Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

J Alzheimers Dis. Author manuscript; available in PMC 2017 October 13.

Published in final edited form as:

J Alzheimers Dis. 2016 September 06; 54(2): 789–791. doi:10.3233/JAD-160719.

Brain Stimulation in Alzheimer's Disease

Itzhak Fried[a,b,*]

[a]Department of Neurosurgery, David Geffen School of Medicine, and Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, CA, USA

[b]Functional Neurosurgery Unit, Tel Aviv Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

Abstract

Deep brain stimulation has been successfully used in treatment of motor symptoms of Parkinson's disease and other movement disorders. In a recent multi-center prospectively randomized study, deep brain stimulation of the fornix was administered in order to ameliorate the cognitive symptoms and clinical course of Alzheimer's disease (AD). The study points to the possibility of modest slowing of the cognitive decline in AD in a subset of patients older than 65, while at the same time highlights the risk of stimulation in exacerbation of this decline in younger patients. The logic of conducting large clinical trials in the face of limited scientific understanding of the pathophysiology of AD and response of affected brain regions to electrical stimulation, is discussed with emphasis on the need to conduct: (i) animal studies in AD models, using precise focused stimulation; (ii) studies in patients who are implanted with depth electrodes for established clinical reasons (i.e., patients with epilepsy or movement disorders); and (iii) smaller adaptive studies in AD patients with systematic alterations of therapeutic parameters such as stimulation protocol.

Keywords

Alzheimer's disease; dementia; deep brain stimulation; fornix; hippocampus; entorhinal area

Alzheimer's disease (AD) poses one of the most acute societal challenges of this century, with increasing staggering numbers of afflicted individuals worldwide. The ominous societal implications of AD have been a clear motivating factor in the large brain research initiatives recently launched in the US, Europe, and elsewhere.

There is clearly an overwhelming translational gap between our understanding of the etiology of AD and its affected brain systems and the ability to offer preventive means or therapeutic means that will influence the disease course or its symptoms.

*Correspondence to: Itzhak Fried, MD, PhD, Professor, Department of Neurosurgery, UCLA, 300 Stein Plaza Dwy, Ste. 562, Los Angeles, CA 90095, USA. Tel.: +1 310 825 8409; Fax: +1 310 825 9385; ifried@mednet.ucla.edu.

DISCLOSURE STATEMENT

The author's disclosure statement is available online (http://j-alz.com/manuscript-disclosures/16-0719r1).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

While the chief avenue of therapeutic intervention in brain disorders has been pharmacological, there is a growing interest in electrical stimulation as means to ameliorate symptoms and course of neurological disease. Deep brain stimulation (DBS) has had considerable success in treating symptoms of various movement disorders, mainly Parkinson's disease (PD), essential tremor, and some forms of dystonia. The development of DBS for PD patients has been largely motivated by the failure of pharmacological treatments, especially at later stages of pharmacological intervention where unacceptable side effects such as dyskinesia emerge. In the same manner, there is growing interest now in development of DBS as a tool to treat severe pharmacologically resistant neuropsychiatric disorders such as major depression, obsessive-compulsive disorder, and post-traumatic stress disorder. The ultimate challenge appears to be the development of DBS to treat cognitive deficits, and specifically memory impairment. Given the potential of DBS to modulate dysfunctional brain circuits and on the background of failure of numerous clinical drug trials, the interest in using DBS to ameliorate the symptoms of AD and its course appears reasonable.

Hamani et al. reported improved memory with stimulation of the fornix, in its anterior part near the hypothalamus, in one patient implanted with DBS leads for obesity [1]. This observation instigated a study of six patients with AD where continuous stimulation of the same target in the anterior fornix for one year demonstrated safety and showed some increase in glucose metabolism but no significant behavioral or clinical effect [2, 3].

On this background, Lozano et al. now report a bold multi-center prospectively randomized study of 42 patients with mild AD to examine the effect of fornix stimulation on the disease [4]. Carrying out a surgical study of this nature in this complex patient population is an enormous challenge and the authors deserve credit for the sound methodology employed to bring this study to conclusion. As to the safety outcome measure, the surgical procedure and stimulation were all well tolerated. The primary clinical outcome of the study was measured by the Alzheimer's disease Assessment Scale-13 (ADAS-Cog13) and Clinical Dementia Ratings (CDR-SB) at 12 months. There was no significant difference in the primary clinical outcome measure between the stimulated and the sham groups, nor was there a difference in the secondary cognitive outcome measures. Patients receiving stimulation showed significant increases in glucose metabolism at 6 months but the increases were not significant at 12 months. In a *post-hoc* analysis, there was a significant interaction between age and clinical outcome with a trend of improvement of the older patients (>65 years) and worsening of the younger patients. While non-stimulated patients in both groups (older and younger) worsened by a mean of about 7–8 points on the ASDAS-Cog13 scores in the course of one year follow-up, the stimulated older patients declined by a mean of only 3 points, but the stimulated younger patients declined by 18 points.

The question can be raised as to rational of subjecting 42 AD patients to complex surgery and subsequent stimulation (or sham) with rigidly and narrowly prescribed parameters and whether there are sufficient scientific data to support this approach.

The authors raise the possibilities that such stimulation may precipitate neurogenesis, may have neurotrophic effects, facilitating expression of synaptic proteins, and drive Papez

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

circuit to improve memory function. Even if one accepts this rational, several critical questions remain, one being the stimulation protocol. For instance, it is not clear what is the scientific basis for applying 130 Hz continuous stimulation to the region of the anterior fornix. The authors mention that the same parameters of open loop continuous stimulation have been beneficial for PD patients, although the application there was in entirely different locations and brain system. Several alternative stimulation protocols include stimulation at different frequency, theta burst stimulation, open rather than closed loop stimulation, stimulation at different stages of information processing, etc.

This study is a good example of the tension between the state of basic scientific knowledge and the clinical translational need. In order for a clinical study of this nature to be successful in the regulatory pathway, it needs to adhere to a strict protocol, which mandates certain decisions. If such protocol decisions are reached without reasonable scientific background, a study may be “a shot in the dark”. Indeed, recent large DBS studies in major depression have failed to show efficacy (Dougherty et al. [5]; closure of BROADEN trial).

The lesser decline in clinical outcome in the study by Lozano et al. [4] between the stimulated and non-stimulated patients in the older AD group is quite modest in magnitude. At the same time, the greater decline in the younger AD patients who received fornix stimulation may serve as warning that electrical stimulation can also have detrimental effect beyond the risks of surgery.

The distance from simple one-way stimulation affecting motor variables, to clinically applicable devices that will treat the cognitive impairment in dementias, and may also ameliorate disease course and quality of life is daunting. Such devices will likely need closed-loop patterned stimulation, controlled by behavioral feedback and brain signals sampled at a spatial resolution not available at current technology. In addition, there is a significant gap between the basic understanding of cognitive mechanisms and disease pathophysiology, and the translational benefits expected of neuromodulation. The 2014 Nobel Prize in Physiology and Medicine recognized the discovery of basic cellular mechanisms underlying spatial navigation in rodents, namely the intricate system of place cells in hippocampus and grid cells in entorhinal cortex, areas which are part of the so called Papez circuit, presumably stimulated via the fornix in the present study. The findings of place and grid cells were extended to humans in the studies carried out in epilepsy patients implanted with depth electrodes [6, 7]. Yet it is still a mystery how massive 130 Hz stimulation of the fornix at currents of thousands of microamperes might affect these intricate networks and their deterioration. This is indeed a knowledge gap that has not yet been adequately addressed even in rodents.

Of note is that there is also a growing literature on noninvasive brain stimulation in AD patient using transcranial magnetic stimulation, transcranial direct current stimulation, and even vagal nerve stimulation [8]. Yet it is difficult to assess the specific brain systems involved, the underlying mechanisms, and the long-term effects of these stimulation methods.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Do the results of this study justify the launching of a much larger study that may be better powered to test efficacy than the smaller samples used in this Phase II study where only *post-hoc* analysis yielded some trends? Clearly, there is a pressing clinical need with the massive prevalence of AD and other dementias. Yet, the limited scientific foundation, and the variability of potential therapeutic parameters may argue for alternative approaches. One approach is to use other patient populations—where electrodes are already implanted for established clinical reasons—to test effect of stimulation on cognitive parameters impaired in AD, specifically episodic memory or spatial navigation. Indeed, such an approach has been employed in neurosurgical epilepsy patients by Suthana et al. [9] where stimulation was applied in the entorhinal area during encoding and by Miller et al. [10] with stimulation applied at the posterior fornix. Another approach is to conduct smaller adaptive trials where several therapeutic variables can be systematically altered. These include stimulation protocols, as considerable variability can be seen even in the few memory trials conducted to date. For instance, Suthana et al. [9] have used 50 HZ stimulation for 5 s on-off periods applied unilaterally, Miller et al. [10] have used unilateral theta burst stimulation over longer period of times (20 min and more), and Laxton et al. [2] have used continuous bilateral 130 Hz stimulation. At the same time, further animal experiments enabling more precise well-defined manipulation of neuronal circuits in disease models should be employed. A good example is a recent study showing that in transgenic mouse models of early AD, direct optogenetic activation of hippocampal memory engram cells results in memory retrieval [11].

Acknowledgments

Support provided by grant from National Institute of Neurological Disorders and Stroke (NS084017).

References

1. Hamani C1, McAndrews MP, Cohn M, Oh M, Zumsteg D, Shapiro CM, Wennberg RA, Lozano AM. Memory enhancement induced by hypothalamic/fornix deep brain stimulation. Ann Neurol. 2008; 63:119–123. [PubMed: 18232017]
2. Laxton AW, Tang-Wai DF, McAndrews MP, Zumsteg D, Wennberg R, Keren R, Wherrett J, Naglie G, Hamani C, Smith GS, Lozano AM. A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. Ann Neurol. 2010; 68:521–534. [PubMed: 20687206]
3. Smith GS, Laxton AW, Tang-Wai DF, McAndrews MP, Diaconescu AO, Workman CI, Lozano AM. Increased cerebral metabolism after 1 year of deep brain stimulation in Alzheimer disease. Arch Neurol. 2012; 69:1141–1148. [PubMed: 22566505]
4. Lozano AM, Fosdick L, Chakravarty MM, Leoutsakos JM, Munro C, Oh E, Drake KE, Lyman CH, Rosenberg PB, Anderson WS, Tang-Wai DF, Pendergrass JC, Salloway S, Asaad WF, Ponce FA, Burke A, Sabbagh M, Wolk DA, Baltuch G, Okun MS, Foote KD, McAndrews M, Giacobbe P, Targum SD, Lyketsos CG, Smith G. A phase II study of fornix deep brain stimulation in mild Alzheimer's disease. J Alzheimers Dis. 2016; 54:777–787. [PubMed: 27567810]
5. Dougherty DD, Rezai AR, Carpenter LL, Howland RH, Bhati MT, O'Reardon JP, Eskandar EN, Baltuch GH, Machado AD, Kondziolka D, Cusin C, Evans KC, Price LH, Jacobs K, Pandya M, Denko T, Tyrka AR, Brelje T, Deckersbach T, Kubu C, Malone DA Jr. A randomized sham-controlled trial of deep brain stimulation of the ventral capsule/ventral striatum for chronic treatment-resistant depression. Biol Psychiatry. 2015; 78:240–248. [PubMed: 25726497]
6. Ekstrom AD, Kahana MJ, Caplan JB, Fields TA, Isham EA, Newman EL, Fried I. Cellular networks underlying human spatial navigation. Nature. 2003; 425:184–187. [PubMed: 12968182]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

7. Jacobs J, Weidemann CT, Miller JF, Solway A, Burke JF, Wei XX, Suthana N, Sperling MR, Sharan AD, Fried I, Kahana MJ. Direct recordings of grid-like neuronal activity in human spatial navigation. Nat Neurosci. 2013; 16:1188–1190. [PubMed: 23912946]

8. Hansen N. Brain stimulation for combating Alzheimer's disease. Front Neurol. 2014; 5:80. [PubMed: 24917846]

9. Suthana N, Haneef Z, Stern J, Mukamel R, Behnke E, Knowlton B, Fried I. Memory enhancement and deep-brain stimulation of the entorhinal area. N Engl J Med. 2012; 366:502–510. [PubMed: 22316444]

10. Miller JP, Sweet JA, Bailey CM, Munyon CN, Luders HO, Fastenau PS. Visual-spatial memory may be enhanced with theta burst deep brain stimulation of the fornix: A preliminary investigation with four cases. Brain. 2015; 138:1833–1842. [PubMed: 26106097]

11. Roy TS, Arons A, Mitchell TI, Pignatelli M, Ryan TJ, Tonegawa S. Memory retrieval by activating engram cells in mouse models of early Alzheimer's disease. Nature. 2016; 531:508–512. [PubMed: 26982728]