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Deep Brain Stimulation of Frontal Lobe Networks to Treat Alzheimer's Disease

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Abstract. The study objective was to evaluate the safety and efficacy of deep brain stimulation (DBS) at the ventral capsule/ventral striatum (VC/VS) region to specifically modulate frontal lobe behavioral and cognitive networks as a novel treatment approach for Alzheimer's disease (AD) patients. This is a non-randomized phase I prospective open label interventional trial of three subjects with matched comparison groups. AD participants given DBS for at least 18 months at the VC/VS target were compared on the Clinical Dementia Rating–Sum of Boxes (CDR-SB), our primary outcome clinical measure, to matched groups without DBS from the AD Neuroimaging Initiative (ADNI) cohort. Serial 2-Deoxy-2-[^{18}F]fluoro-D-glucose (FDG) positron emission tomography (PET) images of AD participants were also compared longitudinally over time. Three AD DBS participants were matched to subjects from the ADNI cohort. All participants tolerated DBS well without significant adverse events. All three AD DBS participants had less performance decline and two of them meaningfully less decline over time on our primary outcome measure, CDR-SB, relative to matched comparison groups from the ADNI using score trajectory slopes. Minimal changes or increased metabolism on FDG-PET were seen in frontal cortical regions after chronic DBS at the VC/VS target. The first use of DBS in AD at a frontal lobe behavior regulation target (VC/VS) was well-tolerated and revealed less performance decline in CDR-SB. Frontal network modulation to improve executive and behavioral deficits should be furthered studied in AD.

Keywords: Alzheimer's disease, deep brain stimulation, executive function, positron-emission tomography, ventral striatum

INTRODUCTION

Recent research efforts toward new treatments for Alzheimer's disease (AD) have so far proven unsuccessful. Even small advances in AD treatments that provide stability or improved functioning for a few years would be impactful [1]. Thresholds required for treatments to be cost effective for AD have been reported to be relatively low [2].

For 30 years, deep brain stimulation (DBS) implants have been performed in over 120,000 patients worldwide with demonstrated benefit in Parkinson's disease, tremor, dystonia, depression, and obsessive-compulsive disorder [3–5]. Additional reports suggest that improving neuronal metabolic rate and activating neurons by brain stimulation techniques including DBS can improve cognitive, behavioral, and functional impairments [6–10]. Previously

[1]Data used in preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report. A complete listing of ADNI investigators can be found at: http://adni.loni.usc.edu/wp-content/uploads/how_to_apply/ADNI_Acknowledgement_List.pdf

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published investigations of DBS in AD targeting memory circuits of the fornix indicated a subset of patients experienced memory enhancement, improved glucose metabolism, and reduced hippocampal atrophy [11–14]. Other DBS AD clinical trials targeting the nucleus basalis of Meynert showed five of eight subjects having stable or improved cognitive scores after at least 12 months stimulation [15, 16].

DBS to specifically modulate frontal networks involved in cognition and behavior is a logical treatment approach for AD patients. AD neurodegeneration propagates over time along neural networks that link the entorhinal cortex to limbic structures (including ventral striatum and nucleus accumbens) and to frontal and posterior neocortex [17, 18]. While memory deficits are common in AD, it is deficits in executive abilities, decision-making, and problem solving, which result in functional impairments and increased supervision needs that are the most challenging for caretakers [19]. The DBS target encompassing the ventral striatum, nucleus accumbens, and anterior limb of the internal capsule sits at the base of the frontal lobes and is a potentially important neuromodulation target in AD. White matter fibers of the frontal lobe and the ventral capsule connect dorsomedial and orbital prefrontal cortices to the ventral striatum [20]. Executive and behavioral self-regulation functions of these frontal cortical-basal ganglia-thalamic circuits include energization (the process of initiation and sustaining any response), monitoring, task setting, and behavioral and emotional self-regulation [21]. In addition, the adjacent septal nuclear complex is an important source of acetylcholine [22], which is implicated in neural networks relevant to memory, and these regions also show degeneration in AD [23, 24]. While never before used as a stimulation target in AD, DBS of this ventral capsule/ventral striatum (VC/VS) region has been performed safely in patients with various neurobehavioral disorders [4, 5, 9, 10].

There have been a few studies, mostly involving treatment resistant depression and obsessive-compulsive disorder subjects, that have specifically looked at executive function changes after DBS using different targets in the VC/VS region. After one year of DBS of the nucleus accumbens for major depression, there were statistically significant improvements noted in neuropsychological testing in domains of attention, learning and memory, executive function (specifically Trail Making Tests A and B, non-verbal fluency, and Stroop interference), and visual perception [25]. After 8 months of DBS of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder, there were no differences in executive function measures (Stroop, verbal fluency, Trail Making test, Wisconsin Card Sort Test, and Tower of London performance) compared to a control group not receiving DBS despite an initial post-operative decline in verbal fluency performance [26]. Other studies have reported no significant change in executive measures after VC/VS DBS either with or without showing some significant improvements in memory [27, 28].

We performed a phase I pilot study evaluating the safety and feasibility of DBS of the VC/VS in AD subjects. Our *a priori* hypothesis was that we would see less decline, as measured by our primary outcome measure, on the Clinical Dementia Rating–Sum of Boxes (CDR–SB) [29], in DBS-stimulated participants relative to matched comparison groups from the Alzheimer's Disease Neuroimaging Initiative (ADNI) study.

MATERIAL AND METHODS

Study design and setting

This is a non-randomized phase I safety and pilot feasibility prospective open label interventional trial with matched comparison groups. AD participants underwent standard stereotactic VC/VS DBS lead placement followed by continuous stimulation for at least 18 months. They were compared on clinical measures over time to matched groups without DBS from the ADNI cohort. CDR–SB was our primary outcome measure. This investigational study met institutional requirements for conduct of human subjects and was registered on ClinicalTrials.gov (Identifier: NCT01559220). We required subject assent and their legally authorized representative written informed consent for study participation. The Ohio State University's Biomedical Sciences Human Subject Institutional Review Board approved the research.

Study participants

Between March 2012 and April 2013, cognitive specialists recruited participants from the Memory Disorders Clinic at Ohio State University. Our plan was to initially recruit 3 subjects for this pilot study. Qualified participants were aged 45–85 years meeting probable AD criteria [30] and probable AD dementia with evidence of AD pathophysiological process

criteria [31] based on amyloid positron emission tomography (PET) and cerebrospinal fluid (CSF) amyloid-β 42 ($A\beta_{42}$) and tau results, receiving a stable dose of a cholinesterase inhibitor and memantine for at least 120 days, and medically stable. Eligible participants had Mini-Mental State Examination (MMSE) scores of 18–24 and daily contact with study partners that accompanied them to all study visits.

Exclusion criteria were significant medical conditions that would interfere with study activities or response to intervention, substance abuse in the past 12 months, significant psychiatric disorder, contraindication for anesthesia, craniotomy, or surgical procedure, or magnetic resonance imaging (MRI) demonstrating damage to the VC/VS region.

Interventions

Screening and baseline assessments of eligible participants included apolipoprotein E (ApoE) genotype, B12, thyroid stimulating hormone; MRI brain; 2-Deoxy-2-[^{18}F]fluoro-D-glucose (FDG) PET; ^{18}F-Florbetapir PET; CSF $A\beta_{42}$ and tau. Four to six weeks following DBS implantation surgery, the stimulator was turned on; stimulation parameters were titrated to final settings over the following 12 weeks and then continued without change for the next 12 months before new adjustments were allowed. An assessment protocol including CDR-SB, MMSE, Self-Administered Gerocognitive Examination, category fluency (Animals), Trails A and B, Boston Naming Test (30 Item), Auditory Verbal Learning Test (AVLT), clock drawing, Alzheimer's Disease Assessment Scale-Cognitive-13 (ADAS-Cog-13) (with delayed word recall and number cancellation), Stroop color and word test, Wisconsin Card Sort Task, Neuropsychiatric Inventory Q (NPI-Q), Geriatric Depression Scale (GDS), and activities of daily living inventory was conducted at baseline before surgery, post surgery before stimulation titration, immediately post-stimulation titration, and then repeated approximately every three months. The FDG PET was conducted at baseline before surgery, one-month post surgery before stimulation titration, immediately post-stimulation titration, and again after 12 and 18 months of brain stimulation.

Fifteen-minute brain PET imaging was performed using low dose FDG [32] of 167 ± 15 MBq, ($4{\cdot}5 \pm 0.4$ mCi) on a time-of-flight PET/CT system (Gemini TF 64, Philips Healthcare) acquired 55 minutes after intravenous FDG administration, and reconstructed as 2x2x2 mm^3 voxels in a 128x128 matrix using a 3D Ramla algorithm (2 iterations, 33 subsets). Quantitative assessment of regional brain metabolism was performed using MIMSoftware (V6.4.3, MIM Software Inc.). Forty-three normal FDG PET brain data sets were used as the standard comparison set. Using whole-brain as the normalization volume, statistical z-scores were calculated on a voxel-by-voxel basis for each participant PET compared to standard normal PET sets to identify metabolic regional variations.

The surgical procedure involved standard stereotactic implantation of DBS electrodes (Medtronic Neurological Model 3391) bilaterally in the VC/VS (Fig. 1A, B) in each participant using anatomical and physiological guidance and single cell microelectrode recording. The specific target was directly visualized on axial, coronal, and sagittal T1, T2, and inversion-recovery magnetic resonance imaging scans, similar to what has been described previously for this target in the literature [33, 34]. The trajectory planning was based on avoidance of vasculature while maximizing the approach through the internal capsule to the ventral striatum and the nucleus accumbens. The anatomical target was visualized on the imaging and in the three patients corresponded to stereotactic targets of 5 to 10 mm lateral to the midline, 2 to 4 mm anterior to the anterior commissure, and 2 to 5 mm ventral to the anterior commissure. Single-cell microelectrode recording verified our anatomical approach of traversing the internal capsule white matter with white matter recordings and cells in the accumbens. Physiological microelectrode recordings were captured for research purposes and did not change our targeting and final implantation of the DBS leads. Intraoperative test stimulation did not disclose any adverse effects. The implanted DBS electrodes were connected to pulse generators (Medtronic Activa SC, PC, or RC systems) in the chest wall in the usual fashion as for all DBS procedures.

Clinical titration of stimulators

Four to six weeks following DBS surgery, a comprehensive, iterative 12-week, three to five-hour weekly titration process to determine the optimal settings for DBS stimulation including lead contact polarity, intensity, pulse width, and frequency, was individualized for each participant. Monopolar settings at each electrode contact identified stimulation thresholds for tolerability evaluating for autonomic signs, muscle twitching, and neuropsychiatric symptoms (e.g., impaired attentiveness,

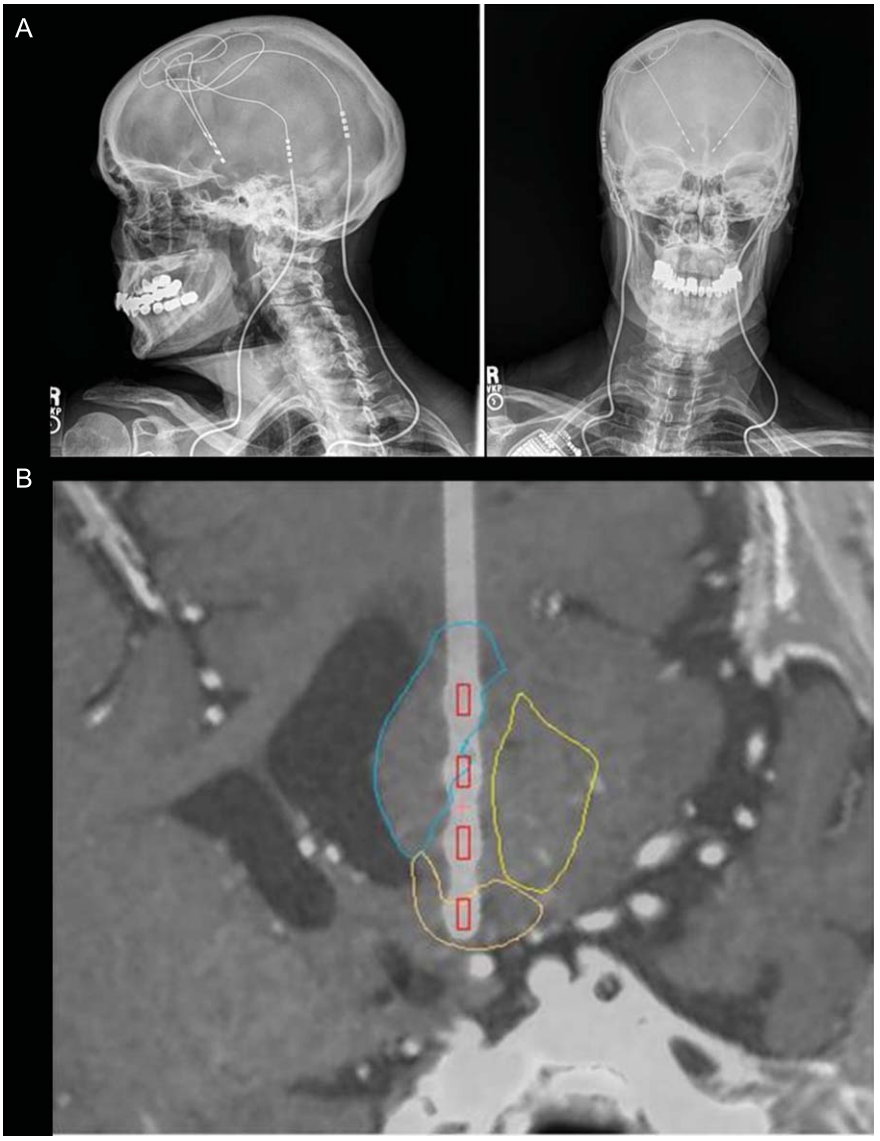

Fig. 1. (A) Lateral and anterior-posterior postoperative skull X-ray. Images demonstrate location of implanted Medtronic DBS lead model #3391 in the ventral striatum/ventral capsule bilaterally. (B) Postoperative CT with MRI Fusion. Image demonstrates location of implanted unilateral left Medtronic DBS lead model #3391 in the ventral striatum/ventral capsule. The CT has been reformatted to along the axis of the DBS lead. Each contact is three mm in length, spaced four mm apart. Structures of relevance: ventral striatum (nucleus accumbens–orange) and surrounding structure of ventral capsule (putamen–yellow and caudate–blue). The CranialVault atlas and the CRAVE software suite were used for anatomical segmentations, image registration, as well as for electrode localization and visualization. The rectangular box represents the contacts for the DBS electrodes.

anxiety, depression, compulsiveness, suspiciousness, and agitation). All adverse effects were transient and reversed with setting adjustments. Multiple independent adjustments were assessed systematically and selected based on best-observed neurocognitive task response focusing on attentional and executive tasks (e.g. shape/letter cancellation, trails, go/no-go, fluency, and semantic/category switching tasks), least amount of undesired neuropsychiatric symptoms, and on subject and caregiver assessments of the changed settings from previous weeks.

Comparison groups

Data used in preparation of this article were obtained from the ADNI database (http://adni.loni.usc.edu). ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator

Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial MRI, PET, other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment and early AD. This initiative includes data from 1,784 total participants ranging in age from 55 to 90, including 341 subjects with AD according to the same AD diagnostic criteria used in the current study [35]. Comparison groups matched to our DBS participants were drawn from the ADNI AD cohort on the basis of similar MMSE scores, age, and ApoE ε4 allele frequency (Table 1). The numbers of matched ADNI subjects identified were 11 for participant one, 78 for participant two, and 7 for participant three. Subjects decline at faster rates for MMSE 4–18 [36], if younger in age [37], and with higher ApoE ε4 allele frequency [38]. Age 65 was selected as a boundary for our matched groups in order to reflect diagnostic criteria for 'early onset' and 'late onset' AD. Our baseline MMSE score range of 18–24 was imposed on our ADNI groups to reflect our *a priori* study inclusion criteria. By creating matched groups, we attempted to control for factors significantly influencing disease progression, independent of DBS status. ADNI subjects were only included in a comparison group if they were assessed at least two times in the first 24 months of enrollment. ADNI data collected beyond 24-month assessments were excluded.

Statistical analyses

In order to make comparisons between individual DBS subjects and their matched groups, we analyzed these data using a Bayesian hierarchical modeling procedure. Given that AD is a degenerative disease, we assumed that dementia severity as measured by CDR-SB would change through time in a linear manner. We therefore used linear models to capture each patient's task performance as a function of months since baseline assessment. Each patient's model contained three parameters: intercept or dementia severity at baseline (α, slope (β), and residual error (ε). Before fitting the models, the data were Box-Cox and z-transformed within group in order to satisfy normality assumptions. Within this framework, a separate model was fit to each DBS subject and matching ADNI cohort. Paired models were linked by hierarchical hyperparameters governing the intercepts (α). Because we were interested in comparing trends across time, a single error term was fit to all subjects (DBS and ADNI), slope was fixed within the ADNI group, and intercept was allowed to vary. Subject-level predictions (for both DBS subjects and each ADNI subject) were determined as follows, using the notation *i* for individual subjects and *j[i]* for the group *j* containing subject *i*:

$$y_{i,x} = a_i + \beta_{j[i]}X + \varepsilon$$

Here, $y_{i,x}$ is the subject's score predicted by the model at time point x months after the baseline assessment. Group j referred to 'ADNI' or 'DBS', such that the ADNI cohort was fit with a single slope and each DBS subject was fit with separate slope. The prior for ε and hyperpriors for α were selected to be uninformative $\left(\varepsilon \sim |\exp(1);\ \alpha_i^{\mu} \sim U(-10,\ 10);\ \alpha_i^{\sigma} \sim inv\Gamma^1(1, 1)\right)$. We selected a normal prior for β, making the assumption that slopes would tend toward zero $\left(\beta_{j[i]} \sim N(0, 1)\right)$. A Student's t error distribution with degrees of freedom fixed at 1 was selected to be robust against outliers [39].

Once we had specified the hierarchical model, we used a differential evolution Markov chain

Table 1
Participant demographics and baseline characteristics of matched cohorts

Alzheimer's disease participant demographics			
	Participant 1	Participant 2	Participant 3
Baseline age	55	76	56
ApoE genotype	ε4/ε4	ε3/ε4	ε3/ε3
Baseline MMSE	23	21	24
ADNI Alzheimer's disease participant-matched group criteria*			
	ADNI AD Group 1	ADNI AD Group 2	ADNI AD Group 3
N	11	78	7
Baseline age	<65	≥65	<65
ApoE genotype	ε4/ε4	ε2/ε4 or ε3/ε4	ε2/ε2, ε2/ε3, or ε3/ε3
Baseline MMSE	18–24	18–24	18–24

ApoE, Apolipoprotein E; MMSE, Mini-Mental State Examination; ADNI, Alzheimer's Disease Neuroimaging Initiative; AD, Alzheimer's disease. *Mean MMSE score over two years in ADNI subjects did not exceed 24.

Monte Carlo sampling algorithm to propose sets of parameters that *could* capture the data [40]. A proposed parameter set was accepted with Metropolis–Hastings probability, then served as the starting point for the algorithm's next proposal if it produced a closer match to the actual data than the previous proposal. This procedure was implemented with 30 chains, each with 500 sampling iterations following 75 burn-in iterations. Model convergence was assessed via visual inspection of the chain weights at each iteration.

The Bayesian modeling procedure allowed us to calculate full posterior distributions of each parameter. We therefore knew every plausible value of each parameter, and the likelihood that each value generated the actual data. For our purposes, we were interested in comparing posterior distributions of slopes between each DBS subject and their ADNI cohort. If DBS treatment has a meaningful effect on the progression of dementia severity (as measured by CDR-SB), we should observe minimal overlap between DBS and ADNI posterior distributions of slope. To assess this, we calculated the pairwise differences of the two distributions ($\beta_{DBS} - \beta_{ADNI}$), separately for each DBS subject. We then calculated the 95% credible interval (CI) of each difference distribution. Given that a difference of 0 would indicate equivalence between DBS and ADNI slopes, we determined if 0 fell within each 95% CI of the difference distributions. For CDR-SB, an equivalence point to the right of the 95% CI provided strong belief that dementia progressed less severely in the DBS patient compared to the ADNI group. We performed the same analysis procedure using scores from 9 secondary task measures and 2 composite scores. Information on secondary outcomes can be found in the Supplementary Materials.

RESULTS

Participants

We had 350 individuals potentially meeting eligibility criteria. Our plan was to initially recruit 3 subjects for this pilot study. Based on close proximity to the hospital, interest in research, and having a reliable caretaker, four participants were recruited, one declined, three enrolled and completed. Participant two had the most typical AD prototype. All available subjects meeting the criteria for the matched comparison groups from ADNI were included as comparators. Participant demographics and matched ADNI group characteristics are outlined in Table 1.

Participant DBS stimulation settings were finalized four months after surgery and kept unchanged for at least 12 months. These settings were subsequently adjusted twice, keeping the active contacts unchanged, for participants one and three in efforts to improve efficacy. Stimulation adjustments initially and subsequently were based on best-observed neurocognitive task response focusing on attentional and executive tasks, least amount of undesired neuropsychiatric symptoms, and on subject and caregiver assessments of the changed settings.

Adverse events

All participants tolerated the procedures and DBS well and there were no serious or permanent adverse events. All stimulation-induced side effects (hot flashes, increased heart rate/palpitations, flushing, paresthesias, muscle twitching, non-specific discomfort, fatigue, and neuropsychiatric symptoms) were transient and reversed with setting adjustments. Mild pain at implantable pulse generator site, headache at incision site, transient visual neglect following surgery, diarrhea, vomiting, rash, rhinitis, arthralgia, fall, hematoma, and depression were reported and all resolved without sequela.

Clinical measures

Figure 2A shows the posterior density distributions of slopes for each DBS subject and ADNI group. We observe strong overlap between DBS subject one and ADNI group 1, but slopes for DBS subjects 2 and 3 cluster closer to zero compared to the relevant ADNI groups. Figure 2B shows raw longitudinal CDR-SB scores for each DBS subject and ADNI subject, which have been adjusted to the same starting point. Since our analysis focused on the slopes fit to the DBS and ADNI subjects, we presented the data in Fig. 2B with a common starting point so that the reader can readily observe differences in score progression. Given that the DBS participant and their matching ADNI group were fit within the same hierarchical model, meaningful differences between DBS subjects and their matched groups were determined from pairwise differences in slope posterior distributions. Here, we report the 95% CI of the difference distribution and the percentile value of the equivalence point, which are further illustrated by Fig. 3.

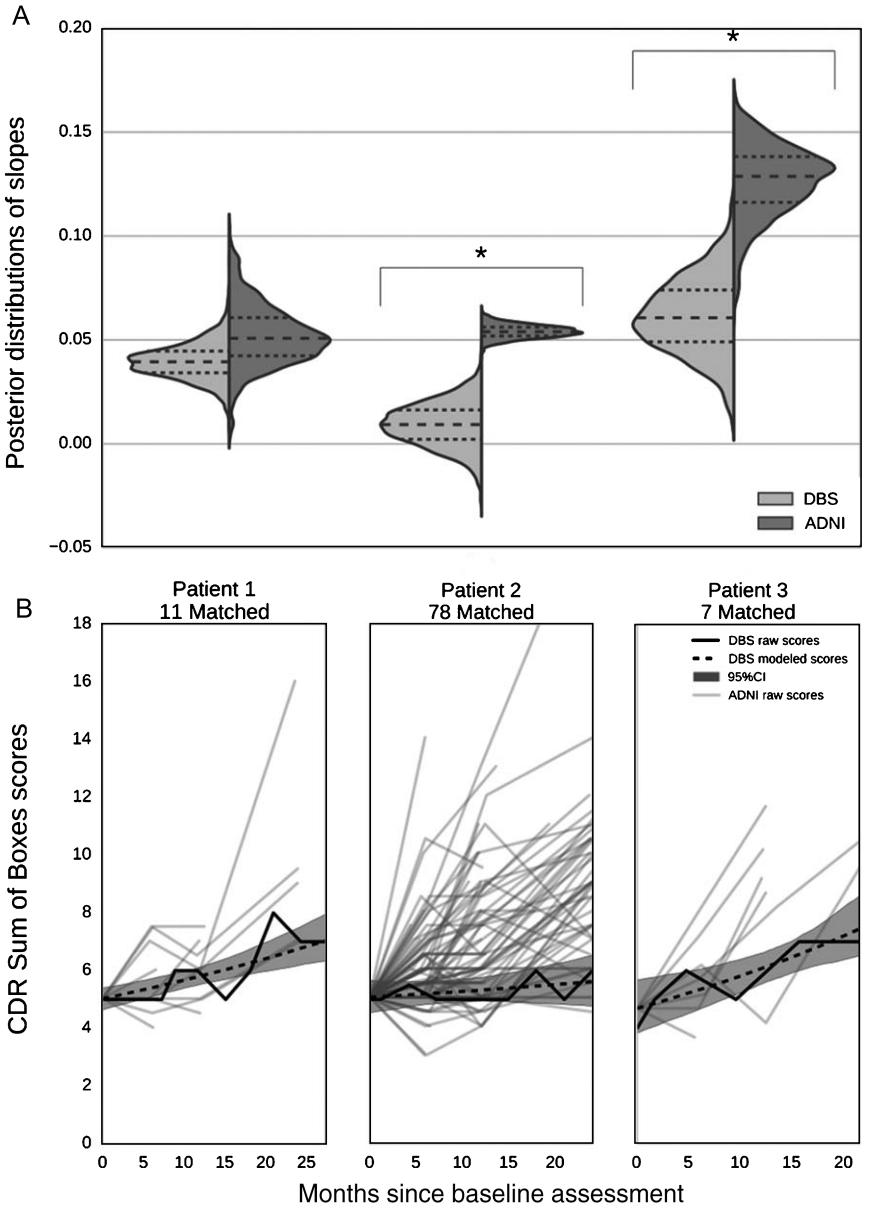

Fig. 2. (A) CDR-SB posterior distributions of slopes. Greater slopes as indicated by the y-axis indicate faster progression of decline over time as measured by the CDR-SB. Posterior slope distributions for each DBS subject and matched ADNI group were calculated via a hierarchical Bayesian framework. Meaningful differences were assessed by comparing the 95% CI of the difference distribution to 0. DBS patients 2 and 3 showed less impairment over time compared to their matched ADNI groups, and are marked with an asterisk. B) CDR-SB score trajectory values. Upward-trending values indicate more impairment as measured by the CDR-SB. Solid black lines are the CDR-SB raw scores for participants one, two, and three obtained during study visits spanning up to 27, 24, and 21 months respectively. Dashed black lines represent the model-predicted scores at each time point. Dark gray bands are the 95% confidence intervals around best-fitting predictions. Thin gray lines are the raw CDR-SB scores across time for each individual subject in the ANDI Alzheimer's disease matched comparison groups 1, 2, and 3.

CDR-SB scores indicated that ADNI groups 1, 2, and 3 experienced more severe symptoms of dementia overall as time progressed (Group 1: mean score at baseline = 4.954, SD = 1.851, mean score 24 months after baseline = 8.800, SD = 3.655; Group 2: mean score at baseline = 4.756, SD = 1.566, mean score 24 months after baseline = 8.311, SD = 3.31; Group 3: mean score at baseline = 5.143, SD = 1.059, mean

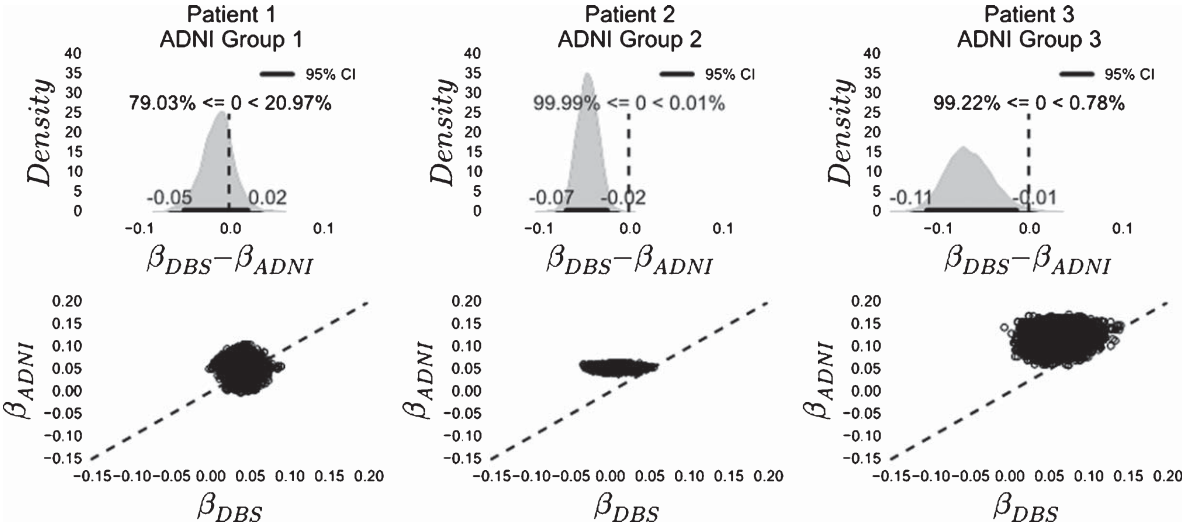

Fig. 3. CDR-SB Slope posterior comparison. The top row shows the pairwise difference distribution comparing each DBS subject's slope posterior to the ADNI group's slope posterior. If 0 fell outside of the 95% CI of the difference distribution, we had strong belief that the DBS patient had a different score trajectory than the ADNI group. Annotations show the boundaries of the 95% CI and the percentage of the distribution that falls on either side of 0. The bottom row shows scatter plots comparing DBS to ADNI posterior distributions of slope, with equivalence shown as a black dotted line.

score 24 months after baseline = 11.500, SD = 1.500). Similarly, all three of our DBS subjects experienced more severe symptoms of dementia over time as well (patient 1: score at baseline = 5.000, score at end of study = 7.000; patient 2: score at baseline = 5.000, score at end of study = 6.000; patient 3: score at baseline = 5.000, score at end of study = 7.000). Results of our Bayesian analysis are given in terms of the posterior difference distribution comparing slope estimates for DBS and ADNI subjects. Here, we provide the bounds of the 95% CI and the percentage of the difference distribution that fell on either side of the zero equivalence point. We had strong belief in an outcome if more than 97.5% of the difference distribution fell on either side of zero. When comparing DBS participant one to Group 1 (early-onset AD, ApoE ε4 homozygous population), there was not a meaningful difference between CDR-SB score trajectories (95% CI = (–0.049, 0.021), 20.968% < 0 < 79.032%). Based on our analysis, we have strong belief that DBS participant two (late-onset AD, single ApoE ε4 carrier) showed less severe decline on CDR-SB over time compared to her matched ADNI groups (95% CI = (–0.066, –0.023), 0.007% < 0 < 99.993%). We also have strong belief that DBS participant 3 (early-onset AD, ApoE ε4 non-carrier) showed less severe decline over time compared to her ADNI matched group (95% CI = (–0.111, –0.013), 0.783% < 0 < 99.217%).

PET assessments

To help evaluate the influence of DBS on brain metabolic patterns for each participant, we subtracted z-score mapping of the FDG PET performed after surgery but prior to DBS titration from the z-score mapping of the FDG PET performed after 17 to 19 months of continual DBS (Fig. 4). After 19 months of continuous DBS, participant one, our primary outcome measure CDR–SB non-responder, showed very little changes in orbitofrontal and pre-frontal regions, while the CDR–SB responders, participant two (after 19 months) and three (after 17 months), demonstrated areas of increased metabolism mostly in orbitofrontal and ventromedial and dorsolateral prefrontal cortical regions.

DISCUSSION

Our pilot phase I study evaluated three mild AD participants longitudinally for 27, 24, and 21 months, respectively, using bilateral DBS at a novel target for AD in the VC/VS region, potentially modulating frontal lobe behavioral and cognitive networks. They experienced no significant adverse events and all still reside at home.

Operationally, we chose CDR-SB a priori as our primary outcome measure, which is a widely used global measure summating six domains of cognitive

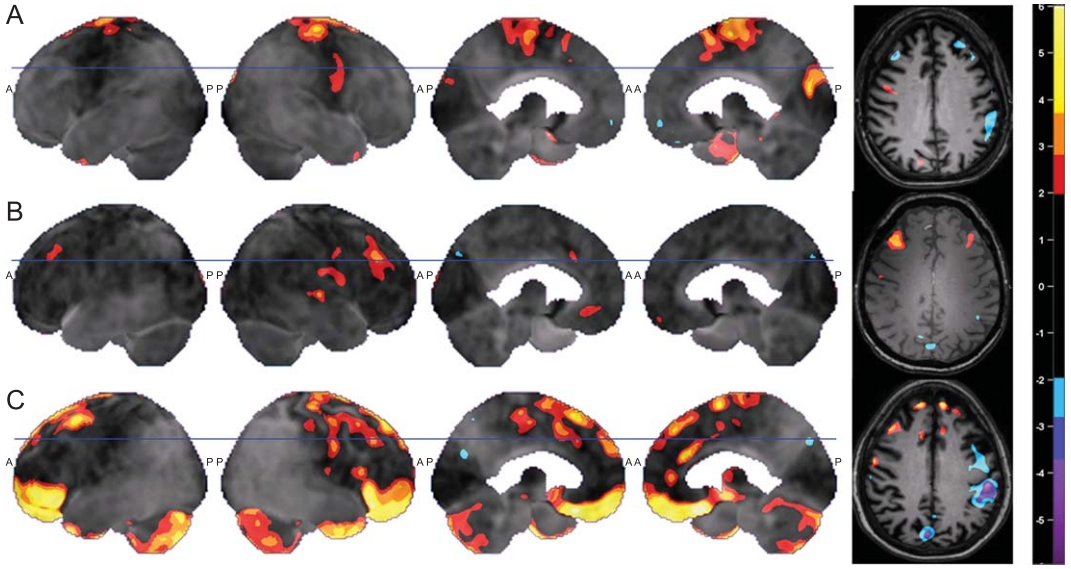

Fig. 4. FDG PET z-score results of participant one (A), participant two (B), and participant three (C). Z-scores differences of the FDG PET performed after surgery but before DBS subtracted from the FDG PET performed after 17 to 19 months of continual DBS were calculated and fused on top of both the PET before DBS in 3D stereotactic surface projection and MRI in one transverse slice (level indicated on the sagittal views) to identify regional metabolism changes after DBS therapy. Statistically significant z-scores differences (labeled on the right side) were highlighted with color-coded overlays. After continuous DBS, areas of significant decreased FDG tracer uptake are indicated in the cold colors while regions of significant increased tracer accumulation are shown in warmer colors.

and functional performance. It has low variability over two years making it an excellent primary endpoint for AD trials [41]. Worsening CDR-SB scores correlate to increasing dementia severity and chance of institutionalization [42]. DBS of the VC/VS showed that all three participants had less decline and two of them (participants two and three) meaningfully less decline on CDR-SB relative to matched comparison groups from ADNI. We achieved our primary study objective for those participants.

Looking at our secondary cognitive outcome measures that could be matched to the ADNI database (Supplementary Table 1), participants two and three showed score trajectories for ADAS-cog total score, Boston Naming Test, category fluency, and Composite 1 either within the 95% CI or meaningfully better than the same matched comparison groups from ADNI. These tasks measuring global cognitive, language, and executive abilities would likely be impacted with modulation of frontal networks. Behavioral symptoms in our participants, as in the ADNI matched groups, were clinically treated. Depressive symptoms responded with typical doses of antidepressants in each of our three participants and participant two started 25 mg quetiapine for mild psychosis at 17 months. No other behaviors required behavioral pharmacotherapy. Six of 11 in the matched ADNI group 1, 25 of 78 in the matched ADNI group 2, and 6 of 7 in the matched ANDI group 3 were on various antidepressants. Four of 78 of the matched ADNI group 2 and none of the subjects in groups 1 or 3 were on antipsychotics. Certainly, treatment of behaviors and depression may impact cognitive and functional abilities but unless the behaviors were severe or the medication doses high, which was not the situation for our participants, the effect on the CDR-SB is likely minimal. Our CDR-SB primary outcome measure, evaluates orientation, memory, executive functioning, problem solving, community affairs, daily affairs, and basic activities of daily living. It does not directly include in its assessment any behavioral evaluation as part of its score. Depression symptoms in AD are very common, are typically mild, and treatments rarely impact cognitive performance [43]. While we did not specifically control for psychotropic medication use, cognitive specialists clinically treated both the ADNI groups and our participant's behavior symptoms. Also given the frequent use of antidepressants in the ADNI control groups and the good tolerability of these agents regarding cognition or function, it is not likely that treatment of the behavioral symptoms in our participants would lead to the meaningful CDR-SB findings of our study. However, this

cannot be excluded and there is also the possibility of VC/VS DBS creating mood changes. We are unable to draw firm conclusions on these issues given our small sample size. Participants and caregivers consistently reported feelings of improved energy, focus, alertness, and attention with DBS; attributes hard to measure objectively but anticipated with modulation of frontal networks.

Functional measures, as assessed by our activities of daily living inventory, for participant two actually improved after 24 months of stimulation. When entering the study, she was not doing any meal preparation. After DBS, she could independently initiate preparations of a simple meal, assemble ingredients, and cook the meal. She was able to organize an outing with respect to transportation and destination, plan for the weather, and bring the needed money. She also regained independence to select her clothing attire.

While metabolism on brain FDG PET typically decreases in frontal regions of AD patients over two years, we observed minimal changes in participant one and increased metabolism in participants two and three in orbitofrontal, ventromedial prefrontal, and dorsolateral prefrontal cortical regions after chronic DBS at the VC/VS target (Fig. 4). While unable to draw firm conclusions given our small sample, this suggests possible physiological effects of DBS. Obsessive-compulsive disorder patients treated with VC/VS DBS and evaluated with PET imaging have shown variable results. In the acute setting, ^{15}O PET showed activation in the orbitofrontal and dorsal anterior cingulate cortex [44, 45]. In another study, in the acute setting (less than 3 months), FDG PET showed reduced metabolism in the anterior cingulate and prefrontal and orbitofrontal cortices [46]. Our FDG PET results represent changes after 17 and 19 months of chronic continuous DBS treatment in AD patients and so we suggest caution when comparing these different groups.

Other phase I open label clinical trials of DBS in AD have focused on the memory targets of the fornix and nucleus basalis of Meynert [11–16, 47]. While they show early promising outcomes, the authors did not compare cognitive measures with any matched comparison groups. Randomized controlled trials of DBS at the fornix were recently reported, showing no significant safety issues but no significant efficacy compared to controls [47].

This is the first report of DBS in AD not pursuing a memory target. Stimulation of different brain targets may have different effects on cognition, memory, behaviors, and functioning. For caregivers, patient's memory impairments can be easily aided with reminders/notes but caregivers find great difficulty in overcoming patient's executive impairments like apathy, impaired initiative, reduced curiosity, diminished self-regulation, poor decision-making, and impaired problem solving. Many of these symptoms have been shown to be impacted by VC/VS DBS in patients with obsessive-compulsive disorder, depression, and addictions [4, 5, 10]. By targeting the VC/VS region we hoped to modulate frontal networks and impact executive functions in our AD participants. Additionally, based on typical AD propagation of neurodegeneration starting in temporal (memory) and extending later into frontal (executive) regions, the more viable neurons in the VC/VS region might serve as better substrate for neuromodulation by DBS.

Our phase I prospective pilot trial has limitations. We must be cautious in our interpretation of our results since we have studied only three participants and have limited analyses. Though we utilized ADNI matched comparison groups to conduct statistical tests, we did not use active (sham) controls in this study and hence are unable to generalize our results. We assessed our results by fitting a Bayesian hierarchical linear model to the dataset. While linear models allowed us to combine data and perform statistics across subjects, it is unlikely that the change in performance metrics across time was indeed linear. Given that we only have a small number of observations per subject, however, linear models allowed us to capture the general trends in the data while not suffering from overfitting. We acknowledge that since ADNI Group 2 contains substantially more subjects than the other two ADNI groups, the parameter estimates generated by our Bayesian hierarchical model may exhibit "shrinkage," such that the posterior is perhaps inappropriately constrained by group-level trends, yet the reduction in uncertainty of the slope parameter posterior is to be expected given the increased number of participants.

In summary, this is the first report demonstrating the safety and efficacy of DBS of the VC/VS in AD subjects. Our preliminary findings of less decline in CDR-SB suggest that stimulation of frontal behavioral and cognitive neural networks in AD patients is a promising treatment modality that should be further studied in a larger randomized controlled study. While the goal of attenuating memory loss receives the majority of attention in AD clinical trials, future research strategies should incorporate efforts to improve behavioral and executive deficits as well.

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SUPPLEMENTARY MATERIAL

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