients relatively early in the course of injury and are unaware of any longitudinal recovery. Clinicians are trained to respect patient preferences at the end of life and often believe they are advocating on behalf of the patient by steering families toward less-aggressive treatment. Palliative measures are often advocated based on an ethical sense that nothing can or should be done for patients with catastrophic brain dysfunction. While this approach is generally appropriate in the neurointensive care unit, it is essential that acute-care clinicians avoid prognostic errors about outcome based solely on decreased consciousness in the setting of brain injury. This reduced level of consciousness may be a precursor to brain death or the beginning of a variable recovery process depending upon the underlying anatomical severity.

Over the past several years, counseling families with regard to the decision to withdraw life-sustaining therapy from patients with severe brain injuries has become more complex. Since the 1968 creation of brain death criteria, the description of brain states has been refined. Patients who are brain-dead and those in a PVS are often believed to be hopelessly damaged and permanently unconscious. A vegetative state is generally considered permanent 3 months after anoxic injury and 12 months after trauma. However, shortly after injury, PVS patients may progress to an MCS, of which the natural history is not yet known. Unlike patients in a vegetative state, the minimally conscious may demonstrate inconsistent evidence of self- and environmental awareness. Patients in an MCS may show a spectrum of behavior ranging from responding to environmental stimuli to following simple commands or possibly the production of incongruous verbal communication. Unfortunately, the diagnostic timeline introduces a piquant paradox. To fully determine whether recovery from the vegetative state is possible, a patient with a traumatic brain injury might have to be observed for as many as 12 months. Currently, decisions about withholding life-sustaining therapy are typically made within days to weeks of presentation for patients with disorders of consciousness because options for withdrawal diminish as the patient moves from the acute to the chronic stage of illness.

Arriving at an accurate diagnosis in a patient with a decreased level of consciousness is challenging. Diagnostic error rates of roughly 40% have been reported in nursing home patients in an MCS who were labeled as vegetative. The most famous example of such cases is that of Terry Wallis, a minimally conscious Arkansas man who was erroneously diagnosed as vegetative 19 years previously; he began to speak fluently in 2003 and it was subsequently learned that he likely experienced episodic consciousness. Two goals should be achieved in the evaluation of patients in PVS and MCS. First, it should be ascertained whether the patient retains the capacity for a purposeful response to stimulation, even if it is inconsistently manifested. Such an aptitude implies at least partial awareness (MCS), which has ramifications...
for subsequent care, level of rehabilitation, and ethical decision making. Second, clinical assessment should also focus upon reproducible communication, as consistent communication is the upper boundary of MCS.15 Monti et al.28 used functional MR imaging to evaluate preserved awareness in a series of 54 patients in PVS and MCS. In this series, 3 MCS and 2 PVS patients were determined to able to modulate their brain activity by generating voluntary, reliable, and repeatable neuroimaging responses in predefined neuroanatomical regions when prompted to perform imagery tasks.28 Neurostimulation for MCS is still an area of investigation and not yet a widely accepted therapy.18 While advances in neuromodulation have the ability to offer new therapeutic interventions for patients with disorders of consciousness, these interventions have not been tested in large clinical trials and have been performed in only a small number of patients. Moreover, conducting clinical research trials in patients with PVS and MCS is difficult as a result of regulatory complexity. These patients are deemed a vulnerable population and thus are subject to special protections with regard to enrollment in clinical trials.9 Although the patient’s surrogate may consent to therapeutic procedures with demonstrated benefit, the surrogate’s ability to authorize enrollment in a research trial is curtailed when the medical benefit of the treatment is yet to be demonstrated.10 Ultimately, these restrictions may result in countering advances in neuromodulation that could aid the population that the United States National Bioethics Advisory Commission has sought to protect from exploitation.10 These issues severely limit the potential for Phase I surgical trials in individuals who are unable provide consent for the very procedure that may restore some of their decision making capacity. Accordingly, some bioethicists have argued that clinical trials to reestablish consciousness would be ethically appropriate, even with the challenges posed by surrogate consent, when these distinctions and the burdens imposed on these patients and families are taken into consideration.12 Overcoming these barriers is essential if translational research is to be accomplished in this population, which has historically been sequestered from clinical research and would otherwise remain in a hopeless clinical situation.14 With improvements in consciousness also comes the possibility of unexpected burdens.12 In some cases, after stimulation, an individual may become more aware of cognitive and physical disabilities that he or she was previously unable to perceive. Cognitive improvements resulting from stimulation would need to be evaluated to determine if the increased awareness of self, others, and the environment is, in fact, a “patient-centered benefit.”12 In this sense, the harm associated with conscious awareness of one’s cognitive and physical impairments might be enough to abolish any benefits. An appraisal should not only be restricted to third-person interpretation, but also a first-person affirmation by the individual who will be summarily required to function with these deficits.18 Furthermore, several studies have determined the prevalence of suicidal ideation in people with traumatic brain injuries as varying between 3% and 33%.34 In light of the increased prevalence of suicidality among people with severe brain injury, what would be the appropriate ethical response to a patient who received DBS only to awaken from a minimally conscious state to express the consistent desire for termination of care? These issues are not isolated to this debate; this “self-awareness paradox” of recovery is frequently encountered after initial injury by severely brain-injured patients who must come to terms with the comprehension of a “new self.”19,32

In cases of disorders of consciousness, evaluating a patient with residual cortical activity and the potential to recover neurological functions for stimulation therapy raises the ethical questions of beneficence and nonmaleficence. Ostensibly, any procedure resulting in an improvement in cognition could be considered a benefit to the patient. However, the crux of this ethical argument hinges upon the degree to which cognitive and physical functions are restored in patients with severe brain injury. If a procedure were to completely restore consciousness as well as cognitive and physical functioning, the procedure would be considered of unequivocal benefit. However, it is conceivable that some patients may experience adverse psychological effects of DBS that would outweigh the benefits of the restorative effects. Furthermore, the difficulty in risk-benefit analysis is complicated by the assertion that restoration of consciousness following brain injury will likely vary along a spectrum. To create a responsible research ethic, current clinical investigators must attempt to balance the principles of respect, beneficence, nonmaleficence, and surrogate consent within an ethical framework.

Conclusions

While the application of DBS for patients in vegetative and minimally conscious states is relatively novel, great promise exists for this neurosurgical intervention in cases in which limited therapeutic options currently exist. Current strategies for the medical management of patients in PVS or MCS are largely guided by principles of sustaining life rather than improving a patient’s clinical situation, primarily because of the very limited interventional options for such patients. The emerging prospect that DBS may be able to restore function to patients in an otherwise hopeless situation may bolster the future use of this technology as both clinicians and patients may begin to view DBS as a practicable treatment.11 However, before DBS can be viewed as a clinically sound therapeutic intervention for patients in MCS or even PVS, significant additional research is necessary. Given the absence of a good translational animal model, short and long-term results and complications remain predominately unknown and untested. Over the past 5 decades, only a handful of studies have been conducted on a wide variety of patients, with only one most recent study of a single patient without confounding factors like spontaneous recovery. By report, the US Food and Drug Administration approved use of this therapy in 11 additional patients to provide more clinical results. Current research is extremely limited both in the number of patients studied, as well as the clinical situations in which to best consider the application of DBS therapy. Hence,
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no definitive conclusions can be made based on current data regarding whether to attempt DBS therapy, or even in which patients it would be most beneficial.

While a better understanding of these clinical issues will invariably emerge following additional trials, the resultant ethical complexity that will almost certainly ensue will likely need to be thoughtfully deliberated on an individual basis. Given the abuses of psychosurgery in the previous century, the use of DBS in the minimally conscious should be supported by strong scientific evidence, stringent oversight, and the full interdisciplinary support of neurosurgeons, neuroscientists, psychiatrists, and physiatrists who can help assess a patient’s suitability for DBS and provide continuous follow-up over time. Nevertheless, a significant hope for the future of this technology exists. We are only beginning to discover the full implications of this application of DBS, and an exciting future may await both patients and providers in a once hopeless clinical situation.

Disclosure

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