Improved Function After Deep Brain Stimulation for Chronic, Severe Traumatic Brain Injury

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BACKGROUND: Severe traumatic brain injury (TBI) damages the frontal lobes and connecting networks, which impairs executive functions, including the ability to self-regulate. Despite significant disabling effects, there are few treatment options in the chronic phase after injury.

OBJECTIVE: To investigate the safety and potential effectiveness of deep brain stimulation (DBS) for individuals with chronic, disabling TBI and problems of behavioral and emotional self-regulation.

METHODS: This study was an open-label, prospective design with serial assessments of behavioral outcomes and positron emission tomography 2 years after DBS implantation. Four participants 6 to 21 years after severe TBIs from automobile crashes were included. Although alert and volitional, all experienced significant executive impairments, including either impulsivity or reduced initiation. DBS implants were placed bilaterally in the nucleus accumbens and anterior limb of the internal capsule to modulate the prefrontal cortex.

RESULTS: The procedure was safe, and all participants had improved functional outcomes. Two years after implantation, 3 met a priori criteria for improvement on the Mayo-Portland Adaptability Inventory-4. Improvement was due largely to better emotional adjustment, although 1 participant showed marked increases in multiple domains. Significant improvement in a composite score of functional capacity indicated improved independence in self-care and activities of daily living. The pattern of change in cognition corresponded with changes in activation of the prefrontal cortex observed in serial scanning.

CONCLUSION: This first study of DBS to this target for severe TBI supports its safety and suggests potential effectiveness to improve function years after injury. The primary impact was on behavioral and emotional adjustment, which in turn improved functional independence.

KEY WORDS: Adult brain injury, Deep brain stimulation, Nucleus accumbens, Traumatic brain injury

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Each year, 1.7 million Americans are treated in medical facilities as a result of a traumatic brain injury (TBI).[1] Although most of these injuries are mild, 25% are classified as moderate or severe TBI and make up the majority of >80 000 new cases of disability resulting from TBI occurring each year.[2] Of patients who require rehabilitation and survive 5 years after their injury, 58% experience moderate or severe disability as a result of a combination of cognitive, motor, and sensory deficits.[3] Disability resulting from these residual impairments is further exacerbated by frontal lobe damage that impairs executive functions of the brain.[4] Among other manifestations, impaired executive functions often include difficulties initiating behavior (abulia in extreme cases) or impaired self-control manifested by impulsivity or disinhibition. Together, these common failures in

ABBREVIATIONS: DBS, deep brain stimulation; **IC,** internal capsule; **MPAI-4,** Mayo-Portland Adaptability Inventory-4; **NAcc,** nucleus accumbens; **TBI,** traumatic brain injury

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self-regulation are key underpinnings of the inability to adequately adapt for motor, cognitive, and sensory deficits, thus reducing their ability to function independently, to resume societal roles, and to participate fully in the community.[5]

Despite the profound disabling effect of impaired self-regulation, there is a paucity of proven interventions to restore these executive functions.[6] We investigated the use of deep brain stimulation (DBS) to restore frontal lobe function with the goal of reducing overall disability caused by severe TBI. In particular, we sought to change goal-directed behavior that was marked by either inaction or impulsivity. Our focus on the nucleus accumbens (NAcc) as the target for DBS was based on >40 years of research implicating this structure as a key node in frontal networks related to motivation and the processing of rewards.[7,8] More specifically, we concur with recent conceptualizations of the role of the NAcc in goal-directed behavior, particularly its contribution to driving choice in the context of ambiguous or competing expected outcomes.[8]

DBS of the NAcc and anterior limb of the internal capsule (IC) has been performed since 1998 in patients with refractory mood and anxiety disorders.[9] The robust connections of this region to frontal lobe networks involved in executive functions make it a potentially important target for neuromodulation.[10-12] The safety and efficacy of NAcc/IC DBS for obsessive-compulsive disorder led to Food and Drug Administration Humanitarian Device Exemption approval in 2009.[9,13,14] In addition, this target is being investigated for other neurobehavioral disorders such as major depression,[15] anxiety disorders, addiction, and eating disorders.[16,17] In this context, we hypothesized that NAcc/IC DBS would improve executive functions regulating emotional and behavioral control, which, in turn, would allow greater functional independence and participation in the community after severe TBI.

METHODS

This open-label, prospective case series investigation met institutional requirements for the conduct of human subjects and was registered on http://www.clinicalTrials.gov (identifier, NCT01277952).

Participants

Four participants (3 men; age, 30-45 years) met the inclusion and exclusion criteria (see **Methods**, **Supplemental Digital Content**, http://links.lww.com/NEU/A834, for complete criteria) and consented to be in the study. Three others were screened; 2 did not meet criteria as a result of extensive damage to the target location, and 1 withdrew before completing the screening process. All 4 participants had chronic, severe disability as defined by the Glasgow Outcome Scale-Extended[18] after severe TBI resulting from automobile crashes 6 to 21 years earlier (Table). Magnetic resonance images obtained at study baseline indicated significant atrophy and abnormalities attributed to prior hemorrhages in all participants. All participants were awake, alert, and able to follow commands; however, all required daily supervision and could not be alone overnight. All required assistance in instrumental activities of daily living, including navigating the community, and 3 required assistance with dressing, grooming, or toileting. Two used wheelchairs as a result of dense hemiparesis.

All 4 participants understood oral communication and could express themselves verbally, although 1 patient had moderate word-finding difficulties. All participants showed deficits in executive function. Two participants' self-regulation was marked by poor initiation, with 1 being abulic. Two showed problems of severe impulsivity marked by disinhibited statements, with 1 manifesting inappropriate sexual behaviors that restricted social participation. The overall common feature of the 4 participants was that sensory, cognitive, and motor impairments resulted in disability exacerbated by problems in emotional and behavioral control. All were receiving pharmacological treatment to control mood, which was only partially effective.

Outcome Measures

The primary outcome measure was the Mayo-Portland Adaptability Inventory-4 (MPAI-4)[19] total raw score. The MPAI-4 was developed for measuring outcomes after TBI. The instrument consists of 35 items rated according to degree of interference with everyday activities and includes 3 subscales: the Ability Index (cognitive, sensory, motor abilities), the Adjustment Index (mood and behavioral regulation), and the Participation Index (self-care and community living). The MPAI-4 was validated with both classic test theory and Rasch analysis.[19] On the basis of the standard error of measurement for a large, untreated population of individuals with severe TBI, the responder criterion of minimal clinically important difference was estimated for the present study to be 3.4 units, which the Food and Drug Administration approved as the a priori criterion for improvement.

Multiple secondary outcomes were evaluated with other measures of function, cognitive abilities, and decision making (processing rewards and punishments). To reduce variability and the number of individual statistical tests conducted, secondary measures were combined into composite scores for each domain: functional, cognitive, and decision making. The functional composite consisted of the MPAI-4 and the Functional Independence Measure,[20] which assesses independence in self-care, toileting, transfers, locomotion, communication, and social cognition. Measurement properties of the Functional Independence Measure have been reported extensively.[21,22] The cognitive composite score comprised the total score from the Repeatable Battery for the Assessment of Neuropsychological Status[23]; the standard scores for the Wechsler Adult Intelligence Scale-III[24] digit symbol, symbol search, letter-number sequencing, and digit span subtests; and T scores from the Trailmaking Test Parts A and B. The decision-making composite included the Iowa Gambling Task,[25] which provided an overall measure of decision making, and the Lane Risk-Taking Task,[26] which evaluated the tendency to choose certain, smaller monetary gains (safe response) over an option that provided both larger gains and losses (risky response). See **Instrumentation**, **Supplemental Digital Content** (http://links.lww.com/NEU/A834) for individual measures.

Procedures

After baseline assessments, the subjects underwent frame-based stereotactic implantation of the DBS lead (Medtronic Neurological model 3391) bilaterally in the NAcc/IC with the use of standard image-guided techniques for anatomical targeting routinely used for DBS surgery. The specific target of the NAcc ventral to the anterior limb of the IC (Figure 1) was directly visualized on axial, coronal, and sagittal T1, T2, and inversion-recovery magnetic resonance imaging scans, similar to what has been described previously for this target.[14,15]

TABLE. Characteristics of Participants[a]

	Participant 1	Participant 2	Participant 3	Participant 4
Age at injury, yr	23	39	19	22
Injury cause	Car crash	Car crash	Car crash	Car crash
Age at implantation, yr	40	45	30	46
Years after injury	18	6	11	21
Glasgow Outcome Scale-Extended score	Low severe	Low severe	Low severe	Upper severe
MPAI-4 score at baseline	55	68	54	51
Baseline clinical imaging findings (no acute pathology noted)	Left parietal and right frontal encephalomalacia and atrophy	Right frontal and temporal lobe encephalomalacia, left frontal lobe atrophy	Left parietal and bifrontal encephalomalacia and atrophy	Right frontal and parietal encephalomalacia and atrophy
	Multiple foci of decreased signal intensity	Multiple foci of decreased signal intensity	Generalized diffuse atrophy	
			Right midbrain and brainstem atrophy	
			Prior basal ganglia hemorrhage	

[a]MPAI, Mayo-Portland Adaptability Index.

The trajectory planning was based on avoidance of vasculature while maximizing the approach through the IC to the NAcc. The target region in these 4 patients was 6 to 12 mm lateral to the midline, 2 to 5 mm anterior to the anterior commissure, and 2 to 5 mm ventral to the anterior commissure (see contact 0 locations in **Table 1**, **Supplemental Digital Content**, http://links.lww.com/NEU/A834). Single-cell microelectrode recording verified our anatomical approach of traversing the IC white matter with white matter recordings and cells in the NAcc/IC. Physiological microelectrode recordings were captured for research purposes and did not change our targeting and final implantation of the DBS leads. The implanted DBS electrodes were connected to pulse generators (Medtronic Activa PC systems) in the chest wall in the usual fashion for all DBS procedures.

After a 6-week postimplantation recovery period and subsequent assessment, we used a comprehensive, iterative titration process to determine the optimal settings for DBS stimulation, including lead contact polarity, intensity, pulse width, and frequency, individualized for each participant. A physician with extensive clinical knowledge of each participant tested the settings during titration by monitoring for side effects. Stimuli (eg, orally presented numbers, phrases) were used to elicit samples of language and attention to assist with monitoring effects on cognitive function. The family was also asked to provide reports of changes in behavior between sessions.

After optimal settings were determined during the titration phase, the stimulation parameters were held constant until the follow-up phases (settings used at each phase for each participant are shown in **Table 2**, **Supplemental Digital Content**, http://links.lww.com/NEU/A834). After titration, participants received 6 weeks of stimulation, followed by 6 weeks of stimulation plus up to 10 h/wk of outpatient rehabilitation that included speech, occupational, and physical therapy, as well as treatment for psychosocial functioning. Assessments were repeated after an initial 9-month follow-up period and at 2 years after implantation. In analyses and figures, the 6 study phases were coded as follows: 1, presurgical baseline; 2, postsurgical baseline; 3, stimulation only; 4, stimulation plus rehabilitation; 5, 9-month follow-up; and 6, 2-year follow-up.

Analysis

For the primary outcome measure and each composite, we used repeated-measures analysis of variance with post hoc pairwise t tests corrected for multiple comparisons to determine whether the measure changed significantly over the course of the study. We used linear mixed-effects regression with permutation-based hypothesis testing (see **Supplemental Digital Content**, http://links.lww.com/NEU/A834) to test the hypotheses that relative neural activity across participants is related to composite scores.

We also used linear mixed-effects regression with permutation-based hypothesis testing to determine, at each voxel in the positron emission tomography (PET) data, whether there was an across-participants relationship between variation in relative PET activity and each of the composite scores. The slope and y intercept of the relationship were allowed to vary by participant. The linear mixed-effects regression model implementing this analysis is described in the **Supplemental Digital Content** (http://links.lww.com/NEU/A834).

RESULTS

All participants tolerated the procedure well, and there was only 1 serious adverse event directly related to the procedure: A short circuit in 1 contact for 1 participant required compensatory settings to optimize the location of stimulation, which in turn caused accelerated battery drain. The original pulse generator battery was replaced with a rechargeable system, resulting in classification as a serious adverse event. The short circuit did not impede stimulation or study participation. There were 9 (possible, probable, or definite) minor adverse events, none of which persisted. These transient minor events included postsurgical periorbital edema, decreased alertness, and vomiting; transient hypersomnia, insomnia, and facial spasms during initial titration of settings; increased aggression when attempting to cycle stimulation off at night; and

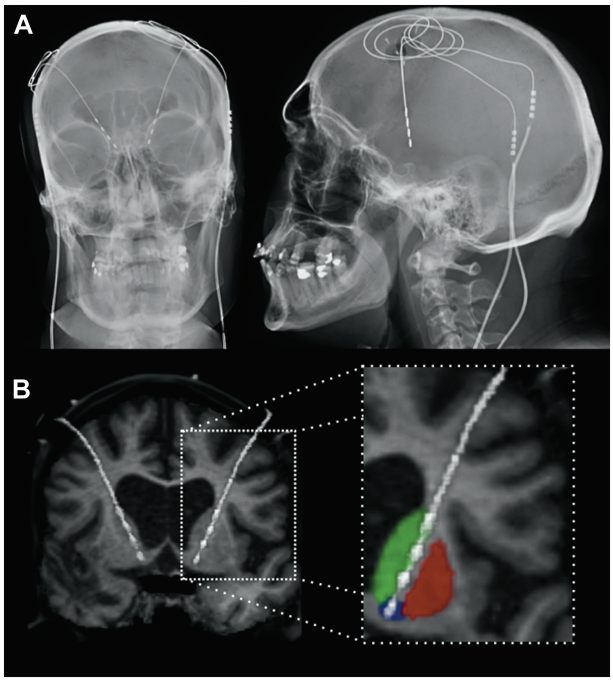


FIGURE 1. *Orientation of the implanted leads.* **A**, *postoperative anterior-posterior and lateral x-rays demonstrating lead placement in participant 2.* **B**, *postoperative computed tomography overlaid on an oblique coronal slice from the preoperative magnetic resonance imaging following the trajectory of the electrodes in participant 2. The left lead (inset) is directed through the anterior limb of the internal capsule and striatum, passing between the caudate (green) and putamen (red) with the tip in the nucleus accumbens (blue). Images are displayed in radiological orientation (left is right).*

failure to reset a stimulator after battery replacement. There were no permanent surgery- or DBS-related adverse events.

Participants 1, 2, and 3 exceeded our a priori Food and Drug Administration criteria for a clinically important difference on the MPAI-4 total score (Figure 2A and **Figure 1**, **Supplemental Digital Content**, http://links.lww.com/NEU/A834; lower scores are better), specifically, a decline of ≥3.5 points from the presurgical baseline to final follow-up. The improvements on the MPAI-4 resulted primarily from better scores on the adjustment subscale (**Table 3**, **Supplemental Digital Content**, http://links.lww.com/NEU/A834). This subscale includes items assessing mood, initiation, appropriateness of social interactions, and self-awareness. All 4 participants improved on the subscale; for 3 of 4 individuals, it was the only subscale that improved. Marked improvements were observed clinically in both the initiation for 2 participants and the impulsivity evident for the other 2 participants. Clinical observation also suggested improved alertness and engagement among all 4 participants. Two participants required less assistance in activities of daily living, and 3 of the 4 increased their involvement in activities outside of the home. Adaptation to disability and the ability to cope with everyday stressors improved in 2 of the 4 participants. Support for the efficacy of the stimulation was also suggested by the changes in pharmacological treatment that were successfully executed. One participant was weaned from quetiapine and clonazepam without adverse effects on mood regulation; attempts to wean before the surgery had not been successful. Another participant no longer required tolterodine to control urinary urgency because he had begun to self-initiate toileting. Risperidone was successfully discontinued for 1 participant without resurgence of disinhibition and aggression observed with previous attempts to wean.

The functional composite score (Figure 2B and **Table 4**, **Supplemental Digital Content**, http://links.lww.com/NEU/A834) increased significantly for all participants (repeated-measures analysis of variance, $F = 16.24$, $P < .001$). Post hoc t tests showed that the functional composite score at the 2-year follow-up (study phase 6) was significantly greater than the presurgical baseline (study phase 1; corrected $P < .001$) and the postsurgical baseline (study phase 2; corrected $P < .001$). At the 9-month follow-up (study phase 5), the functional composite score was significantly greater than the presurgical baseline (study phase 1; corrected $P < .001$) and the postsurgical baseline (study phase 2; corrected $P = .005$). Improvement in the functional composite score reflected improved independence in self-care and activities of daily living. Two participants improved by at least 10% in the physical assistance required for these activities; all 4 participants improved by at least 10% in the amount of cognitive assistance required.

Changes were also observed in participants' cognitive composite scores (repeated-measures analysis of variance, $F = 5.531$, $P = .003$); however, the pattern was a negative quadratic (Figure 2C and **Table 5**, **Supplemental Digital Content**, http://links.lww.com/NEU/A834). Post hoc t tests showed that the cognitive composite score at the end of stimulation with rehabilitation (study phase 4) was significantly greater than the presurgical baseline (study phase 1; corrected $P = .002$), postsurgical baseline (study phase 2; corrected $P = .01$), and 2-year follow-up (study phase 6; corrected $P = .02$). On an individual basis, 3 of 4 participants showed their best cognitive performance after rehabilitation. For the 1 participant who did not, rehabilitation was quite fatiguing, and the best cognitive composite score was after study phase 3, stimulation only. None of the analyses with the decision-making composite score were significant (**Table 6** and **Figure 2**, **Supplemental Digital Content**, http://links.lww.com/NEU/A834). However, the 2 participants whose behavior was marked by impulsivity showed less impulsive decision making over the course of the stimulation. The improved scores indicated that these individuals were making fewer choices based solely on immediate gain and were instead considering the net or long-term results of their choices. It was not clear that the other 2 participants grasped the tradeoffs posed by these tasks.

To examine the relationship between changes in composite scores and metabolic activation, serial fluorodeoxyglucose PET scans were taken at each study phase (see **Supplemental Digital Content** [http://links.lww.com/NEU/A834] for a complete description).

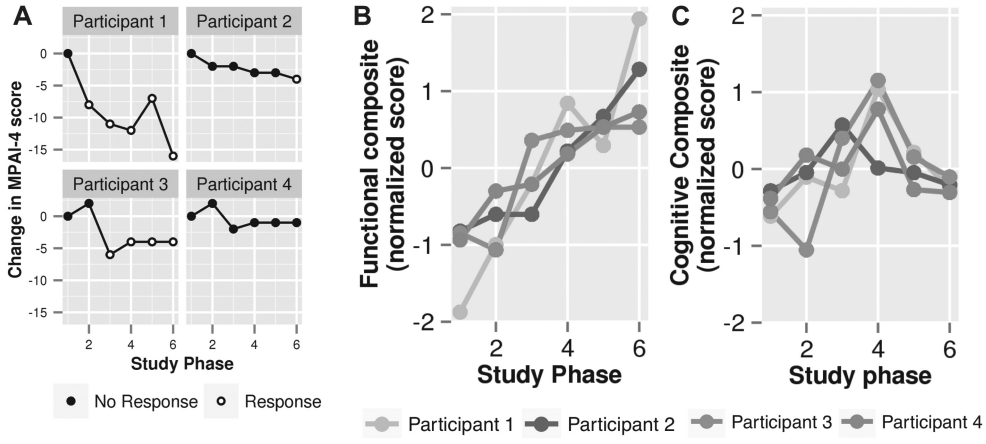


FIGURE 2. *Functional and cognitive improvements.* **A**, *Mayo-Portland Adaptability Index-4 (MPAI-4) scores for each participant. Scores are relative to presurgical baseline. Points in blue indicate a response (decrease of at least 3.5 points) compared with the presurgical baseline. Participants 1 through 3 had declines in their MPAI-4 scores >3.5 points.* **B**, *the trajectory of the normalized functional composite scores.* **C**, *the trajectory of the normalized cognitive composite scores. Color version available online only.*

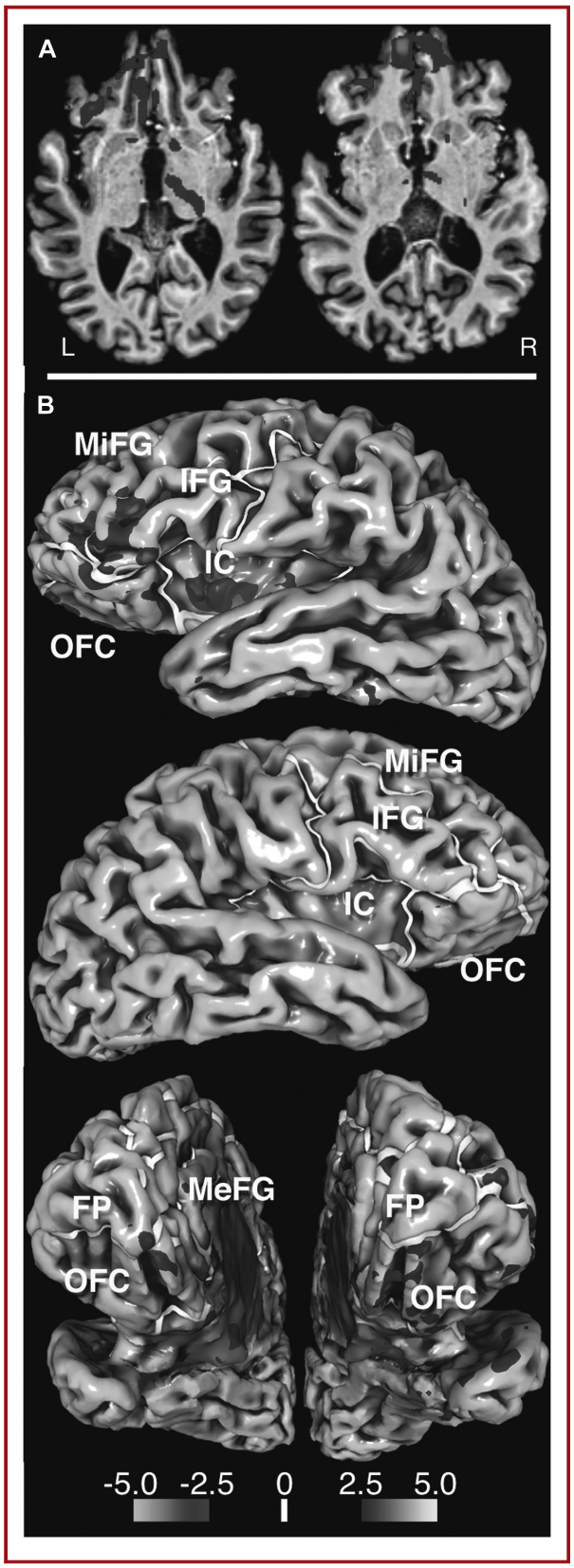
The functional composite score was not significantly correlated with relative PET activity (minimum $P = .41$). In contrast, the cognitive composite score was significantly correlated with relative PET activity (minimum $P < .01$; **Figure 3**, **Supplemental Digital Content**, http://links.lww.com/NEU/A834). As shown in Figure 3A and 3B, voxels surpassed the significance thresholds in the following areas: bilateral medial frontal cortex, left orbitofrontal cortex, bilateral anterior insula, bilateral accumbens near the stimulation site, right thalamus, left middle and inferior frontal gyrus, and left anterior cingulate, as well as along the inferior temporal lobe (not shown in Figure 3). In all regions, for all participants, a higher cognitive composite score predicted decreased relative PET activity.

DISCUSSION

In addition to affecting other parts of the brain, severe TBIs have a profound effect on the frontal lobes, manifesting in chronic impairments in self-care, activities of daily living, and executive functions, including emotional regulation and behavioral control. DBS of the thalamus has previously been attempted in patients with TBI in the vegetative or minimally conscious state with the goal of improving arousal and attention.[27,28] The goal of our study, however, was to specifically investigate DBS for the larger group of patients with severe TBI whose primary limitations after acute recovery were not due to poor arousal but were related to residual sensory, motor, or cognitive impairments to which they are not successfully adapting as a result of concomitant deficits in emotional and behavioral control. For these individuals, disability is the confluence of impairments limiting function and poor adaptation to those impairments. All subjects in our study had chronic (6-21 years after injury), severe deficits and required assistance from another person for activities of daily living and supervision in the home and community. The choice of target for DBS was intended to provide a means of modulating frontal lobe networks, particularly those regulating emotion and behavior. We expected that better self-regulation would allow better adaptation to residual sensory, motor, and cognitive impairments, which would in turn allow greater independence in self-care and activities of daily living, as well as participation in the community.

Results of the present study indicated that DBS of the NAcc/IC was safe. This result is not surprising because this target has a decade of safety data for patients with obsessive-compulsive disorder, depression, and other conditions. Our safety profile was consistent with previous studies in that there was a near absence of serious adverse events directly related to the treatment procedure. Furthermore, of 7 individuals who met inclusion criteria, only 2 were disqualified because localized brain damage precluded safe placement of the electrodes bilaterally. Thus, at this juncture, we would conclude that for a substantial proportion of individuals with severe disability resulting from TBI, DBS targeting the NAcc/IC can be performed safely.

Results of the present study also suggested that DBS can significantly improve functional independence. Three of our 4 participants met a priori criteria for improvement 2 years after implantation. Although 1 participant made dramatic changes on all 3 subscales of our primary outcome measure, improvement for the other 3 participants was limited to the adjustment subscale. This observation was consistent with our expectation that DBS to this target would improve emotional regulation and behavior control. Also as expected, the linear pattern of significant improvement for the functional composite scores suggested that there may be carryover from improved executive control to



a reduction in support required from another person to perform self-care and activities of daily living. Examination of the trajectories shown in Figure 2 indicated that most participants made steady progress up to and including their 2-year follow-up (the decline for participant 1 at the 9-month follow-up was due to unrelated, extraordinary life circumstances occurring simultaneously). Even the participant who did not qualify as a responder showed progressive improvement on the functional composite score.

An unexpected finding was the negative quadratic relationship between cognitive composite scores and study phase, indicating that cognitive abilities improved initially and then declined. Cognitive function increased with stimulation and, for 3 of 4 participants, increased further with rehabilitation. However, as time passed without continued training, performance returned to baseline for all participants. The cognitive composite score was composed of granular abilities dependent primarily on information processing speed, working memory, and recall. The everyday lives of our participants did not afford them opportunities to specifically practice granular cognitive skills, which may have led to their decline after rehabilitation. In contrast, opportunities for emotional regulation, behavior control, self-care, and activities of daily living would have continued after rehabilitation, which may account for those gains being sustained. This explanation would suggest that the greatest gains from DBS to this target for this population will occur when stimulation can be combined with rehabilitation and optimized enrichment of everyday activities.

It is not clear why change in PET results was more closely associated with the cognitive than the functional composite score. One explanation is that voxel-level representation of metabolic activity captures brain function indicative of cellular phenomena that may be more closely associated with the performance of the types of granular cognitive skills tested here. Independence in self-care and activities of daily living as captured in the functional composite score may be more dependent on the efficacy of networks in the brain, for which our PET results were not sensitive. Potentially consistent with this explanation was the observation that improved cognitive performance was associated with relatively less metabolic activity in select areas of the prefrontal cortex. The improved capability, although short-lived, appeared to be accomplished with greater metabolic efficiency.

FIGURE 3. *Correlation of composite scores with relative metabolic activity. The* t *statistic of the cognitive composite score (***A** *and* **B***) relative to positron emission tomography activity was determined in a common group space and projected onto the baseline T1-weighted magnetic resonance imaging of participant 1. Axial slices (***A***) show the areas of significance in the orbital frontal cortex (OFC), right thalamus, and bilateral nucleus accumbens. Results projected onto the partially inflated cortical surface (***B***) show the cortical extent, with significant regions in the OFC, medial frontal gyrus (MeFG), middle frontal gyrus (MiFG), inferior frontal gyrus (IFG), insular cortex (IC), and temporal pole. There are additional significant regions along the left inferior temporal lobe (not shown). FP, frontal pole. Color version available online only.*

CONCLUSION

This is the first study demonstrating the safety and efficacy of DBS to the NAcc/IC for individuals who incurred severe, chronic, disabling TBI 6 to 20 years after injury. DBS of this target appears to be safe. Two years after implantation, 3 of our 4 participants met a priori criteria for clinically important improvements marked by greater emotional regulation and behavior control. Three of our 4 participants demonstrated steady gains in functional independence up to and including the 2-year follow up. The open-label study design does not preclude the possibility that an attention placebo effect caused or contributed to the outcomes reported here. However, the results support the need for further investigations using randomized, sham-controlled comparisons.

Disclosures

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COMMENTS

There are currently few therapeutic options for chronic behavioral and emotional sequelae of traumatic brain injury. To evaluate neuromodulation as a novel approach, 4 patients with sustained behavioral and executive dysfunction many years after severe automobile accidents were treated with deep brain stimulation of the bilateral nucleus accumbens and anterior limb of the internal capsule. Each participant underwent programming titration based on clinical response and was assessed before and after rehabilitation and again at 9 and 24 months. By the end of the study, 3 of the 4 participants were found to have at least a 3.4-point improvement in the Mayo-Portland Adaptability Inventory-4, which was defined as the minimal change for meaningful improvement. The authors conclude that deep brain stimulation of fibers connected to the prefrontal cortex

may be an option for chronic behavioral and emotional problems after traumatic brain injury.

Traumatic brain injury is a major clinical problem, and discovery of a neuromodulation option would be a fantastic accomplishment. It is therefore unfortunate that this study was not appropriately controlled, because it is impossible to determine the contribution of placebo effect, Hawthorne effect, response to concomitant rehabilitation, regression to the mean, or even late natural recovery, any one of which could explain the findings. Although a majority of subjects did meet criteria for response that were defined a priori, the actual change was fairly small and possibly clinically insignificant. Finally, deep brain stimulation of the target selected for this study appears to be searching for an indication; it has previously been used to treat obsessive-compulsive disease, major depression, Tourette syndrome, and Alzheimer-type dementia. It is suspicious that conditions with such diverse pathophysiology seem to demonstrate similar response when this target is stimulated. This study offers tantalizing hints that deep brain stimulation might help social and behavioral deficits long after brain injury, but definitive proof will require future study.

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The authors report a phase I, Food and Drug Administration–approved trial of deep brain stimulation (DBS) of patients having chronic disability years after traumatic brain injury (TBI). Four patients, each of whom had magnetic resonance imaging evidence of cerebral atrophy, had bilateral DBS systems placed in the anterior limb of the internal capsule/nucleus accumbens. This was an open-label study with the primary outcome measure being improvement on the Mayo-Portland Adaptability Inventory-4, a psychological metric developed for measuring outcomes after TBI that probably is not familiar to many neurosurgeons. It has been validated with psychological and statistical means.

There were no lasting adverse outcomes in any of the patients. Three of the 4 participants had significant improvement, mainly on the adjustment subscale of the Mayo-Portland Adaptability Inventory-4. This measures mainly mood, initiation, appropriateness of social interactions, and self-awareness. The authors note the possible bias in an open-label study such as this. Fluorodeoxyglucose positron emission tomography scans showed that a higher cognitive score predicted decreased positron emission tomography activity in the frontal lobes. The authors note, "Two participants improved by at least 10% in the physical assistance required for these activities; all 4 participants improved by at least 10% in the amount of cognitive assistance required."

Given that each of the patients included in this study had brain atrophy, as expected years after severe TBI, it is no surprise that the actual clinical benefits observed were relatively modest. This loss of functional brain tissue will remain the main limitation for DBS and other neuro-augmentation procedures for individuals with brain injury. However, the measurable improvement seen in this pilot study raises intriguing questions: Would a more complex stimulation platform, beyond single bilateral electrodes, yield greater benefit? Would stimulation in the subacute phase after TBI likewise be more beneficial and perhaps (a Holy Grail of DBS) neuroprotective and mitigate the degree of brain atrophy?

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