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Original Article

Deep Brain Stimulation Influences Brain Structure in Alzheimer's Disease

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ABSTRACT

Background: Deep Brain Stimulation (DBS) is thought to improve the symptoms of selected neurological disorders by modulating activity within dysfunctional brain circuits. To date, there is no evidence that DBS counteracts progressive neurodegeneration in any particular disorder.
Objective/Hypothesis: We hypothesized that DBS applied to the fornix in patients with Alzheimer's Disease (AD) could have an effect on brain structure.
Methods: In six AD patients receiving fornix DBS, we used structural MRI to assess one-year change in hippocampal, fornix, and mammillary body volume. We also used deformation-based morphometry to identify whole-brain structural changes. We correlated volumetric changes to hippocampal glucose metabolism. We also compared volumetric changes to those in an age-, sex-, and severity-matched group of AD patients ($n = 25$) not receiving DBS.
Results: We observed bilateral hippocampal volume increases in the two patients with the best clinical response to fornix DBS. In one patient, hippocampal volume was preserved three years after diagnosis. Overall, mean hippocampal atrophy was significantly slower in the DBS group compared to the matched AD group, and no matched AD patients demonstrated bilateral hippocampal enlargement. Across DBS patients, hippocampal volume change correlated strongly with hippocampal metabolism and with volume change in the fornix and mammillary bodies, suggesting a circuit-wide effect of stimulation. Deformation-based morphometry in DBS patients revealed local volume expansions in several regions typically atrophied in AD.
Conclusion: We present the first in-human evidence that, in addition to modulating neural circuit activity, DBS may influence the natural course of brain atrophy in a neurodegenerative disease.

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Conflicts of interest: A.M.L. is a consultant to Medtronic, St Jude, and Boston Scientific. A.M.L. serves on the scientific advisory board of Ceregene, Codman, Neurophage, Aleva and Alcyone Life Sciences. A.M.L. is co-founder of Functional Neuromodulation Inc. and holds intellectual property in the field of Deep Brain Stimulation. All other authors declare no relevant conflicts.

Authorship contributions: T.S., A.W.L., and A.M.L. conceived and designed the study. T.S. supervised all data collection and analysis, and drafted most of the manuscript. M.M.C. collected deformation-based morphometry data, performed neuroimaging data quality control, and wrote part of the Methods. A.B., M.L., and T. O. collected and analyzed MRI volumetric data. A.W.L., D.F.T-W. and M.P.M performed and analyzed clinical assessments. C.I.W. and G.S.S. collected and analyzed PET data and wrote part of the Methods. All authors contributed to critically revising the manuscript, and approved the final version before submission.

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Introduction

Chronic, high-frequency, electrical deep brain stimulation (DBS) is an effective treatment for movement disorders such as Parkinson's disease, tremor, and dystonia [1]. More recently, DBS has been used on an experimental basis to treat patients with intractable psychiatric conditions including major depression [2,3], obsessive compulsive disorder [4,5], and anorexia nervosa [6]. The therapeutic mechanism of action underlying DBS in these various neuropsychiatric disorders remains uncertain, but likely involves modulation of activity within dysfunctional neural circuits [7]. As such, DBS is considered a symptomatic therapy, affecting neural circuit function, but is thought to be unable to influence progressive neurodegenerative processes acting on these circuits. Nevertheless, given the success of DBS in treating the symptoms of Parkinson's disease, its use in other neurodegenerative disorders including Alzheimer's disease (AD) is now also being considered.

AD is a neurodegenerative disease characterized by atrophy in several brain structures—notably the hippocampus—with amyloid and tau deposition, formation of neurofibrillary tangles, and cerebral hypometabolism most notably in posterior cortical regions [8]. These pathophysiological changes result in dysfunction in several neural circuits, including the default mode network [9] and the memory circuit of Papez [10]. In a recently published phase I clinical trial [11], we assessed the safety and possible benefits of DBS in six AD patients. Bilateral DBS applied to the fornix—the principal outflow tract from the hippocampus—was able to drive physiological activity within the memory circuit, and may have been associated with slowing in the expected rate of cognitive decline in some patients.

These promising results point to the potential effectiveness of fornix DBS as a symptomatic therapy in AD. However, additional findings from the trial, coupled with data from recent DBS studies in animal models, raise the possibility that fornix DBS might, additionally, induce plastic effects both within the memory circuit and across the entire brain. In particular, positron emission tomography (PET) data acquired serially from the AD patients enrolled in the trial showed a sustained increase in cortical glucose metabolism over one year in contrast to the cortical hypometabolism that is typically observed over time in AD [12]. Additionally, in rodents, DBS applied to several nodes of the memory circuit stimulates neurogenesis in the dentate gyrus of the hippocampus [13,14]; these new neurons are of normal morphology, integrate themselves into functional circuits, and appear to enhance memory [14,15].

Based on these observations, we hypothesized that the effects of fornix DBS may extend to changes in brain structure, and possibly to a slowing of progressive neurodegeneration in patients with AD. To test this hypothesis, we quantitatively analyzed serial structural magnetic resonance imaging (MRI) scans of the brain in AD patients treated in our phase I trial of fornix DBS. Specifically, we measured the volumes of the hippocampus, fornix, and mammillary bodies—critical components of the Papez circuit—in all patients at baseline and following one year of continuous fornix stimulation. We also looked for evidence of brain-wide structural changes, using a hypothesis-free, data-driven method known as deformation-based morphometry (DBM) [16]. Finally, we compared hippocampal volume changes over time in patients treated with DBS to those seen in an age-, sex-, and severity-matched group of untreated AD patients. Taken together, our results suggest that DBS may be accompanied by changes in brain structure, and in some cases prevent the progression of focal brain atrophy, in patients with a neurodegenerative disease.

Materials and methods

Participants

Patient selection, the DBS surgical implantation procedure, clinical evaluation, and follow-up have previously been addressed in detail in Laxton et al. [11]. Briefly, inclusion criteria were as follows: men or women, aged 40–80 years; satisfied the diagnostic criteria for probable AD; received the diagnosis of AD within the past 2 years; Clinical Dementia Rating (CDR) [17] score of 0.5 or 1.0; score between 18 and 28 on the Mini Mental State Examination (MMSE) [18]; on a stable dose of cholinesterase inhibitors for a minimum of 6 months prior to DBS implantation surgery. Exclusion criteria included: pre-existing structural brain abnormalities (such as tumor, infarction, or intracranial hematoma); other neurologic or psychiatric diagnoses; medical comorbidities that would preclude safe surgical implantation of a DBS system. The Research Ethics Boards of the University Health Network and the Centre for Addiction and Mental Health approved this study. Informed consent was obtained from either the patient or a surrogate after the nature and possible consequences of DBS surgery were explained. Patient demographics, medication use, and baseline and one-year Alzheimer's Disease Assessment Scale-Cognitive Subscale-11 (ADAS-Cog) [19] scores are reported in Table 1. Additional neuropsychological data included: MMSE, verbal fluency as measured using animal fluency, intelligence quotient (IQ) measured using the Wechsler Abbreviated Scale of Intelligence [20], trail making test A and B [21], and face recognition using the Wechsler Memory Scale, 3rd edition [22] (Supplementary Tables 1 and 2). To provide a better indicator of hippocampus-mediated cognitive outcomes, we devised a composite measure comprised of the mean percent change over one year of fornix DBS across four memory-related neuropsychological measures: 1) the word recall component of the ADAS-Cog; 2) the word recognition component of the ADAS-Cog; 3) immediate face recognition; and 4) delayed face recognition.

MRI volumetry of hippocampus, fornix, and mammillary bodies

Structural MRI scans were obtained at three time points: on the day of DBS implantation (i.e., pre-DBS), on the day immediately following initial DBS insertion (i.e., immediate post-DBS), and one year later (i.e., delayed post-DBS). Patient 4 was also re-scanned at three years. Immediate post-DBS scans were used as baseline scans in all assessments of volumetric change, in order to control for any image artifacts caused by—or potential volumetric influence due to—the presence of the DBS electrodes. All scans analyzed in this study, therefore, contained DBS electrodes at the fornix target. MRI scans were acquired with a 1.5 Tesla GE Signa EXCITE scanner (GE Healthcare, Waukesha, WI). A T1-weighted, three-dimensional spoiled

Table 1
Sex, age, baseline and one-year cognitive scores, and medication treatments for all six patients treated using fornix DBS. Note that higher ADAS-Cog scores represent worse performance.

Patient	Sex	Baseline age (years)	Baseline ADAS-Cog	One year ADAS-Cog	Medication
1	Female	51	18.67	20.66	Donepezil
2	Female	69	18.30	23.33	Galantamine
3	Male	58	28.67	42.67	Galantamine
4	Male	62	11.67	7.33	Donepezil
5	Male	60	24.00	30.67	Donepezil, Memantine
6	Male	64	13.33	15.33	Rivastigmine

ADAS-Cog: Alzheimer's Disease Assessment Scale-Cognitive Subscale.