Deep brain stimulation for dementias

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OBJECTIVE The aim of this article is to review the authors’ and published experience with deep brain stimulation (DBS) therapy for the treatment of patients with Alzheimer’s disease (AD) and Parkinson’s disease dementia (PDD).

METHODS Two targets are current topics of investigation in the treatment of AD and PDD, the fornix and the nucleus basalis of Meynert. The authors reviewed the current published clinical experience with attention to patient selection, biological rationale of therapy, anatomical targeting, and clinical results and adverse events.

RESULTS A total of 7 clinical studies treating 57 AD patients and 7 PDD patients have been reported. Serious adverse events were reported in 6 (9%) patients; none resulted in death or disability. Most studies were case reports or Phase 1/2 investigations and were not designed to assess treatment efficacy. Isolated patient experiences demonstrating improved clinical response after DBS have been reported, but no significant or consistent cognitive benefits associated with DBS treatment could be identified across larger patient populations.

CONCLUSIONS PDD and AD are complex clinical entities, with investigation of DBS intervention still in an early phase. Recently published studies demonstrate acceptable surgical safety. For future studies to have adequate power to detect meaningful clinical changes, further refinement is needed in patient selection, metrics of clinical response, and optimal stimulation parameters.

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KEYWORDS Alzheimer’s disease; cognitive decline; deep brain stimulation; dementia; functional neurosurgery; Parkinson’s disease

The proportion of older people in the global population is constantly growing, with projections indicating that by 2050 more than 22% of the world’s inhabitants will be older than 60 years of age. Concurrent with the aging of the populace, the global prevalence of dementia is expected to increase from 35.6 million cases in 2013 to more than 115.4 million by 2050. As a result, the health and social burden of neurodegenerative conditions resulting in cognitive impairment and dementia will increase dramatically. Although much progress has been made in understanding the neurobiology of dementias, no treatments are currently available to significantly alter their natural history. An emerging avenue of therapy currently under investigation is deep brain stimulation (DBS), which has demonstrated an ability to engage and regulate dysfunctional neuronal circuits across multiple neural networks. Furthermore, cellular responses that occur after DBS may direct trophic effects to local neural tissue, potentially counteracting chronic degenerative disease processes. In this manuscript, we provide a summary of the current body of literature examining different DBS targets under investigation for the treatment of dementia and present our own experience with the use of DBS for dementia. Topics addressed include the biological rationale of therapy, anatomical targeting, and the clinical responses and adverse effects that may be encountered.

Rationale for DBS Therapy in Dementias

The underlying premise of DBS for many neurological and psychiatric illnesses is circuit dysfunction across single or multiple neural networks. Through metabolic, functional, and electrophysiological studies, key aberrant nodes are identified that may be accessible for therapeutic intervention. DBS treatment of those nodes can disrupt abnormal circuit activity or drive and thereby rescue un-
derperforming circuits, restoring the normal physiological network activity. In patients with dementia, key dysfunctional circuits governing memory and cognition, such as the cholinergic signaling system, pose attractive targets.

In addition to the direct electrical effects of DBS, cellular trophic changes also occur locally at distant interconnected sites. In rodent studies examining DBS of the anterior thalamus and entorhinal cortex, an up to 3-fold increase in neurogenesis was observed in the subgranular zone of the dentate gyrus, concurrent with improved performance on spatial memory–associated tasks. After behavioral assessments, these cells expressed c-fos, which is repressed by antimitotic agents, suggesting that the cells are physiologically active and able to integrate within working neural circuits. In humans, analogous hippocampal neurogenesis also occurs in adults, but whether this capacity can be leveraged by DBS to reverse cellular degeneration in various types of dementia remains unknown.

**Treatment of Alzheimer’s Disease**

**General Considerations**

More than a century ago, Alois Alzheimer first described amyloid plaques and neurofibrillary tangles as the neuropathologic hallmarks of the disease subsequently named after him. Since then, a unifying model of Alzheimer’s disease (AD) pathogenesis has remained controversial. However, on a macroscopic level, disease progression is believed to originate from cellular dysfunction due to aberrant deposition of amyloid-β and tau that incrementally accumulates, causing local synaptic dysfunction that then leads into further dissolution of larger networks governing memory, executive function, and language. On positron emission tomography (PET) and functional MRI, hypometabolism and network disruption are observed across mesial temporal and parietal memory association areas, with compensatory changes observed in the resting state networks within the precuneus (i.e., midline parietal cortices) and multiple subcortical areas at the earliest stages of the disease. Anatomical studies reveal progressive early cell loss and atrophy within the entorhinal cortex, hippocampus, amygdala, and posterior cingulate, with subsequent evolution into the temporal lobe and global neocortex closely mimicking the spread of neurofibrillary tangles in the Braak staging system.

Pharmacological treatments for AD generally consist of agents that increase cholinergic or glutamnergic signaling, but these therapies offer only mild temporary clinical gains. Disease progression is inexorable, with a median life expectancy of 3.7–7.6 years after diagnosis; several factors, such as the severity of illness at the time of diagnosis, influence life expectancy. Interestingly, an older age of AD onset has been associated with a slower rate of cognitive decline rather than a younger age, suggesting that AD onset in the young may represent a different disease phenotype.

**Fornix Stimulation**

**Rationale and Targeting**

Table 1 presents a summary of DBS targeting data reported on the rationale for, and targeting of, fornix stimulation. The cognitive effects of fornix stimulation were first encountered incidentally during bilateral DBS treatment of the hypothalamus in a cognitively normal 50-year-old patient being treated for obesity. Intraoperative stimulation of either electrode elicited vivid déjà vu experiences. Trajectory analysis of the electrode position revealed that its ventral leads were adjacent to the columns of the fornix. Three weeks postoperatively, the patient exhibited multiple improvements (several standard deviations) on the California Verbal Learning Test and Spatial Associative Learning Test. Additional analysis with standardized low-resolution electromagnetic tomography showed that lead activation drove electrophysiological activity in the medial temporal structures and hippocampus.

Anatomically, the fornix is the principal output tract of the hippocampus, containing over 1.2 million axon fibers that project into the circuit of Papez. Injury to the fornix has long been known to cause anterograde amnesia, and the effects of stimulation are thought to conversely drive activity throughout its associated memory networks that may be leveraged in patients with AD. Stereotactic targeting of the fornix involves placement of leads 2 mm anterior and tangential to the columns of the fornix through a transventricular trajectory with an entry point approximately 2 cm lateral to the midline (Fig. 1A). The

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**TABLE 1. Summary of stereotactic targeting**

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>Pathology</th>
<th>Target</th>
<th>Stereotactic Coordinates*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turnbull et al., 1985</td>
<td>AD</td>
<td>NBM</td>
<td></td>
</tr>
<tr>
<td>Freund et al., 2009</td>
<td>PDD</td>
<td>NBM</td>
<td>x = 12.5 mm lateral to wall of 3rd ventricle; y = 4 mm posterior to anterior border of AC; z = −5 mm from midcommissural plane</td>
</tr>
<tr>
<td>Laxton et al., 2010</td>
<td>AD</td>
<td>Fornix</td>
<td>Target depth is 2 mm dorsal to optic tract &amp; 2 mm anterior to column of fornix</td>
</tr>
<tr>
<td>Kuhn et al., 201527</td>
<td>AD</td>
<td>NBM</td>
<td>x = 26.5 ± 3.9 (range 20–33.2); y = 7.7 ± 1.1 (range 6.2–10); z = −7.1 ± 1.3 (range 5.2–10)</td>
</tr>
<tr>
<td>Kuhn et al., 201528</td>
<td>AD</td>
<td>NBM</td>
<td>NA</td>
</tr>
<tr>
<td>Lozano et al., 2016</td>
<td>AD</td>
<td>Fornix</td>
<td>x = 4.4 ± 1.1; y = 9.8 ± 1.8; z = −7.2 ± 1.5</td>
</tr>
<tr>
<td>Gratwicke et al., 2018</td>
<td>PDD</td>
<td>NBM</td>
<td>x = 19.8 ± 1.7 (range 17.6–23.0); y = 6.0 ± 1.5 (range 4.9–9.5); z = 4.9 ± 1.2 (range 2.9–6.4)</td>
</tr>
</tbody>
</table>

* Stereotactic coordinates are given as distance in millimeters from the midcommissural point unless otherwise stated. For first listed study by Kuhn et al. and the studies by Lozano et al. and Gratwicke et al., the mean values of the coordinates are provided with SDs and ranges.
depth of the ventral-most contact lies just proximal to the mammillary body (Fig. 1B). Intraoperative stimulation of the deepest contact should elicit autonomic signs such as blood pressure variation, tachycardia, and diaphoresis. In our experience, a small proportion of patients may also experience autobiographical memories when the most dorsal contact is stimulated above 7 V.

Outcomes and Adverse Events

Table 2 summarizes the DBS clinical data reported on the outcomes and adverse events of fornix stimulation. Laxton et al. performed a Phase 1 study, evaluating 6 patients with probable early AD (Mini-Mental State Examination scores above 20) treated with continuous bilateral fornix stimulation for 12 months. Parameters of stimulation consisted of a monopolar setting with amplitudes of 3–5 V, a frequency of 130 Hz, and a pulse width of 90 μsec. Increased fluorodeoxyglucose uptake across the temporoparietal lobes was seen on 1-month postoperative PET imaging and persisted up to 1 year after surgery in all patients. At 1 year after surgery, 5 patients demonstrated a decreased rate of cognitive decline based on their Mini-Mental State Examination scores compared to their clinical course before surgery. No adverse events were encountered during follow-up.

The results of a follow-up Phase 2 randomized, multicenter, double-blind, controlled trial (ADvance) assessing 42 patients with mild AD were reported in 2016 by Lozano et al. The study participants were men and women aged 45–85 years with probable AD according to the NINDS-ADRDA (National Institute of Neurological Disorders and Stroke–Alzheimer’s Disease and Related Disorders Association) criteria and mild dementia, classified as a score of 0.5 or 1 on the Clinical Dementia Rating Sum of Boxes (CDR-SB) and scores of 12–24 on the Alzheimer’s Disease Assessment Scale–Cognitive subscale 13 (ADAS-Cog 13). Postoperatively, patients were randomized to receive either sham or active stimulation of the top or second from top contact with monopolar settings of 3.0–3.5 V, 130 Hz, and 90-μsec pulse width for 12 uninterrupted months.

At the end of the study, changes in ADAS-Cog 13 and CDR-SB scores did not differ significantly between the treatment and sham groups. On PET imaging, the “on” group demonstrated statistically significant increases in metabolism across several brain regions 6 months after randomization that were not sustained at 12 months. Interestingly, on post hoc analysis, different clinical outcomes were associated with age. Younger patients (age < 65 years) showed the greatest cognitive decline across treatment and sham groups, with young patients who received stimulation demonstrating the greatest degree of decline across all groups. Patients older than 65 years showed the least decline on the ADAS-Cog 13 and CDR-SB at 12 months, as well as the greatest magnitude of metabolic increase throughout the entire patient population. Given that young AD patients are known to have a worse clinical course than older patients, and that they were overrepresented in the ADvance trial (28.6% vs 4% in the general population), these considerations are informative for the design of future trials.

A detailed summary of the safety outcomes in the ADvance trial has been published previously. Briefly, 5 (11.9%) of 42 patients experienced a serious adverse event. Of these 5 patients, 2 developed an infection in the location of the internal pulse generator that required explantation of the device, 1 patient returned to surgery for repositioning of the lead based on suboptimal placement seen on imaging, 1 patient developed bilateral chronic subdural hematomas that required evacuation, and 1 patient experienced severe headache and nausea requiring 2 additional nights of hospitalization.

**Nucleus Basalis of Meynert Stimulation**

**Rationale and Targeting**

Cholinergic signaling of the hippocampus and associated networks plays a significant role in encoding and consolidation of nascent memories. The nucleus basalis of Meynert (NBM) is a pivotal cholinergic relay that projects widespread connections to the neocortex and mesial temporal lobes. In AD patients, selective cell loss is observed in the NBM, but not in adjacent subcortical structures, which supports the role of cholinergic deficiency as a
cause of cognitive decline and the use of anticholinesterase inhibitors as pharmacological therapy. In rodent studies, stimulation of the NBM has been shown to enhance visual memory and global cortical acetylcholine signaling. In this report, a patient with early AD underwent placement of a unilateral electrode in the left NBM. No clinical benefit was reported after 9 months of therapy, but at the 2-month follow-up fluorodeoxyglucose-PET imaging showed that the patient’s stimulated left temporal and parietal lobes had undergone metabolic decline at half the rate of the contralateral hemisphere.

Outcomes and Adverse Events

The first report of NBM targeting for the treatment of AD was published in 1985 by Turnbull et al. In this report, a patient with early AD underwent placement of a unilateral electrode in the left NBM. No clinical benefit was reported after 9 months of therapy, but at the 2-month follow-up fluorodeoxyglucose-PET imaging showed that the patient’s stimulated left temporal and parietal lobes had undergone metabolic decline at half the rate of the contralateral hemisphere.

In 2015, Kuhn et al. reported the results of a Phase 1 clinical trial involving 6 patients with mild to moderate AD based on NINDS-ADRDA criteria and with cerebrospinal fluid changes involving tau and amyloid-β42 associated with AD. All 6 patients underwent bilateral placement of electrodes in the NBM Ch4i and then participated in a 2-week-long randomized, double-blind, sham stimulation, controlled phase in which they were assigned to a treatment group with monopolar stimulation of the deepest contact (2.5 V, 20 Hz, 90 μsec) and then converted to sham stimulation or vice versa. All patients then participated in an open-label stimulation phase until 1 year after surgery. At the end of follow-up, 2 patients showed declines in their ADAS-Cog 13 scores, 3 patients showed...
no changes, and 1 patient demonstrated an improvement of 9 points. Metabolic PET imaging was performed longitudinally in 4 patients, 3 of whom demonstrated a 2%–5% global increase in glucose metabolism, most prominently in the temporal regions, that was sustained to 1 year after surgery. No adverse events associated with surgery or stimulation were reported.

Kuhn et al. later reported on NBM stimulation in 2 additional AD patients who were younger and had less severe baseline ADAS-Cog scores than the 6 patients in their earlier cohort. These 2 patients underwent open-label stimulation with 2 years of follow-up. There were no adverse events associated with surgery or stimulation. At the end of the study, one patient exhibited a 7-point decline in the ADAS-Cog score after 26 months of follow-up and the other patient showed no cognitive decline after 24 months of stimulation.

**Treatment of Parkinson’s Disease–Associated Dementia**

**General Considerations**

Dementia is common in Parkinson’s disease (PD) patients, with a prevalence ranging from 24% to 31% according to a meta-analysis of several cross-sectional studies. Furthermore, 19%–38% of PD patients, even at the time of diagnosis, may have mild cognitive impairment (MCI), a condition defined by the Movement Disorder Society Task Force as decreased performance in one or several neuropsychiatric or cognitive domains below the age-expected norm but not exceeding the threshold for diagnosis of Parkinson’s disease dementia (PDD). In PD patients with a disease duration exceeding 10 years, the incidence of dementia can exceed 75%, and PD patients with MCI may represent a vulnerable population likely to undergo decline sooner.

The cognitive profile of the PDD patient differs from that of the AD patient, with PDD consisting of heterogeneous deficits involving executive function, visuospatial function, and, less prominently, memory. Furthermore, cardinal features of PD are neuropsychiatric symptoms, including visual hallucinations, delusions, depression, anxiety, and sleep disorders—all occurring frequently in PD patients without dementia. The presence of visual hallucinations is strongly correlated with cognitive dysfunction and a higher risk of progression to dementia.

The pathogenic basis of cognitive decline in PDD is still not fully understood, but, as in AD, the disruption of cognitive circuits may begin with primary local cellular pathology, which in the case of PD are Lewy bodies. Neuropathologic studies indicate a strong correlation between the neuroanatomical spread of Lewy bodies and the severity of cognitive impairment and dementia. Anatomically, PDD patients also exhibit progressively more global brain atrophy and pronounced cell loss in the limbic and paralimbic structures than PD patients without dementia compared to age-related normal controls. Biochemically, deficits in cholinergic signaling are a critical disease process in PDD that appear to be even more significant than changes in AD. Cholinesterase inhibitors offer a mild to modest benefit in PDD, similar to that afforded AD patients.

**Rationale and Targeting**

In PDD, the NBM has been shown to lose up to 70% of its cellular population with less marked deficits found in comparable AD patients, which suggests that the NBM may be an even more critical substrate to modulate in patients with PDD. As previously discussed, targeting specific subsections of the NBM is challenging given its lack of definite anatomical borders, but multiple groups have chosen to target the intermediate nucleus of the NBM (Ch4i) as in AD therapy.

**Outcomes and Adverse Events**

The first instance of NBM stimulation for treatment of a patient with PDD was described in a case report by Freund et al. The investigators treated a 71-year-old...
man with PD and evidence of PDD based on *Diagnostic and Statistical Manual of Mental Disorders, 4th Édition* (DSM-IV) criteria. One week before surgery, the patient underwent a neuropsychological battery that included the Letter-Number-Span test, Digit Symbol Test, Trail Making Test Part B, and Rey Auditory Verbal Learning Test (AVLT). Bilateral electrodes were subsequently implanted in the subthalamic nucleus and NBM Ch4i. For the first 6 weeks after surgery, the patient had only the subthalamic nucleus stimulation turned on, and yet he demonstrated generalized improvement in his neuropsychiatric test scores except for the AVLT, which was interpreted as generalized gains due to improved motor function rather than improved memory. The patient was then treated with stimulation of both NBM leads with a monopolar stimulation setting for the bottom 2 contacts (1.0 V, 20 Hz, 120 μsec). Over the course of 8 weeks after both leads were activated, the patient displayed further improvement in his entire neuropsychological battery, including the AVLT. These gains were negated when the NBM stimulation was stopped but were restored 3 months later upon resumption of stimulation. No adverse events occurred in association with surgery or stimulation.

A Phase 1 randomized, double-blind, crossover clinical trial was completed in 2017 by Gratwicke et al. Six patients with PDD who were diagnosed using criteria from the Movement Disorder Society underwent placement of bilateral NBM electrodes targeting the NBM Ch4i region with a trajectory that also intersected the globus pallidus interna. The study then proceeded into a double-blind phase in which patients were first assigned to receive either sham stimulation or active treatment for 6 weeks followed by crossover. Cognitive and neuropsychiatric evaluation occurred before surgery and after each randomization period. The stimulation settings were variable amplitude, 20-Hz frequency, and 60-μsec pulse width. At the end of the trial, no significant changes in cognitive performance were encountered. However, scores on the Neuropsychiatric Inventory, which assesses dementia-related behavioral disturbances, showed statistically significant improvement between sham and stimulation. The predominant driver of the Neuropsychiatric Inventory improvement was cessation of visual hallucinations in 2 patients that occurred during stimulation but then recurred immediately after cessation of stimulation. One serious adverse event occurred in 1 patient involving erosion of an electrode cap through the scalp 15 months after surgery, requiring reoperation.

We are currently conducting a Phase 1 randomized, double-blind, crossover clinical trial (NCT02924194) evaluating 6 patients with PD and MCI. Eligible patients are those diagnosed with the amnestic subtype of PD-MCI and selected by a consensus committee of movement disorder specialists who determined that they would benefit from DBS treatment of the globus pallidus interna for motor symptoms. The selected patients are implanted with bilateral electrodes in the NBM Ch4i and globus pallidus interna, and then they are assigned to either a sham group for 3 months, followed by a 3-month crossover and then by an open-label period. The primary outcome measure is patient safety, including adverse events, and the secondary outcome measure is cognitive performance assessed annually by ADAS-Cog 13 scores during the 3-year open-label phase. Currently, we have completed lead placement in 3 patients and anticipate completion of the study in 2021.

**Discussion**

Seven studies have examined DBS as a therapeutic intervention for the treatment of AD or PDD in 64 patients (Table 1). Despite individual patient experiences, no conclusive evidence regarding benefits associated with DBS can be made on a higher-order level; most of these studies were either case reports demonstrating proof-of-concept or Phase 1 investigations not designed to evaluate efficacy. However, these preliminary data demonstrate several topics worth considering as future studies are pursued.

First, surgical risk and morbidity appear to be quite low among these patients, with a low incidence of major adverse events. Similarly, no discrete stimulation-related adverse events were observed, but the clinical course of patients under 65 years of age in the AD/ DBS trial is concerning. At the end of 1 year of treatment, 6 patients younger than age 65 in the stimulation group had a 2-fold higher decline in their ADAS-Cog 13 scores and an 8-fold higher decline in their CDR-SB scores compared to patients in the sham group, with the difference with respect to CDR-SB scores reaching statistical significance. Given the small numbers of patients and reports indicating that young AD patients may represent a more aggressive AD phenotype, it is uncertain whether DBS should be withheld from this patient population. At the very least, narrower age restrictions should be used in future fornix DBS trials for AD.

Second, given the inexorable, but heterogeneous progression of cognitive decline in both AD and PDD patients, establishing controls to detect meaningful clinical responses is a considerable challenge. No objective quantitative measures of disease severity are available, and patients frequently have incongruent clinical and radiographic disease severity; moreover, rates of disease progression vary within as well as among individuals. Overcoming this limitation necessitates either very large patient groups to follow or the use of additional radiographic or biochemical correlates of disease severity.

Lastly, refinement of both target localization and stimulation parameters is warranted. For both fornix and NBM DBS, the choice of stimulation parameters has been somewhat arbitrarily derived from animal models. Varying stimulation settings, locations, and cycling variables to maximize current density or prevent tachyphylaxis may significantly impact the biological effects of therapy. However, a short-term measure of response is needed. Furthermore, for NBM targeting, greater consensus is needed on target planning and on standardized anatomical landmarks used to localize the target.

**Conclusions**

DBS treatment of dementias is still in a nascent phase because of the inherent complexity of the disease processes, the heterogeneous rates of clinical progression, and the variable phenotypic presentation of patients. Early stud-
ies show individual patient responses that deviate from the expected natural history of their disease but population-wide effects have yet to be demonstrated. To propel future studies, we need further refinement of patient selection, consolidation with other markers of disease severity, and iterative exploration of different stimulation parameters.

Acknowledgments

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: both authors. Acquisition of data: both authors. Analysis and interpretation of data: both authors. Drafting the article: both authors. Critically revising the article: both authors. Reviewed submitted version of manuscript: both authors. Administrative/technical/material support: both authors. Study supervision: both authors.

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