The Neurosurgical Treatment of Alzheimer's Disease: A Review

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Key Words

Alzheimer's disease · Deep brain stimulation · Neurosurgery · Therapy effects · Cognition

Abstract

Background: Alzheimer's disease (AD) is a debilitating neurological illness of increasing prevalence. Because many patients are affected and current treatments have limited effectiveness, other therapeutic strategies are urgently needed. **Objectives:** Here we provide a review of the neurosurgical approaches that have been attempted or are currently being investigated for the treatment of AD. **Methods:** Computerized database searches identified all of the published studies in the English-language literature examining the surgical treatment of AD since 1950. **Results:** The following 5 categories of neurosurgical treatment were identified: cerebrospinal fluid shunting, intraventricular infusions, tissue grafting, gene therapy, and electrical neural stimulation. **Conclusions:** While none of the neurosurgical approaches applied to the treatment of AD have proven effective to date, recent trials involving gene therapy and electrical neural stimulation are showing promising early results. Larger trials investigating these treatments have been proposed or are currently under way.

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Introduction

The field of neurosurgery has traditionally focused on the identification and elimination of structural pathologies in the brain and spine. More recently, however, neurosurgeons have made important contributions to the treatment of functional neurological disorders. Deep brain stimulation (DBS) has become a well-established therapeutic modality in the treatment of some movement disorders, and it may also have a role in the treatment of certain neuropsychiatric conditions [1–3]. Perhaps less well known, however, is that over the past 40 years neurosurgeons have also attempted to apply neurosurgical approaches to the treatment of dementia, and specifically Alzheimer's disease (AD). In this paper, we review the published literature examining the neurosurgical treatment of AD in humans.

Methods

The primary literature search was made using Ovid OLDMEDLINE 1950–1965, Ovid MEDLINE 1966–2012, Ovid MEDLINE Corrections, Ovid MEDLINE in Process and Other Non-Indexed Citations, EMBASE (Excerpta Medica Database), and All EBM (Evidence-Based Medicine) Reviews (Cochrane Database of Systematic Reviews, American College of Physicians Journal Club, Database of Abstracts of Reviews of Effects, and Cochrane Central Register of Controlled Trials). The search terms were as follows: 'Alzheimer' OR 'dementia' AND 'surg' AND 'tri-

Table 1. Categories of neurosurgical therapy applied to the treatment of AD

CSF shunting
Intraventricular infusions
Tissue grafting
Gene therapy
Electrical neural stimulation

al' OR 'treatment' OR 'therap' (all terms in title or abstract). Then a search using the MESH headings 'Alzheimer, surgery' and then 'Alzheimer, drug therapy' was made using PubMed. This yielded a set of relevant articles. The reference sections of each of these articles were then examined to find pertinent articles not identified with the original database searches. These articles were then entered into the Web of Science to identify articles that had cited them. Finally, PubMed searches were conducted with the search terms 'shunt', 'infusion', 'omentum', 'transplantation', 'gene therapy', 'vagus nerve stimulation', and 'deep brain stimulation', along with 'Alzheimer' and 'dementia'. With each search, the PubMed function 'Related Citations' was used to identify any other potentially relevant studies.

The literature search outlined above identified 24 articles describing trials of surgical AD treatments with human participants. These trials can be divided into the following 5 categories of surgical approaches: cerebrospinal fluid (CSF) shunting [4–7], intraventricular infusions [8–16], tissue grafting [17–19], gene therapy [20, 21], and electrical neural stimulation [22–26] (table 1). The specific treatment strategies within each category are described in detail below (table 2).

Published Human Trials of Neurosurgical Treatments for AD

CSF Shunting

Interest in the potential benefits of CSF shunting for the symptomatic treatment of patients with dementia arose after the work of Adams et al. [27]. They were the first to propose the dementia syndrome of normal pressure hydrocephalus and to describe how it could be treated with CSF shunting. Following the report of Adams et al, Appenzeller and Salmon [4] and Salmon [5] described the use of ventriculoatrial shunting to treat patients with cerebral atrophy and dementia. The postulated rationale for this intervention was that, by lowering intracranial pressure, CSF shunting could enhance cerebral blood flow and thereby increase nutrient support to degenerating but still partly functional neurons. Although the authors claim that CSF shunting was beneficial to these patients, methodological deficiencies, including participant heterogeneity, subjective outcome measures and a

brief follow-up interval, limit the interpretation of these studies.

More recently, Silverberg et al. [6] revisited the potential for CSF shunting to treat AD. The rationale for this work was based on research showing abnormal clearance of tau and A β proteins in the CSF of AD patients [28]. By increasing CSF clearance, Silverberg et al. [6] hypothesized that shunting could help to clear these toxic proteins and thereby slow or stop the progression of disease. After a promising pilot study [6], a larger, multicenter, randomized, double-blind, placebo-controlled, clinical trial involving 215 participants was halted for futility after it was unable to show any benefit with treatment [7]. Interest in CSF shunting for AD has since waned.

Intraventricular Infusions

Several agents have been infused into the cerebroventricular system of AD patients in an attempt to treat the condition. The substances that have been used in human trials can be divided into 2 categories: cholinergic agents (bethanechol chloride and nerve growth factor, NGF) and neuroprotective factors (monosialotetrahexosylganglioside, GM1).

Bethanechol Chloride

Harbaugh et al. [12] reported the first attempted therapeutic infusion of a cholinergic agent into the CSF of AD patients. The rationale for such an approach was based upon the cholinergic hypothesis [29] that decreased synthesis of acetylcholine is a fundamental neurochemical factor related to the cognitive deficits in AD. Bethanechol chloride, a water-soluble muscarinic agonist, was delivered using a fully internalized, continuous infusion device. This initial trial was then soon followed by similar studies conducted by Penn et al. [13] and Read et al. [14]. In these studies, intraventricular bethanechol chloride commonly induced nausea with no clear therapeutic benefit. Harbaugh [10] and Harbaugh et al. [11] went on to conduct a larger placebo-controlled, double-blind, single crossover study and found that intraventricular bethanechol chloride did not produce clinically meaningful improvements in AD. No further studies investigating this therapeutic strategy have been published.

Nerve Growth Factor

The next agent to be tried was NGF. Exogenously delivered NGF has been shown to rescue compromised cholinergic neurons and reverse memory impairments in animal studies [30, 31]. Given that the remaining cholinergic

Table 2. Summary of neurosurgical trials for AD

Study: first author	Technique	Design	n	Follow-up, months	Outcome		
					improved	no change	worsened
<i>CSF shunting</i>							
Appenzeller [4]	VA shunt	Case study	1	–	1	–	–
Salmon [5]	VA shunt	Case series	18	2	7	8	3
Silverberg [6]	VP CogniShunt	Open-label RCT	29	12		Possible benefit	
Silverberg [7]	VP CogniShunt	Double-blind RCT	215			No benefit	
<i>Intraventricular infusions</i>							
Harbaugh [12]	Bethanechol	Phase 1 trial	4	8		Positive subjective response	
Harbaugh [11]	Bethanechol	Double-blind crossover	49	3.5		No benefit	
Penn [13]	Bethanechol	Double-blind crossover	10	6		No benefit	
Read [14]	Bethanechol	Phase 1 trial	5			No benefit	
Seiger [15]	NGF	Case study	1	3		Improved verbal episodic memory	
Eriksdotter-Jönhagen [9]	NGF	Case series	3	3		No benefit	
Augustinsson [8]	GM1 ganglioside	Phase 1 trial	5	12	2	–	3
Svennerholm [16]	GM1 ganglioside	Phase 1 trial	5	12	1	2	2
<i>Tissue grafting</i>							
Goldsmith [17, 40, 41]	Omental flap to cortical surface	Case series	22	–	13 ¹	–	–
Rafael [18]	Omental graft to medial forebrain	Case study	1	12	1 ¹	–	–
Shankle [19]	Omental flap to cortical surface	Case series	6	16–50		Possible benefit	
<i>Gene therapy</i>							
Tuszynski [21]	Autologous NGF fibroblasts	Phase 1 trial	8	22		Improved rate of cognitive decline	
Eriksdotter-Jönhagen [20]	Encapsulated NGF cell biodelivery	Phase 1 trial	6	12	2	–	–
<i>Electrical neural stimulation</i>							
Sjogren [25]; Merrill [24]	VNS	Phase 1 trial	17	12		12 (improved or no change)	5
Turnbull [23]	NBM electrode	Case report	1	9		No benefit ¹	
Laxton [22]	Fornix DBS	Phase 1 trial	6	12		Possible benefit in some patients	
Fontaine [26]	Fornix DBS	Case report	1	12		Stabilization on clinical scales/PET	

n = Number of participants; RCT = randomized controlled trial; VA = ventriculoatrial; VP = ventriculoperitoneal.

¹ Subjective conclusion of the authors, no objective evidence provided.

gic neurons in AD patients are known to express NGF receptors, and that intracranial NGF infusion had already been performed in a small number of Parkinson's disease (PD) patients, the stage was set for an attempt in AD.

In 1993, Seiger et al. [15] published the first use of intraventricular NGF infusion to treat an AD patient. A follow-up study by the same group in 1998 reported 2 additional patients along with their previously published case [9]. Side effects of treatment, in particular pain, weight loss, insomnia, anxiety, and confusion, were a significant issue in all 3 cases. The lack of clinical efficacy and prominent side effects make intraventricular NGF infusion an unsuitable therapy for AD patients.

GM1 Ganglioside

A third strategy for the treatment of AD using intraventricular infusion was reported by another group in Sweden in 1997 [8]. This group had been investigating the use of gangliosides, abundant neuronal plasma membrane components, for the treatment of AD. Experimental evidence shows that gangliosides can have neuritogenic and neuronotrophic properties [32–34]. After the failure of an open-label study delivering the ganglioside GM1 parenterally to AD patients [35], the researchers initiated 2 studies of intraventricular GM1 infusion combined with a cognitive training program [8, 16], suggesting that GM1 infusion may be therapeutically useful for

Fig. 1. **a** Mean total MMSE scores before and after NGF treatment (error bars, SEM). **b** Mean annualized change in MMSE score in the year before treatment and in time epochs of 1–12, 6–18 and 12–24 months after treatment. **c** Median MMSE scores are also shown. Reprinted with permission from Tuszynski et al. [21].

AD patients. Ultimately, however, the design of both studies precludes any determination of causality between the surgical therapy and outcomes, and does not rule out the possibility that the clinically relevant therapeutic intervention was in fact related to other factors such as the associated training program.

Tissue Grafts

Omentum

Based on animal studies demonstrating increased cerebral blood flow with omental autografting to the cortical surface of the brain [36–38], Goldsmith et al. [39] have proposed the therapeutic application of omental grafts for human conditions associated with cerebral ischemia. Postulating that the neuronal degeneration of AD could be related to decreased cerebral blood flow, Goldsmith [17, 40], Goldsmith et al. [41], Rafael et al. [18], and Shankle et al. [19] have investigated whether omental grafts could slow or reverse AD-related cognitive decline in small case series. As Goldsmith [42] has acknowledged, however, a more rigorous, prospective, controlled study will be necessary if omental grafting for AD is to be considered a viable therapeutic option.

Neural Tissue

Although transplantation of neural tissue has been proposed as a potential treatment option for AD [43], no human trials have yet been reported.

Gene Therapy

Targeted gene therapy is an emerging therapeutic approach in neurosurgery for a range of neurological disorders, including brain tumors [44], PD [45, 46] and AD

[20, 21]. A considerable amount of preclinical research shows that NGF stimulates cholinergic function, prevents the degeneration of cholinergic neurons and enhances memory [30, 31, 47].

Tuszynski et al. [21] performed the first therapeutic trial of targeted NGF gene therapy in AD patients. They employed an ex vivo technique in which the patients had their own genetically modified NGF-secreting fibroblasts stereotactically implanted into their basal forebrain. The patients' scores on the Mini Mental State Examination (MMSE) [48] and on the Alzheimer's Disease Assessment Scale – cognitive subscale (ADAS-Cog) [49] showed an improved rate of decline (fig. 1, 2). Furthermore, whereas progressive decreases in neocortical glucose metabolism are expected in AD patients, serial 18-fluorodeoxyglucose (FDG) PET scans in 4 of the subjects showed significant increases in neocortical glucose metabolism at 6–8 months after treatment, particularly in those regions known to receive cholinergic basal forebrain projections (fig. 3).

Building on this ex vivo NGF gene therapy technique, Bishop et al. [50] have developed an in vivo approach using the CERE-110 adeno-associated virus-based (AAV2) human NGF gene delivery vector. A phase 1 clinical trial of CERE-110 (AAV2-NGF) gene therapy in human AD patients has been conducted (NCT00087789) [51] and a double-blind, sham surgery-controlled, phase 2 study is ongoing (NCT00876863) [50].

Similar to the ex vivo genetic modification of autologous fibroblasts to produce NGF developed by Tuszynski et al. [21], Eriksdotter-Jönghagen et al. [20] and Wahlberg et al. [52] have developed an encapsulated cell biodelivery technique using cells genetically modified to secrete NGF.

Fig. 2. **a** Mean total ADAS-Cog scores 2 weeks before NGF and subsequently (error bars, SEM). **b** Mean annualized changes in ADAS-Cog over time epochs of 1–12, 6–18 and 12–24 months after treatment. **c** Median ADAS-Cog scores are also shown. Reprinted with permission from Tuszynski et al. [21].

Fig. 3. Averaged FDG PET scans in 4 subjects treated with NGF, overlaid on standardized MRI templates. Flame scale indicates FDG use/100 g tissue/min; red color (color in online version only) indicates more FDG use than blue color. Reprinted with permission from Tuszynski et al. [21].

The encapsulated cell biodelivery implant consists of a genetically modified NGF-secreting human cell line encapsulated behind a semipermeable hollow fiber membrane that allows the influx of nutrients and the efflux of NGF. A total of 6 AD patients were enrolled in this open-label phase 1 study. The surgical procedure was performed successfully in all patients, with no serious adverse events. The authors reported positive findings in cognition, EEG and nicotinic receptor binding in 2 of 6 patients. The usefulness of this approach will require further study.

Electrical Neural Stimulation

Over the past 20 years, the clinical application of electrical neural stimulation has advanced dramatically. Two prominent modalities of clinical neural stimulation are vagus nerve stimulation (VNS), used to treat epilepsy and depression [53], and DBS, which has become an established treatment for the motor manifestations of movement disorders such as PD, dystonia and essential tremor [54–61].

In addition to their local effects, these therapies modulate the downstream neuronal circuits functionally connected with the stimulated target structures [62–67]. These widespread circuit effects are important as they relate to an emerging conception of the pathogenesis of neurodegenerative disorders such as AD. The pathological processes in specific brain areas that occur in AD, such as the nucleus basalis of Meynert (NBM) and the entorhinal cortex, create abnormalities that affect not only the immediate structures involved but also the downstream areas that receive inputs from them within a network of functional connectivity [68]. Thus, AD is associated with default mode network dysfunction [69] and abnormalities in glucose utilization across wide cortical and subcortical areas [70, 71]. Because AD can be considered a brain circuit dysfunction disorder and the clinical rationale of electrical neural stimulation is the modulation of neuronal circuits, both VNS and DBS are being investigated for the treatment of AD [22, 24, 25, 72].

Vagus Nerve Stimulation

The possibility that VNS could enhance cognition and memory performance was first demonstrated in animal studies [63, 73] and then in a group of depressed patients [74]. These studies provided the empirical rationale for a trial of VNS in AD patients.

Sjogren et al. [25] and Merrill et al. [24] conducted 2 studies to assess the effect of VNS on cognition in AD patients. After 1 year, 12 of 17 patients improved or did not

decline from baseline on the ADAS-Cog and MMSE. In addition, 12 of 17 patients showed no change or some improvement from baseline on the Clinician Interview-Based Impression of Change (CIBIC) scale [75]. Controlled studies of VNS for AD are needed.

Nucleus Basalis of Meynert DBS

Neurodegeneration in the NBM and dysfunction in its associated neuronal circuitry are key pathological features of AD. Turnbull et al. [23] were the first to report the effects of NBM DBS in an AD patient. These researchers implanted a DBS electrode in the patient's left NBM.

The authors reported no clinical benefit with stimulation. Stimulation did affect cerebral glucose metabolism, however. Using FDG PET scans, the researchers compared the changes in glucose utilization over time in the patient's unstimulated right hemisphere with his stimulated left hemisphere. In the patient's right hemisphere, glucose utilization in the frontal, temporal, parietal, and occipital lobes decreased by 21, 24, 10, and 7.5%, respectively. In contrast, glucose utilization in the stimulated left hemisphere decreased by only 12% in the frontal lobe and 4.1% in the occipital lobe, showed no change in the parietal lobe and actually increased by 1.5% in the temporal lobe. Despite demonstrating that NBM DBS can be performed safely and produce a robust, pathophysiologically relevant biological effect, the authors did not pursue further investigations of this therapy.

More recently, Freund et al. [76] investigated the effects of NBM DBS in a 71-year-old man with dementia associated with PD. To address both the motor and cognitive aspects of his condition, the patient underwent stereotactic insertion of bilateral subthalamic nucleus (STN) and NBM DBS electrodes. STN DBS was initiated first and maintained throughout the study. The patient's motor function improved with STN DBS, but his cognitive impairment remained unchanged. After NBM stimulation was initiated, the authors reported that the patient exhibited a marked improvement in his overall cognitive function, as measured by the Rey Auditory Verbal Learning test, the Clock Drawing task and the Trail Making task – part A. As a further test of the NBM DBS effect, the researchers subsequently turned off the stimulator for 1 week without informing the patient, and then turned it back on. When the NBM DBS was off, the patient returned to his baseline state of dementia. Then, with NBM DBS back on, the initial gains in cognitive function were reestablished.

In a separate paper, the authors report the patient's improvement in praxis with STN and NBM stimulation [77]. Prior to surgery, the patient was unable to demon-

Fig. 4. a Location of DBS electrode in a sagittal MRI (left) and projected onto a stereotactic atlas 3.5 mm from the midline (right). The electrodes were positioned immediately anterior and parallel to the vertical segment of the fornix within the hypothalamus. Each electrode has 4 stimulation contacts. The ventral-most contact, design-

nated contact 0, was in proximity to the optic tract and anterior to the mammillary bodies. **b** T2-weighted or proton density MRIs of 6 AD patients showing the position of the fornix/hypothalamic DBS electrodes in axial (top), coronal (middle) and sagittal (bottom) planes. Reprinted with permission from Laxton et al. [22].

Fig. 5. a Decrease in individual MMSE scores in 6 patients in the 11-month period before surgery compared to the 11-month period after DBS surgery. A negative score indicates an increase (improvement) in MMSE. Individual bars before and after surgery correspond to patients 1–6 in sequence. **b** ADAS-Cog scores in 6 AD patients at baseline or after 1, 6 or 12 months of DBS. The last point on the graph represents the predicted 12-month ADAS-Cog score as predicted on a regression formula based on a meta-analysis of >50 studies [86]. Reprinted with permission from Laxton et al. [22].

strate how to brush his teeth, how to use a hammer or how to wind a watch, whether he was given verbal instructions or shown the behavior and asked to imitate it. With STN and NBM DBS on, he could perform these behaviors quickly and efficiently.

Based on these results, the authors concluded that NBM DBS had a broadly positive effect on their patient's cognitive function, although this effect was not specific to memory and may reflect a more general 'tuning' of the widespread neocortical projections of the NBM. Their re-

sults are intriguing and warrant the continued investigation of NBM DBS for the treatment of dementia, including AD. This group of researchers is currently conducting a trial of NBM DBS for AD (NCT01094145).

Fornix DBS

The fornix is a fundamental structure in the neuroanatomy of declarative memory, and fornix lesions produce memory impairments [78–80]. Axonal degeneration and dysfunction in the fornix are believed to contrib-

ute to the pathogenesis of AD [81]. Fornix DBS has been shown to enhance memory in rodent models of cognitive impairment [82].

The potential for fornix DBS to enhance memory in a human has recently been examined by our group [83]. We speculated that this approach could be applied to drive neurophysiological activity in patients with dementia and, on this basis, conducted a phase 1 clinical trial of fornix DBS in AD patients [22].

A total of 6 patients with early AD were enrolled in the study (fig. 4). The surgery and chronic fornix stimulation were safe and well tolerated in all patients. Although the small sample precludes definitive statements regarding possible efficacy, there was suggestive evidence from sequential MMSE and ADAS-Cog assessments that the rate of cognitive decline may have improved in some patients relative to baseline and to historical controls [84] (fig. 5). The physiological effects were more impressive, however. Fornix stimulation produced direct and transsynaptic sequential activation of downstream targets along the well-characterized connection pathways between the fornix and hippocampus that underlie declarative memory function. FDG PET scans showed a pattern of increased temporoparietal glucose metabolism that was maintained with chronic fornix DBS up to 1 year after surgery [85] (fig. 6). These results indicate that fornix DBS produced large and sustained changes in cognitive and limbic brain areas known to be adversely affected in AD.

Similar findings have been reported by a separate group in France [26]. In a single patient with early AD, it was found that clinical measures of cognition and memory, as well as cerebral glucose metabolism, stabilized for up to a year following the initiation of chronic bilateral fornix DBS.

A double-blind, controlled phase 2 trial of fornix DBS for AD, in which participants are randomly assigned to early versus 6-month postoperative initiation of stimulation, is currently under way (NCT01608061).

Mechanisms of DBS for AD

As described above, functional neuroimaging has shown that DBS in AD patients drives neural activity rather than suppresses it. The mechanisms by which DBS influences neural activity are complex and multifactorial [for a detailed review, see 86]. Electrode configuration, parameter settings and stimulation timing influence the effect of DBS. At very high current settings, anterior nucleus of thalamus DBS can impair memory performance in rodents [87]. However, when the electrode, parameters and timing are correct, stimulation can enhance memory

Fig. 6. PET scans of glucose metabolism. Voxel-wise (SPM5) results are displayed on a 3D MR rendering of a representative subject for the comparison of AD patients to controls (a), 1 month of DBS to baseline (b) and 12 months of DBS to baseline (c). The metabolic values that are shown are scaled to mg/100 g tissue/min; blue color represents areas of decreases and red indicates areas of increases in glucose metabolism. Reprinted with permission from Laxton et al. [22].

and cognitive function, as has been demonstrated in animal studies using anterior nucleus of thalamus [88], entorhinal cortex [89], hippocampal [90], fornix [82], and dorsolateral prefrontal cortex stimulation [91].

An intriguing potential mechanism by which DBS may influence memory has recently been identified: hippocampal neurogenesis. The promotion of neurogenesis has been demonstrated in rodent studies involving the electrical stimulation of the anterior nucleus of thalamus [88, 92, 93], hippocampus [94, 95] and entorhinal cortex/perforant path [89, 96, 97]. Researchers investigating the functional significance of stimulation-induced neurogenesis have found compelling memory effects. Both entorhinal cortex [89] and anterior nucleus of thalamus [88] stimulation can enhance memory in rodents. However, when neurogenesis is blocked by temozolomide, or when memory testing occurs before new neurons can mature,

stimulation is not associated with memory enhancement. Thus, stimulation-induced memory enhancement may depend, at least in part or in certain contexts, on the ability of electrical neural stimulation to induce the development of functionally mature hippocampal neurons. The stimulation of neurogenesis with DBS has not yet been demonstrated in humans. Determining the optimal target location and stimulation parameters to treat AD with DBS, and the mechanisms responsible for its effects, will require further research.

Summary and Conclusions

Neurosurgeons may have an important role in the development of novel AD treatments. Over the past 40 years, various neurosurgical AD therapies have been at-

tempted, including CSF shunting, intraventricular infusions, tissue grafting, gene therapy, and electrical neural stimulation. Among these, gene therapy and electrical neural stimulation, particularly fornix and NBM DBS, have emerged as viable, potentially beneficial treatment modalities for AD. These therapeutic modalities can influence neuronal activity within the pathological circuits associated with AD and may produce clinically useful improvements in cognitive function. Future studies investigating neurosurgical therapies for AD are warranted.

Disclosure Statement

Dr. Lozano owns intellectual property rights in the field of DBS for AD.

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