

A Phase I Trial of Deep Brain Stimulation of Memory Circuits in Alzheimer's Disease

Adrian W. Laxton, MD,¹ David F. Tang-Wai, MDCM, FRCPC,^{2,5} Mary Pat McAndrews, PhD,³ Dominik Zumsteg, MD,⁴ Richard Wennberg, MD, FRCPC,⁵ Ron Keren, MD, FRCPC,² John Wherrett, MD, FRCPC,^{2,5} Gary Naglie, MD, FRCPC,² Clement Hamani, MD, PhD,² Gwenn S. Smith, PhD,⁶ and Andres M. Lozano, MD, PhD, FRCSC¹

Objective: Alzheimer disease (AD) is characterized by functional impairment in the neural elements and circuits underlying cognitive and memory functions. We hypothesized that fornix/hypothalamus deep brain stimulation (DBS) could modulate neurophysiological activity in these pathological circuits and possibly produce clinical benefits.

Methods: We conducted a phase I trial in 6 patients with mild AD receiving ongoing medication treatment. Patients received continuous stimulation for 12 months. Three main lines of investigation were pursued including: (1) mapping the brain areas whose physiological function was modulated by stimulation using standardized low-resolution electromagnetic tomography, (2) assessing whether DBS could correct the regional alterations in cerebral glucose metabolism in AD using positron emission tomography (PET), and (3) measuring the effects of DBS on cognitive function over time using clinical scales and instruments.

Results: DBS drove neural activity in the memory circuit, including the entorhinal, and hippocampal areas and activated the brain's default mode network. PET scans showed an early and stable reversal of the impaired glucose utilization in the temporal and parietal lobes that was maintained after 12 months of continuous stimulation. Evaluation of the Alzheimer's Disease Assessment Scale cognitive subscale and the Mini Mental State Examination suggested possible improvements and/or slowing in the rate of cognitive decline at 6 and 12 months in some patients. There were no serious adverse events.

Interpretation: There is an urgent need for novel therapeutic approaches for AD. Modulating pathological brain activity in this illness with DBS merits further investigation.

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Alzheimer disease (AD) is characterized by a progressive disturbance in cognitive function, with memory being particularly affected. Various pathological processes, including the deposition of fibrillar forms of amyloid beta protein, neuronal degeneration, synaptic loss, defects in neurotransmission, and disruption of neural network activity, have been implicated as possible contributors to the dysfunction.¹⁻³ Pathological studies in AD have shown that these disturbances can occur in widespread brain regions but with a predilection for involvement of neural circuits serving memory. Neuroimaging has played

a critical role in identifying the topography of dysfunctional brain areas, showing both morphological and volumetric structural changes, particularly in the entorhinal cortex and hippocampus, predating the cognitive symptoms and tracking with disease severity.^{4,5}

The structural abnormalities in AD are tightly coupled to functional disturbances. Regional reduction in glucose utilization in the temporal lobe and posterior cingulate area is a common finding in positron emission tomography (PET) and single photon emission computed tomography in patients with AD early in the disease course, as well as

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A.M.L. is a Tier 1 Canada Research Chair in Neuroscience and holds the R.R. Tasker Chair in Functional Neurosurgery at the University of Toronto. G.N. holds the Mary Trimmer Chair in Geriatric Medicine Research at the University of Toronto.

Address correspondence to Dr Lozano, University of Toronto, Toronto Western Research Institute, 399 Bathurst St. WW 4-447, Toronto, Ontario M5T 2S8, Canada. E-mail: lozano@uhnresearch.ca

From the ¹Division of Neurosurgery, ²University Health Network Memory Clinic, and ³Department of Psychology, Toronto Western Hospital and Research Institute, University of Toronto, Toronto, Ontario, Canada; ⁴Division of Neurology, University of Zurich, Zurich, Switzerland; ⁵Division of Neurology, Toronto Western Hospital, University of Toronto, Toronto, Ontario, Canada; and ⁶Department of Psychiatry, Johns Hopkins University, Baltimore, MD.

Additional Supporting Information may be found in the online version of this article.

in healthy individuals at genetic risk.^{6–8} Several brain regions, including frontal, precuneus/posterior cingulate, and temporal areas, also have a propensity for fibrillar amyloid deposition as visualized at autopsy and in vivo using radioligands such as Pittsburgh compound B,⁹ both in AD patients and in nondemented older subjects.^{10,11} Recent evidence suggests amyloid pathology interferes with synaptic transmission and the normal activity of brain regions supporting various cognitive and memory functions.^{3,12} However, the mechanism linking amyloid deposition and functional deficits remains controversial. The pathophysiologic significance of the amyloid deposition on neuronal function is complex, as suggested by the observation of amyloid deposition in a significant number of cognitively healthy older subjects¹² and by postmortem studies in AD patients treated with amyloid immunization that show disease progression, despite evidence of amyloid clearance from the brain.¹³ The sensitivity of amyloid imaging for diagnosis, prognosis, and longitudinal AD progression are improved considerably, however, when amyloid imaging is combined with measures of neuronal dysfunction, such as cerebral glucose metabolism or brain volume.^{10,14,15}

Although details of the mechanism remain unclear, there is general agreement that these molecular and structural abnormalities produce functional alterations of the brain areas they affect. The evidence of functional alterations in memory networks is seen not only in AD patients but also in the elderly.^{3,16} Recent evidence shows that both aged individuals and AD patients have defects in heteromodal interconnected cortical areas known collectively as the *default mode network*.^{17–20} Normal individuals show correlated activity within the default network during resting states and deactivation of the network when performing many cognitive tasks. In contrast, older individuals, particularly those with accumulation of brain amyloid, lose the expected deactivation and toggling of the default network during cognitive tasks.^{17,21} Defects in default mode network function as a consequence of amyloid deposition or through other mechanisms may be responsible for some of the multimodal cognitive and behavioral deficits in AD.^{3,20,22} A corollary of these findings is that malfunction in 1 diseased brain area interferes secondarily with the activity of others, which may perhaps be less affected by molecular and structural pathology but whose function is nevertheless disrupted by virtue of being linked in the network. This suggests that AD may not only be a degenerative disease but can also be considered as a system-level disorder, affecting several integrated pathways linking select cortical and subcortical sites working in concert to serve aspects of memory and cognition. If this is true, then there should be interest in modulating the activity of

these dysfunctional networks in an attempt to normalize their function. However, the extent to which these various functional abnormalities can be ameliorated or reversed over the long term by drugs that have symptomatic effects or by manipulating levels of deleterious proteins or any by other means is largely unknown.

Advances in neurosurgical techniques and the introduction of deep brain stimulation have made possible the modulation of the activity of several brain circuits, including pain circuits,²³ motor circuits in patients with Parkinson disease,^{24,25} essential tremor,²⁶ dystonia,²⁷ and Huntington disease,²⁸ as well as circuits modulating mood in patients with treatment-resistant depression.^{29,30} Interventions in these dysfunctional circuits can have local, trans-synaptic, and remote effects,^{25,29} and in some cases can produce striking clinical improvements beyond what is achievable with medications.

We recently reported the possibility of modulating memory in a patient with obesity using deep brain stimulation (DBS) of the fornix and hypothalamus.³¹ We provoked reversible memory phenomena (retrieval of distinct autobiographical episodes) with acute high-intensity stimulation. Source localization of the acute electroencephalographic (EEG) effects indicated activation in the hippocampal formation and the medial temporal lobe. These physiological changes were associated with acute and sustained improvements in memory, particularly those known to be dependent on hippocampal integrity, such as verbal recollection. These preliminary observations in a single subject support the notion that the neural elements subserving certain memory functions are accessible in humans, and that it is feasible to modulate their activity using electrical stimulation of the fornix/hypothalamus.

The fornix is a large axonal bundle that constitutes a major inflow and output pathway from the hippocampus and medial temporal lobe. In humans it is estimated to have 1.2 million axons.³² That the fornix is important in memory function is supported by the observation that lesions in the fornix in experimental animals and humans are well known to produce memory deficits.^{33–36} We hypothesized that it might be possible to use DBS of the fornix to drive its activity and to modulate the circuits mediating memory function in patients with impairments in this domain. We considered that patients with early or mild AD would retain sufficient structural integrity in these circuits so that, given the unrelenting progressive nature of the impairment and the unfavorable natural course of the illness, there was compelling reason to consider this experimental approach. Using the stimulation protocol used in our sentinel case as a launching point,³¹ we tested the hypothesis that stimulation in the fornix/hypothalamus could alter activity in medial temporal memory circuits,

thereby providing a safe and potentially beneficial effect on memory in 6 patients with early AD.

Subjects and Methods

Patients

Six participants were recruited through the Memory Clinic at the Toronto Western Hospital for this pilot study. The criteria for inclusion were: (1) men and women aged 40 to 80 years old, who (2) satisfied the diagnostic criteria for probable AD,³⁷ (3) have received the diagnosis of AD within the past 2 years, (4) have a Clinical Dementia Rating (CDR) score of 0.5 or 1.0,³⁸ (5) have a score between 18 and 28 on the Mini Mental State Examination (MMSE),³⁹ and (6) have been taking a stable dose of cholinesterase inhibitors for a minimum of 6 months. The exclusion criteria were: (1) pre-existing structural brain abnormalities (such as tumor, infarction, or intracranial hematoma), (2) other neurologic or psychiatric diagnoses, or (3) medical comorbidities that would preclude patients from undergoing surgery.

Informed Consent Process

The study was approved by the research ethics board (REB) of the University Health Network and the Center for Addiction and Mental Health. Written informed consent was obtained from patients or surrogates, who for these patients were spouses or children. The REB monitored the process and obtained informed consent independent of the investigators. The trial was registered with the National Institutes of Health's ClinicalTrials.gov (registration No. NCT00658125). The REB monitored the progression of the study and required a report of the course of patients 1 and 2 at 6 months of stimulation before approving enrollment of the next 4 patients.

Surgery

A Leksell stereotactic frame was applied to the patient's head under local anesthesia the morning of the procedure. Magnetic resonance imaging (MRI) of the brain was obtained. The right and left fornix were readily seen on MRI images. The electrode target was chosen to lie 2mm anterior and parallel to the vertical portion of the fornix within the hypothalamus. The ventral-most contact was 2mm above the dorsal surface of the optic tract, approximately 5mm from the midline. With the targets identified, deep brain stimulation electrodes (model 3387; Medtronic, Minneapolis, MN) were implanted bilaterally with fluoroscopic guidance while the patient was awake. Once the electrodes were placed, stimulation was applied to survey for recollective experiences and adverse effects including distracting or unpleasant sensations (eg, sweating, hallucinations, visual sensations, and tingling). The electrodes were internalized and connected to an internal pulse generator (model Kinetra, Medtronic) implanted in the subcutaneous layer of the patient's chest while the patient was under general anesthetic. On the day following surgery, an MRI was obtained to confirm electrode placement. Patients were discharged 1 to 3 days following the operation with stimulators turned off.

Clinical Evaluation and Follow-up

Patients were seen 2 weeks after discharge from the hospital to have the stimulators turned on. Each contact was tested by fixing the frequency at 130Hz and the pulse width at 90 microseconds and increasing the voltage from 1 to a maximum of 10V. As in the operating room, high voltage settings, usually >7V, produced flushing, a sensation of warmth, and increases in heart rate and blood pressure. Final voltage settings were below the threshold voltage for recollective experiences and mildly unpleasant sensations. All patients had chronic stimulation at 3.0 to 3.5V with the frequency set at 130Hz and the pulse width at 90 microseconds. Stimulator settings and medications were kept constant for 12 months. Patients had neurological, neurosurgical, and neuropsychological assessments at baseline and 1, 6, and 12 months following surgery.

The main outcome measure from the neuropsychological assessment was the Alzheimer's Disease Assessment Scale, Cognitive Subscale (ADAS-Cog).⁴⁰ This was chosen due to its widespread use in clinical dementia trials as well as algorithms to predict rate of decline in AD patients as a function of baseline scores.^{41,42} It includes components assessing declarative memory, orientation, praxis, and receptive and expressive language. Other measures included the MMSE,³⁹ the CDR,³⁸ the Clinicians' Interview-Based Impression of Change Plus Caregiver Input,⁴³ and the Quality of Life Alzheimer Disease Scale.⁴⁴ MMSE data were available 1 year prior to the patients enrolling in the trial, so that the trajectory of clinical change for the year preceding and following DBS could be compared.

Standardized Low-Resolution Electromagnetic Tomography

Standardized low-resolution electromagnetic tomography (sLORETA) was used in the period of 6 to 12 months after insertion of the DBS electrodes to identify brain areas showing a focal change in activity in the EEG in response to stimulation in all patients. For sLORETA, bipolar stimulation of the hypothalamus was conducted at 3Hz, with each electrode contact investigated independently (130Hz was not used because of associated high-frequency electrographic artifacts that preclude analysis with sLORETA) as previously described.³¹ The intensities applied varied between 1 and 10V, and the pulse width was 450 microseconds. Five hundred consecutive stimuli were time-locked, and the evoked responses were averaged and compared with baseline EEG activity. sLORETA presents blurred images of statistically standardized current density distributions on a cortical grid of 6,239 voxels with accurate localization.⁴⁵

PET Image Acquisition and Analysis

PET scans with the radiotracer [¹⁸F]-2-deoxy-2-fluoro-D-glucose ([¹⁸F]-FDG) to measure regional cerebral glucose metabolism were acquired preoperatively and with the stimulators on after 1 and 12 months of continuous DBS. The PET scans were performed in 5 patients (numbers 2–6) on the CPS/Siemens high-resolution research tomography scanner at the Centre for Addiction and Mental Health. [¹⁸F]-FDG was synthesized as described.^{46,47} During the radiotracer uptake period, subjects

TABLE : Patient Demographics, Medication Use, and Baseline MMSE Scores

Subject	Gender	Age, yr	Medication	Baseline MMSE
1	F	51	Donepezil	23
2	F	69	Reminyl	24
3	M	58	Reminyl	15
4	M	62	Donepezil	27
5	M	60	Donepezil, memantine	19
6	M	64	Rivastigmine	26
Mean	2 F, 4 M	60.7		22.3

MMSE = Mini Mental State Examination; F = female; M = male.

were maintained in a quiet, dimly lit room, with eyes open and ears unoccluded. Thirty minutes after a $5\text{mCi} \pm 10\%$ radiotracer injection, patients were positioned in the scanner, and a 20-minute emission scan was obtained, followed by a transmission scan. The last 10 minutes of the emission scan (40 minutes post- ^{18}F -FDG administration) were used for quantitative analysis.

Glucose metabolic rates were calculated (in $\text{mg}/100\text{g}/\text{min}$) on a pixel by pixel basis by using a single venous blood sample (obtained 20 minutes after radiotracer injection) fit to a population curve.⁴⁸ This quantification method has been validated against arterial blood sampling and is sensitive to disease and medication effects in AD.⁴⁹ For the ^{18}F -FDG quantitative images, PET to PET registration was performed with statistical parametric mapping, version 5 (SPM5, Institute of Neurology, London, UK) using the normalized mutual information algorithm. The images were spatially normalized into standard 3-dimensional space relative to the anterior commissure using the Montreal Neurological Institute (MNI) ICBM 152 stereotactic template within SPM5. Voxel-wise, statistical analyses were performed with SPM5. The glucose metabolism images were smoothed with an isotropic Gaussian kernel (full width half maximal, 4mm). The glucose metabolic rates were normalized by scaling to a common mean value across all scans, after establishing that the global means did not differ significantly between groups and across conditions ($p > 0.1$). A between-subject comparison of baseline cerebral glucose metabolism in the AD patients and 6 demographically matched normal controls (age 68.5 ± 9 years, 2 females/4 males) was performed using a 2-sample t test to evaluate the preoperative pattern of deficits in cerebral glucose metabolism in the AD group. A within-subject comparison of the baseline and 1-month and 1-year post-DBS conditions was performed using the flexible factorial option (paired t test) in SPM5. For all analyses, the voxels that were reported (1) were significant at a t threshold >3.51 ($z > 2.98$, $p < 0.001$; uncorrected for multiple independent comparisons), (2) were significant at the cluster level

($p < 0.01$, corrected for multiple independent comparisons), and (3) had a cluster size (K_E) >50 voxels. Brain locations are reported as x, y, z coordinates in MNI space with approximate Brodmann areas (BAs) identified by mathematical transformation of SPM5 coordinates into Talairach space (<http://www.mrc-cbu.cam.ac.uk/Imaging/>).

Results

Patients

All 6 patients met National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association diagnostic criteria for probable AD.³⁷ As part of the inclusion criteria, all were on stable doses of acetyl cholinesterase inhibitors for a minimum of 6 months prior to study enrollment and throughout the 12-month study period. All patients scored 20 or higher on the screening MMSE test 3 to 4 months prior to surgery, but in 2 patients the MMSE score dropped to 15 and 19 in the preoperative assessment within 1 month of surgery. The subjects' demographics are shown in the Table.

Intraoperative Findings with Stimulation

DBS electrodes were inserted first on the right and then the left, within the hypothalamus in contact with the anterior border of the vertical portion of the fornix (Fig 1). Monopolar stimulation was applied after each electrode insertion at each of the 4 contacts at 130Hz with 90-microsecond pulse widths, increasing the voltage by 1.0 V every 30 seconds until an observable effect was reported or observed, or until the maximum intensity of 10V was reached. Two of the 6 patients reported stimulation-induced experiential phenomena. Patient 2 reported having the sensation of being in her garden, tending to the plants on a sunny day with stimulation. In her case, this sensation outlasted the stimulation by several seconds. At certain contacts and settings, there was a pleasurable, warm sexual sensation that was clearly time-locked with the application of electrical stimulation. With stimulation, Patient 4 reported having the memory of being fishing on a boat on a wavy blue colored lake with his sons and catching a large green and white fish. On later questioning in both patients, these events were autobiographical, had actually occurred in the past, and were accurately reported according to the patient's spouse. These sensations occurred at relatively high settings, with thresholds of 5 to 6V. In 5 subjects, increasing the current intensity to 7 to 10V produced a sensation of warmth accompanied by generalized flushing and increases in heart rate up to 120 per minute and increases in blood pressure by up to 20mmHg systolic. In 1 patient, Patient 6, no acute stimulation effects were seen even at maximum currents.

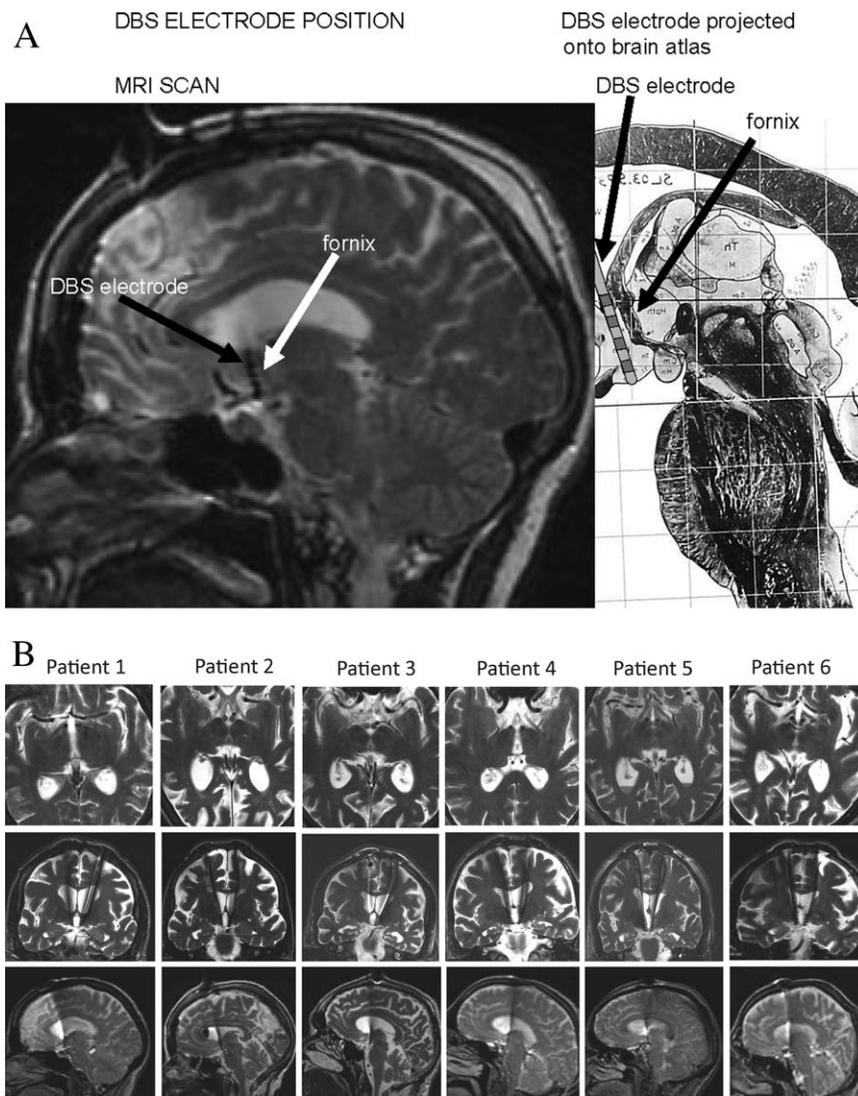


FIGURE 1: (A) Location of deep brain stimulation (DBS) electrode in a sagittal magnetic resonance image (MRI)(left) and projected onto a stereotactic atlas 3.5mm from the midline (right). The electrodes were positioned immediately anterior and parallel to the vertical segment of the fornix within the hypothalamus. Each electrode has 4 stimulation contacts. The ventral-most contact designated 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.

Patient Outcomes

We used the ADAS-cog and changes in the MMSE as the primary measures to examine for the possible effects of stimulation on disease severity (Fig 2). In general, surgery was well tolerated, with 3 patients showing a slight worsening (with increases in the ADAS-cog), and the other 3 showing a mild improvement, with lowering in ADAS-cog scores after 1 month of stimulation compared to 1 month before surgery. After 6 months of stimulation, 4 of 6 patients showed improvement, with lowering of 1.3 to 4.0 points in the ADAS-cog scores. After 12 months of stimulation, 1 patient (Patient 4) continued to score 4.4 points lower on the ADAS-cog than at baseline, 2 patients showed a 2-point increase, 1 patient

showed a 5-point increase, and 2 in other patients the scores increased by >5 points. The rate of change in the ADAS-cog scores in AD patients is variable, nonlinear, and controversial, with historical figures suggesting an increase in the range of 3 to 10 points per year and a mean increase of 6 to 7 points per year.⁵⁰ Overall, there was a mean increase of 4.2 points in the ADAS-cog in the 6 DBS patients over 12 months. The expected change after 12 months of disease progression was calculated according to a regression formula based on a meta-analysis of >50 studies involving more than 19,000 AD patients.⁴¹ Two of the patients experienced a less than expected increase in score, 1 experienced a more than expected increase, and in 3 patients the ADAS-cog scores

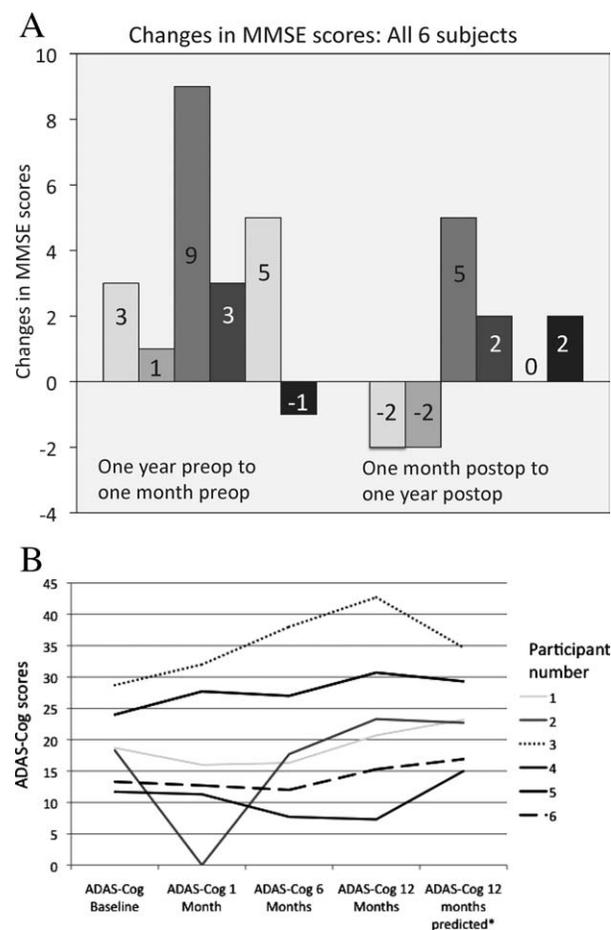


FIGURE 2: (A) Decrease in individual Mini Mental State Examination (MMSE) scores in 6 patients in the 11-month period before surgery compared to the 11-month period after deep brain stimulation (DBS) surgery. A negative score indicates an increase (improvement) in MMSE. Individual bars before and after surgery correspond to Patients 1 to 6 in sequence. **(B)** Alzheimer's Disease Assessment Scale, Cognitive Subscale (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.⁴¹

were within 2 points of the expected change after 12 months (see Fig 2B). Interestingly, the patient who had the most vivid experiential experience with stimulation (Patient 4) showed the greatest improvement in ADAS-cog scores, with a drop of >4 points after a year and with all the benefit arising from improvements in the memory subscales. Patient 2 who also had experiential phenomena with stimulation had a 2-point amelioration on the MMSE but had a decline from the expected range in the ADAS-cog.

To support these observations, we also assessed changes in MMSE scores over time. The change in MMSE score from baseline to 12 months ranged from an improvement of 2 points to a decline of 8 points.

The expected rate of decline in this population is also variable and difficult to ascertain but has been estimated at approximately 10% of a total score of 30, or 3 points/year.⁵⁰ In comparing the rate of decline in the 11 months preceding surgery to the 11 months after surgery, we see a decrease in the rate of decline from a mean rate of 2.8 to 0.8 points across the 6 patients (Supporting Information Fig 1).

We examined whether there was a relationship between disease severity and likelihood of benefit with DBS. We found a strong correlation ($r = -0.925$, $p = 0.008$) between preoperative cognitive function as assessed with MMSE or ADAS-cog and the propensity for response to DBS, with the least affected patients having less decline in ADAS-cog scores after 12 months of stimulation (see Supporting Information Fig 1). It should be noted, however, that the rate of change in ADAS-cog scores in AD is nonlinear, with a tendency for the less severe and the most advanced patients to show a lesser decline.⁴² On the other hand, Patient 3, who was the most severely affected at baseline and had shown rapid progression with a fall in the MMSE of 9 points in the year prior to DBS, showed the largest decline in the MMSE in the year following surgery.

Because the fornix is within the circuit mediating memory, we considered the possibility that the DBS at this site would have a preferential effect on memory function. The ADAS-cog scale measures memory, language, and praxis domains. We sought to determine whether there was a selective effect in any of these domains with stimulation. In 2 of the 3 patients showing improvement or the least increase in the ADAS-cog scores after 12 months of DBS (Patients 4 and 6), the amelioration in the ADAS-cog scores with DBS was driven almost entirely by improvement in the recall and recognition components of the ADAS-cog (Supporting Information Fig 2). These observations suggest the possibility that DBS may drive the function of this memory circuit. The differential response across subjects suggests a possible relation between disease severity and the functional integrity of the fornix-hippocampus circuit and the propensity for benefit with DBS.

We also assessed the impact of fornix DBS on global function and quality of life (QOL) measures. The changes in the cognitive measures were accompanied by 2- to 5-point improvements in the AD-specific QOL scale at 12 months in 4 of 6 patients (Patients 1–4). Although suggestive of a benefit, the significance of the QOL measures is not clear due to their variable relation to cognitive function and the lack of contemporaneous control patients. Consistent with the QOL literature in dementia,⁵¹ the patients reported better overall outcomes

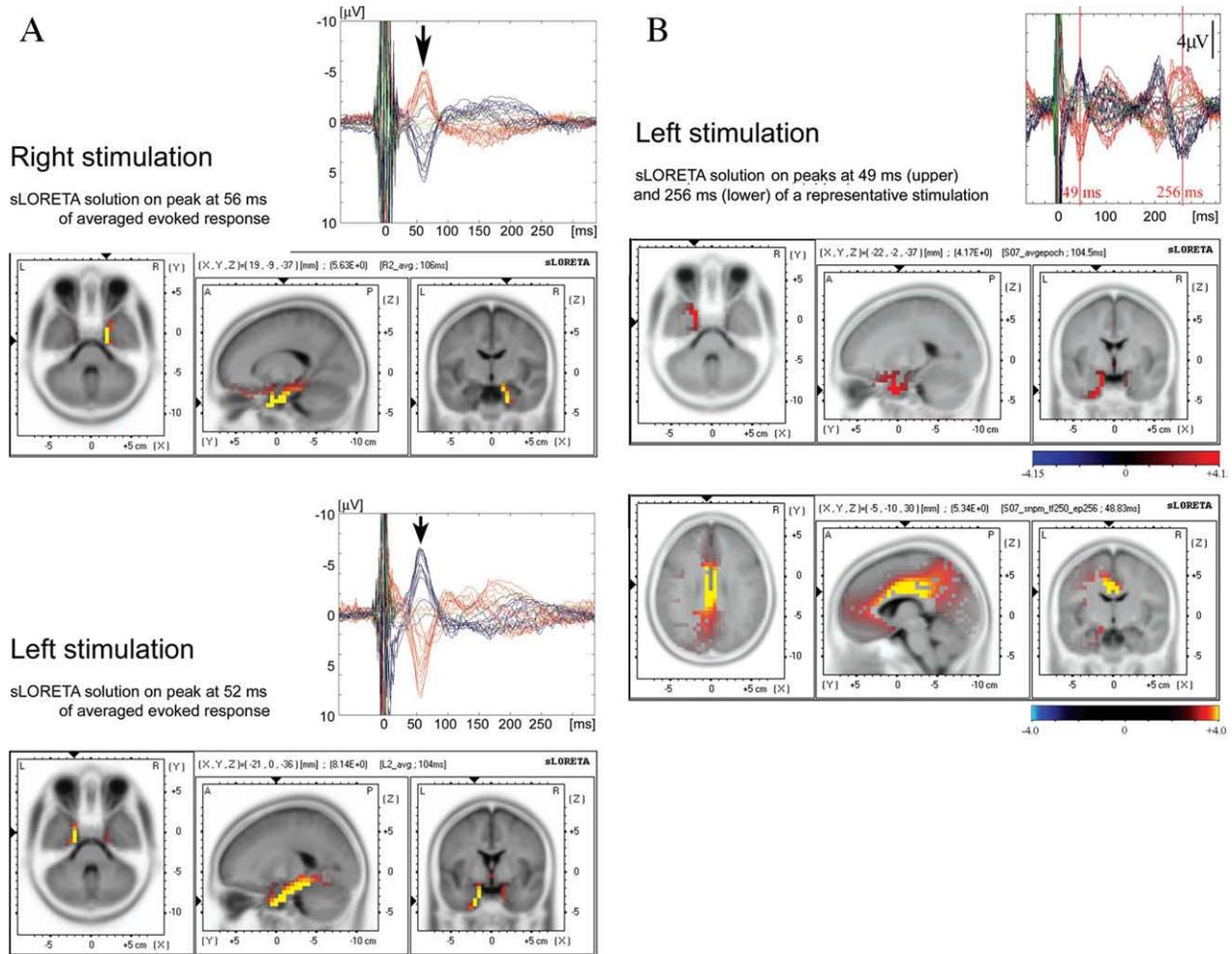


FIGURE 3: Fornix/hypothalamic stimulation leads to localized changes in the activity of ipsilateral mesial temporal lobe structures (mainly the hippocampus and parahippocampal gyrus), the cingulate gyrus, and the precuneus at longer latencies. (A) An averaged standardized low-resolution electromagnetic tomography (sLORETA) 3-dimensional reconstruction during fornix/hypothalamic stimulation shows the activation of ipsilateral hippocampal structures with a latency of approximately 50 milliseconds after stimulation in 6 patients (black arrow). (B) At longer latencies of up to 256 milliseconds, activation shifts from the mesial temporal structures to the cingulate gyrus and the parietal lobe, with representative data from Patient 4. In flame scale, yellow indicates greatest increase.

than their spouses. On the Clinician Interview Based Impression of Change scale, a global measure of outcome in this progressive disease, 4 subjects reported no change after 12 months, 1 reported minimal improvement, and 1 reported minimal worsening. In comparison, 2 patients were said to show no changes and 4 to be minimally worse as assessed by the informant and a treating neurologist at 1 year.

sLORETA

We hypothesized that stimulation of the fornix/hypothalamus would drive activity in downstream projection structures. We used sLORETA to identify and map which brain areas were affected by electrical stimulation. Stimulation of the fornix/hypothalamus through the implanted DBS electrodes produced short latency-specific

and localized changes in the activity of ipsilateral mesial temporal lobe structures. Across the 6 patients, the peak of the first obvious evoked response after stimulation had a latency of 38 to 52 milliseconds and was localized to hippocampus and parahippocampal gyrus (Fig 3A). The evoked responses and their sources were unequivocal and consistent, with all patients showing a similar pattern. The evoked response was absent on the right side in 1 patient (Patient 3), whose right electrode was situated in the ventricle adjacent to the hypothalamus and fornix (see Fig 1B). At longer latencies after stimulation (102–256 milliseconds), significant activation of the cingulate gyrus, especially the mid and posterior cingulate gyrus and precuneus area of the parietal lobe, were seen (see Fig 3B). The changes were almost exclusively ipsilateral to the side of stimulation. These findings are consistent

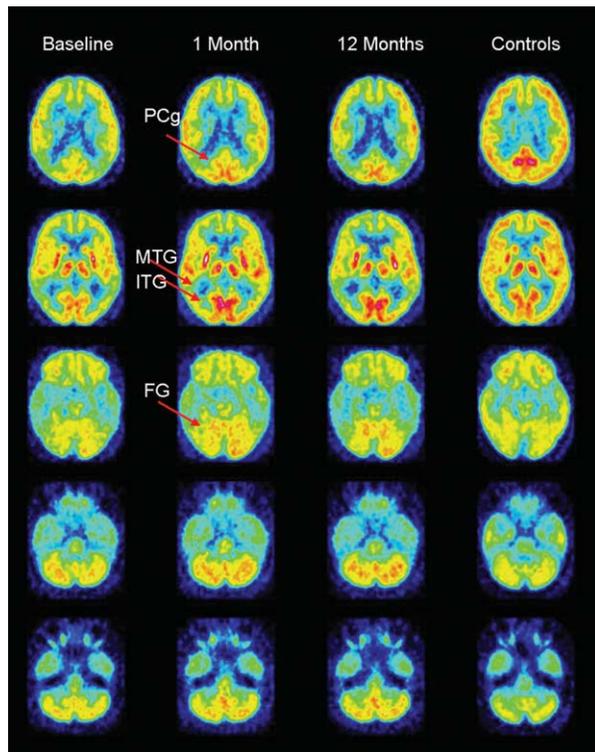


FIGURE 4: Summed positron emission tomography scans in 5 Alzheimer disease patients (Patients 2–6) and 6 age-matched healthy controls at baseline (1 month before surgery) and after 1 or 12 months of continuous bilateral deep brain stimulation (DBS) of the fornix/hypothalamus. Representative axial sections show increases in brain metabolism at 1 month, particularly in the temporal, posterior cingulate, and parietal regions, that are sustained at 12 months. Flame scale indicates fluorodeoxyglucose use per 100g tissue/min, with red showing highest and blue lowest. The patients remained on the same medications from baseline to 12 months while receiving DBS. PCg = posterior cingulate gyrus; MTG = middle temporal gyrus; ITG = inferior temporal gyrus; FG = fusiform gyrus.

with the direct and trans-synaptic sequential activation of downstream targets related to the known connectivity of the fornix and hippocampus and show that DBS drives activity in this important memory circuit and the closely synaptically connected brain's downstream default mode network.

PET

PET measures of cerebral glucose metabolism were used to characterize the activity of brain networks preoperatively and to provide topographic and quantitative measures of the effects of DBS. Resting state scans were performed before surgery and after 1 and 12 months of continuous fornix/hypothalamic DBS. DBS remained on during the scans. The results of the voxel-wise analyses of the comparison between AD patients and controls and the comparison in the AD patients of baseline to 1 month of DBS,

baseline to 12 months of DBS, and 12 months of DBS to 1 month of DBS are shown in the Supporting Information Table. The summed PET images for the 5 patients across conditions and the control subjects are shown in Figure 4. The results of the voxel-wise comparisons displayed on a 3-dimensional magnetic resonance rendering of a representative subject are shown in Figure 5. Plots of regional metabolism in selected areas for the individual subjects are shown in Supporting Information Figure 3A(left precuneus) and 3B (left anterior cingulate gyrus).

Pretreatment

Consistent with previous studies,^{6,7} the AD patients showed significant reductions in glucose metabolism, particularly in the temporal and parietal regions, compared to healthy controls (see Figs 4 and 5 and Supporting Information Table).

One Month of DBS

After 1 month, DBS was accompanied by widespread changes in metabolic activity in cortical areas (see Figs 4 and 5 and Supporting Information Table). Increased metabolism after 1 month of DBS compared to baseline was observed in temporal and parietal cortical regions that are affected in AD, as well as primary sensory and motor regions and cerebellum that are relatively spared in AD. The temporal cortical regions included the left middle and both inferior temporal gyri. The parietal cortical regions showing significant increases included both the fusiform gyri and superior parietal lobules, right precuneus, left posterior cingulate gyrus, and inferior parietal lobule. The sensory and motor and cerebellar regions showing increases included portions of the left pre- and postcentral gyrus, bilateral lingual and bilateral cuneus gyri, left medulla, and cerebellum (bilateral dentate and culmen). Decreased metabolism was observed in anterior cortical areas, including the bilateral anterior cingulate, right medial and middle frontal and bilateral regions of the precentral gyri, and subcortical areas, including the left caudate and thalamus (medial dorsal nuclei).

One Year of DBS

The pattern of regional glucose metabolism after 1 year of constant DBS was examined to determine whether the changes seen after 1 month of stimulation were sustained and to ascertain the effects of chronic stimulation in the context of the known progressive nature of the degeneration in AD. In contrast to the known transient effect of medications, the comparison of 1 year of DBS to baseline showed that the increased metabolism seen after 1 month of stimulation persisted in many of the most affected brain areas. The temporal cortical regions that were increased included the right superior temporal, left superior, and

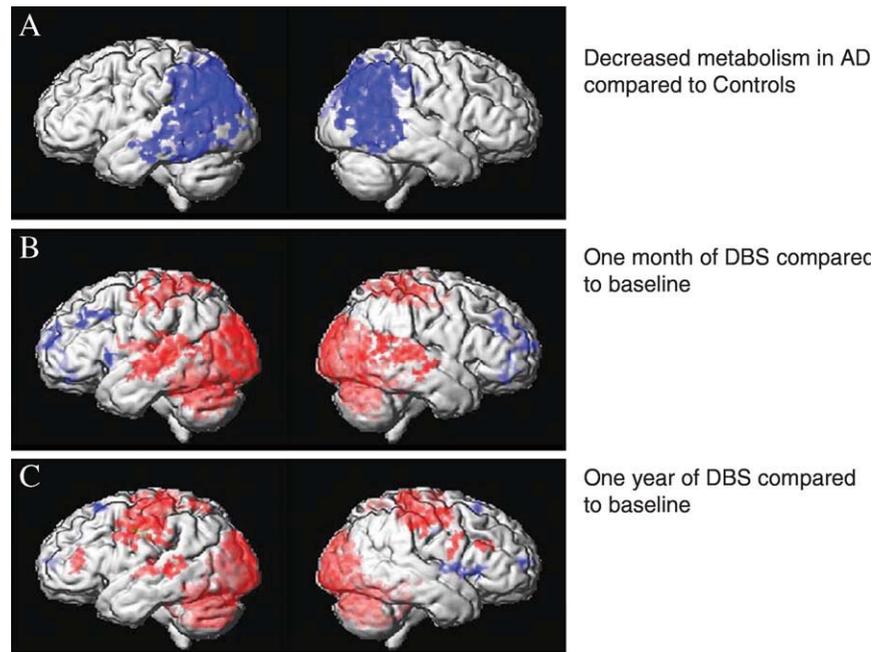


FIGURE 5: Positron emission tomography scans of glucose metabolism. Voxel-wise (SPM5) results are displayed on a 3-dimensional magnetic resonance rendering of a representative subject for the comparison of (A) Alzheimer disease (AD) patients to controls, (B) 1 month of deep brain stimulation (DBS) to baseline, and (C) 12 months of DBS to baseline. The metabolic values that are shown are scaled to mg/100g tissue/min, with blue representing areas of decreases and red areas of increases in glucose metabolism.

middle temporal gyri. The parietal regions that were increased included the left posterior cingulate, bilateral precuneus, and bilateral inferior parietal lobule gyri. As in the 1-month DBS condition, increased metabolism was observed in regions relatively spared in AD, including the bilateral paracentral lobule and right precentral gyri, bilateral postcentral gyri, right lingual gyrus, cerebellum (left tonsil and bilateral declive), and left claustrum. Decreased metabolism was again observed in the left anterior cingulate, left middle frontal, and right inferior frontal gyri.

One Year Compared to 1 Month of DBS

The comparison of 1 year to 1 month DBS demonstrated increases over the course of DBS in anterior cortical regions, as well as sensory and motor regions and parietal cortices. Increased metabolism was observed in anterior regions, including the left anterior cingulate gyrus, right medial, and bilateral middle frontal gyrus. In the parietal cortex, the bilateral inferior parietal lobule was increased. The sensory and motor regions showing increased metabolism after 1 year compared to 1 month of DBS included the precentral gyrus and postcentral gyrus. Increased metabolism was also observed in the right thalamus (ventral posterior medial nucleus). Decreased metabolism was observed in temporal cortices, including the right superior and inferior temporal gyrus, right fusiform gyrus, and cerebellum (right declive). Whereas many temporal and parie-

tal regions showed persistent metabolic increases after 1 year of DBS relative to baseline, the comparison of 1 year to 1 month revealed increased metabolism in anterior cortical and subcortical regions that were decreased relative to baseline at 1 month post-DBS.

The brain areas that demonstrated the greatest increases in metabolism with DBS are among those known to have large accumulations of amyloid deposits, the greatest impairment in glucose utilization, and the greatest physiologic dysfunction in AD patients.^{9,12} DBS also produced long-lasting increases in glucose utilization in the posterior cingulate lobe, parietal lobe, and precuneus, which are important components of the brain default mode network that are most affected early in the course of AD.^{3,20,22} The results shown here indicate that fornix/hypothalamic DBS produces striking and sustained changes in cognitive and limbic brain areas and modulates the activity of the default network, providing a possible biological basis for the observed changes in certain AD patients.

Adverse Effects

Surgery was well tolerated. Patients were discharged 1 to 3 days after surgery. Stimulation-related adverse effects were autonomic and cardiovascular in nature and occurred at high stimulation settings. In dose-finding experiments, at the upper levels of stimulation at 7 to 10V, 5 of 6 patients experienced a sensation of warmth,

flushing, and sweating. In 3 patients, there were increases in heart rate and blood pressure seen at stimulation $>7V$. Chronic stimulation settings were chosen at levels approximately 50% of the voltage threshold for adverse effects. No patient developed sleep disturbances, weight changes, evidence of hypothalamic dysfunction, or metabolic or endocrine abnormalities after 1 year of DBS, as assessed by either medical history or standard laboratory tests. After the initial surgery, no patient required hospitalization during the 12 months of the study.

Discussion

Principal Findings

The application of DBS in the hypothalamus and fornix of these 6 patients with mild AD was safe and produced strong biological effects. Stimulation drove physiologic activity and produced large and sustained changes in glucose metabolism in brain regions that were dysfunctional. With the caveat that this pilot trial is open label and uncontrolled, there is a suggestion that the rate of cognitive decline after surgery is diminished after DBS in these patients. There is also the suggestion that less severely affected patients are perhaps more likely to benefit, as we speculate due to having more of the integrity of the circuitry preserved. The early evidence suggests a clear relation with less severely affected patients less likely to decline after DBS (Supporting Information Fig 1).

Anatomical and Functional Specificity of Stimulation

The brain regions that showed the most prominent changes in their electrophysiologic activity with stimulation were specific and synaptically connected within the circuit of Papez and the downstream default mode network. The sLORETA analysis showed that stimulation produced strong early ipsilateral activation in the hippocampus and mesial temporal lobe, structures intimately involved in memory function. This finding made us consider the possibility that fornix/hypothalamic stimulation could have a preferential effect on recall and recollection. The improvement in ADAS-cog scores when they occurred were driven predominantly by improvements in memory-related measures of the 11 component ADAS-cog scale, in the patients showing improvement or less than expected decline with DBS (see Supporting Information Fig 2). This improvement or reduced decline in the memory-related measures of the ADAS-Cog was associated with increased metabolism in the left superior and middle temporal gyrus and bilateral precuneus based on voxel-wise correlations with the glucose metabolism data. In addition, we found that patients who were less severely affected were more likely to be what we could consider as possible responders to fornix/hypothalamic DBS and

to show improvement or less than expected decline in cognitive function (see Fig 2). These observations are consistent with the notions that better preserved circuit integrity, as may be expected in milder patients, may be a predictor of response to DBS and that stimulation at this site may show preferential effects on memory function versus some of the other elements of cognitive function that are impaired in AD.

Physiological Effects on the Default Mode Network

The sLORETA studies showed that stimulation of the fornix/hypothalamus produced clear and specific activation of the posterior cingulate and medial parietal lobe, with a mean latency of 250 milliseconds, approximately 200 milliseconds after activation of the mesial temporal structures (see Fig 3). Thus both the sLORETA findings and the PET metabolic studies (see Figs 4 and 5 and Supporting Information Table) show that DBS has effects on brain areas that closely overlap with the brain default mode network. This network, components of which include the medial temporal lobe, part of the medial prefrontal cortex, and the posterior cingulate cortex, along with the adjacent precuneus and the medial, lateral, and inferior parietal cortex, was identified on the basis of coherent low-frequency ($<0.1\text{Hz}$) neuronal oscillations, and is so named because it preferentially activates when individuals focus on internal tasks, such as daydreaming, envisioning the future, retrieving autobiographical memories, and gauging others' perspectives.^{18,20} Regions within the default network show structural and functional connectivity that converges on the posterior cingulate, extending into the precuneus, which is strongly interconnected with the hippocampal formation.^{17,20} The observations in AD patients of reduced resting state metabolism and of impaired functional deactivation in the default network during memory tasks in subjects of advanced age and particularly with brain amyloid accumulation^{3,17,19} provide additional support to the hypothesis that this circuit plays a critical role in modulating memory functions. The consequences of modulating neural activity of this network as we have done here are not known, but the ability to reach and influence the activity of this network with DBS introduces an interesting, adjustable, and reversible means of changing the activity of this network and potentially ascertaining its function(s).

Metabolic Effects on Large-Scale Brain Networks

DBS reversed the reduced cortical glucose utilization in the temporal and parietal regions in the AD patients (see Figs 4 and 5 and Supporting Information Table). Increased cerebral glucose metabolism relative to baseline, for example in the precuneus, was observed at 1 month after DBS treatment, persisted to 1 year, and was seen in

all patients regardless of clinical course (see Supporting Information Fig 3). The increases in metabolism were observed in temporal and parietal cortical areas that are the earliest and most severely affected in the course of AD^{7,8} and were found as well in downstream connections, the precuneus and the posterior cingulate regions, which are important components of the default network. The increases in cerebral metabolism in temporal cortical regions are greater at 1 month compared to 1 year post-DBS. However, at 1 year, metabolism was still increased relative to baseline in an extensive network of temporal and parietal regions. The areas of increase included not only the cortical heteromodal association areas that are most affected in AD, but also included the primary sensory and motor cortices, striatum, thalamus, and cerebellar regions, which show lesser degrees of AD pathology and are relatively spared in previous studies of cerebral glucose metabolism in AD.^{6,52} Increased metabolism was observed in pre- and postcentral gyrus, occipital cortex, and cerebellum, all regions that are relatively less affected in AD (including the subjects enrolled in this study), even in more advanced stages of the illness. Thus, DBS increased metabolism in the regions affected in AD, but in addition, DBS also had effects along more widely distributed cortical regions that are relatively spared in AD, presumably related to subcortical-cortical or cortical-cortical trans-synaptic effects of stimulation.

Interestingly, DBS was also associated with decreased metabolism in subregions of the anterior cingulate and the medial frontal cortices, most pronounced after 1 month of DBS but persisting after 12 months. This robust finding, seen in all patients tested (see Supporting Information Fig 3), suggests that DBS may be actively suppressing anterior cingulate metabolism. This observation may be biologically significant, as recent work reveals that the default mode network shows strong anticorrelations in resting-state functional MRI studies with an anterior network that includes the anterior cingulate and other components and serves as a task-positive, salience, or executive-control network.⁵³ The observation that DBS increases activity in the default mode network while decreasing metabolism in the more anterior executive network is also consistent with the recent finding of reduced connectivity of the default mode network and increased connectivity of the anterior network in AD compared to controls.⁵⁴ Dysfunction in this anterior network could predict impairments in executive function tasks, but we were unable to detect this with the instruments we used in this small sample. In the future, we will need to examine whether the divergent changes in metabolism occurring in these anterior regions are associated with changes in psychomotor or executive domains.

Metabolic Effects of DBS in Comparison to Other Interventions in AD

The cerebral metabolic effects of DBS should be interpreted relative to the long-term effects of pharmacotherapy (acetylcholinesterase inhibitors) on cerebral metabolism, as well as the longitudinal decline in cerebral metabolism over 1 year. Whereas the short-term effects of cholinesterase inhibitors have been studied, there are few reports of longer treatment duration. Several studies have shown short-term metabolic increases by cholinesterase inhibitors, including donepezil, galantamine, and phenserine.⁵⁵⁻⁵⁷ The increases are observed in frontal and parietotemporal cortical areas that are most affected in AD. The increases in metabolism are observed over a relatively short interval (3 months), and metabolism returns to pretreatment levels after longer term treatment (6 months).^{56,57} One year of rivastigmine treatment was associated with a significant increase in cerebral glucose metabolism in right frontal association cortex, right putamen and globus pallidus, and bilateral cingulate gyrus (BA 24, 32).⁵⁸ The other cortical regions showed non-significant increases in metabolism relative to baseline, in contrast to the untreated AD group, which showed significant decreases in metabolism in cortical association areas. Long-term rivastigmine treatment prevented the decline in cerebral glucose metabolism over the course of 1 year.

In contrast to the effects of cholinesterase inhibitors, both 1 month and 1 year of DBS were associated with an increase in cerebral glucose metabolism relative to baseline in a network of brain regions that was much more extensive than that observed with cholinesterase inhibitor treatment. Over the course of 1- to 2-year follow-up, AD patients consistently showed progressive metabolic decreases in cortical association areas, with relative sparing of primary sensory (visual, somatosensory) and motor cortical areas, basal ganglia, thalamus, and cerebellum.^{6,58,59} The progressive metabolic decline observed over the 1-year course of AD further underscores the significance of the extensive metabolic increases associated with DBS and may provide a biological basis for potential stability or improvement in cognition.

Choosing Stimulation Parameters and Mechanism of Action

Stimulation parameters were chosen empirically, and there may be opportunities for optimization. Our starting point for stimulation was 3.5V, 130Hz, and pulse width of 90 microseconds, settings that are similar to those used in DBS for Parkinsons disease. We increased the intensity of stimulation until adverse effects were encountered, usually at 6 to 8V, and reduced stimulation

by 50%. We used several observations in choosing the parameters for chronic stimulation. First, as we detected a dose-response relationship between stimulation and the magnitude of change in the EEG as seen by the sLOR-ETA analysis, we wanted to use relatively high settings. Second, we wanted stimulation to be free of any perceived sensations or adverse effects. We opted for continuous uninterrupted stimulation, as is used in Parkinson disease and dystonia DBS. We do not know, however, whether the circuitry changes as a consequence of prolonged stimulation, or whether ongoing stimulation is necessary after a prolonged period of stimulation.

We are also not certain which neural elements are responsible for the observed effects and whether there is anterograde and/or retrograde transmission of the stimulation effects. Whereas there is degeneration in the Papez circuit in AD, the pattern to activation with fornix stimulation in our patients and the response latencies as seen with the EEG analysis were similar to that previously reported in our cognitively intact patient who also received hypothalamic stimulation and had enhancement in his memory function.³¹ As for the initial patient and now our 6 AD patients, our leading hypothesis is that the stimulation produces activation of the axons of the fornix. This in turn activates the immediate downstream structures and subsequently the polysynaptically connected secondary structures, including the default mode network. The increasing latency of activation in the cingulate and parietal areas versus the hippocampus that we found using sLORETA is consistent with this notion. The reason for postulating the fornix and perhaps the mammillothalamic tract over other structures, especially hypothalamic nuclei and particularly the mammillary bodies, is that first, axons are more sensitive than neuronal cell bodies to the effects of electrical stimulation,⁶⁰ and second, we have seen that the acute experiential effects of stimulation are produced at a similar current threshold along the 4 electrode contacts that lie at various points along the vertical axis of the fornix. Were the effects mediated by the mammillary bodies, one would predict lower threshold at the deepest contact followed by increasing threshold at each of the more dorsal contacts. The predominantly ipsilateral physiological effects of stimulation seen with sLORETA (see Fig 3) and the lateralized specialization of memory, with the right side preferentially mediating spatial memory and the left verbal memory, speaks for the need for bilateral stimulation in widespread disorders like AD.

Other Supporting Observations

Although no clear clinical benefit can be claimed in this phase I study, the findings of activation of memory cir-

cuits and improvement in glucose metabolism and the possible effect on clinical outcome mirror recent findings of DBS for Parkinson disease and for depression. In Parkinson disease, subthalamic nucleus and globus pallidus DBS is associated with activation of brain areas involved in the planning and initiation of movement,²⁵ and in patients with severe depression, DBS of the subcallosal cingulate gyrus reversed the abnormalities in resting glucose metabolism across brain regions implicated in depression.²⁹ In another phase 1 trial, nerve growth factor (NGF) gene therapy for AD⁶¹ showed interval increases in brain metabolism and a similar potential clinical benefit (an annual decline in the ADAS-cog of 6.2 points in the 8 patients receiving NGF gene therapy versus the 4.2-point decline in the DBS patients we report here). We have preliminary evidence in laboratory rodents that electrical stimulation of the Papez circuit (of which the fornix and hippocampus are part) using homologous parameters can enhance neurogenesis in the hippocampus.⁶² Although the mechanism(s) is uncertain, we hypothesize that this may be due to stimulation-dependent release of neurotrophic factors in the hippocampus. Recent work suggests that enhancing the delivery of the neurotrophin brain-derived neurotrophic factor in animal models of AD may reverse synaptic loss and improve cognitive function.⁶³ Whether DBS regulates neurotrophin expression and neurogenesis in humans and whether this occurs in the diseased hippocampus of patients with AD is not known. The availability of animal models of AD will facilitate the examination of these questions.

Limitations

Our study has a small sample size and was geared to determine safety rather than efficacy, as is appropriate in a phase 1 trial. Further, the clinical results were evaluated in an open-label fashion, without a sham surgery control group, and the use of historical controls has difficulties. In addition, we are dealing with a progressive disease, with ongoing degeneration of the neural circuit that is being stimulated. Despite these caveats, we have shown that in this small group of patients, the procedure is well tolerated and produces biological effects with respect to activating the target circuits and reversing some of the metabolic abnormalities in glucose utilization.

Conclusions

Some 4.5 million Americans suffer with AD, and these numbers are expected to nearly triple by the year 2050.⁶⁴ Approved treatments are directed at modulating neurotransmission in general and are not regionally targeted or specific. There is major dysfunction in cognitive and

memory circuits in AD. As we have shown here, DBS offers the possibility of modulating these specific brain circuits in an adjustable and reversible fashion, and it appears that this approach can be safe. These safety and biological effects are sufficiently compelling to warrant a more thorough appraisal of the possible therapeutic benefits of this strategy in AD. Possible next steps include a controlled trial comparing DBS to best medical management or a double-blinded assessment of patients randomly assigned to receiving stimulation immediately after surgery or with a delay of several months.

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Potential Conflicts of Interest

A.M.L. holds intellectual property in the field of deep brain stimulation.

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