Title
Brain stimulation and memory

Journal
Brain, 138(Pt 7)

ISSN
0006-8950

Author
Fried, Itzhak

Publication Date
2015-07-01

DOI
10.1093/brain/awv121

Peer reviewed

BRAIN
A JOURNAL OF NEUROLOGY

SCIENTIFIC COMMENTARIES

Brain stimulation and memory

This scientific commentary refers to 'Visual-spatial memory may be enhanced with theta burst deep brain stimulation of the fornix: a preliminary investigation with four cases', by Miller *et al.* (doi:10.1093/brain/awv095).

Loss of memory is one of the most devastating afflictions of the human condition. With ageing of the population, the looming spectre of neurological disorders affecting cognition in huge numbers of individuals is a critical societal concern. While major efforts are being directed toward prevention of degenerative diseases such as Alzheimer's disease and Parkinson's disease, notable success has already been achieved in the treatment of motor symptoms in Parkinson's disease and other movement disorders using direct stimulation of specific brain centres. The extension of this therapeutic modality known as deep brain stimulation (DBS) to neuropsychiatric conditions such as severe major depression or refractory obsessive-compulsive disorder is underway. The ultimate frontier may well be the application of neuromodulation to the cognitive domain in general and to memory specifically. Several studies have explored the effect of DBS on memory in humans, focusing on the medial temporal lobe with its efferent and afferent associated pathways. In this issue of *Brain*, Miller *et al.* (2015) provide intriguing preliminary data on the effect of fornix stimulation on spatial memory, in patients implanted with intracranial depth electrodes for the treatment of refractory epilepsy.

The transition from basic science to clinical application is complex and highly challenging. In a much publicized article, Alivisatos *et al.* (2012) proposed the Brain Activity Map Project, a large-scale recording effort to map brains in a stepwise progression from *Caenorhabditis elegans* with its 302 neurons, through various species including the one-million-neuron Etruscan Shrew (smallest mammal), and culminating in the human brain. The project aims to 'record every action potential from every neuron within a circuit', and estimates that it will take 15 years to achieve full characterization of mouse neocortex. Such ambitious goals are laudable but may not be compatible with the real-life impatience of individuals suffering the effects of neurological disorders. At the same time enormous efforts and funding are being dedicated to other major brain initiatives in the USA, Europe and elsewhere. Some of these are bold endeavours directed at neuropsychiatric and cognitive disabilities, such as the recent DARPA-funded initiative aimed at restoring memory function in neurological patients (Restoring Active Memory-RAM) (Miranda *et al.*, 2015). Yet such endeavours involving human subjects should be conducted with independent medical, scientific and ethical oversight, to assure safety and scientific validity and avoid pitfalls of unrealistic expectations for early 'big wins'.

The paper by Miller *et al.* uses a unique clinical opportunity in the form of patients with pharmacologically resistant epilepsy who have already been implanted with brain depth electrodes to identify the seizure onset zone for potential surgical cure. In four such patients, Miller and co-workers applied electrical stimulation of the fornix during neuropsychological tests designed to examine memory function, finding better performance with stimulation during a spatial memory task.

The study by Miller *et al.* follows several other notable efforts in this area. Hamani *et al.* (2008) reported improved memory with stimulation of the fornix, albeit in the anterior part near the hypothalamus, in one patient implanted with DBS for obesity. This observation instigated a study of six patients with Alzheimer's disease where continuous stimulation of the same target in the anterior fornix for 1 year produced some increase in metabolism but no significant behavioural or clinical effect (Laxton *et al.*, 2010; Smith *et al.*, 2012). This study was followed by a larger study of 42 patients with early Alzheimer's disease, implanted with DBS electrodes in the anterior fornix. The results of this study are still pending. Another study performed in patients already implanted with depth electrodes found that stimulation of the entorhinal region—a critical area in the medial temporal lobe memory circuit projecting directly to the hippocampus—enhancedmemory in a spatial navigation task (Suthana *et al.*, 2012).

There are three novel features of the study by Miller *et al.* that warrant special attention. First, the location of stimulation is not the anterior fornix (i.e. near the hypothalamus) as was the case in previous reports in

implanted patients with Alzheimer's disease, nor the entorhinal region as reported by Suthana *et al.* (2012) but rather the posterior fornix just behind the tail of the hippocampus, and thus closer to the hippocampus than the anterior fornix. Second, theta burst stimulation was used, which may offer some advantages, perhaps in terms of eliciting long-term potentiation in the hippocampus. Finally, the duration of stimulation, although not described in detail by the authors, appears to be equivalent to the duration of the specific neuropsychological tests (~60 min) with at least 20 min of additional stimulation preceding testing. This makes the duration of stimulation in the order of 80 min and is obviously much shorter than the continuous 1-year fornix stimulation at 130 Hz used in the DBS study of patients with Alzheimer's disease, which was not linked to a particular task and followed the protocol customarily used in movement disorders (Laxton *et al.*, 2010). It is also considerably longer than the short stimulation in the study by Suthana *et al.* (2012), which was linked to a particular phase of information processing, namely encoding or learning. The study by Miller *et al.* does not separate the effect of stimulation on learning and recall.

While using novel features, the study by Miller *et al.* should also be viewed with considerable caution. The number of patients is small, only four. One of these patients had only two sessions (one stimulation, one sham), making these data more vulnerable to order effects. Only descriptive presentation of the results was used and no statistical analysis was used. Only one of two memory tests, that of spatial memory, showed improvement with stimulation (the other actually showing decline in some patients). Thus, better-controlled larger studies are needed.

The study was conducted in epilepsy patients in whom electrodes had already been implanted for clinical reasons. This approach, also used by Suthana *et al.* (2012), appears to provide a reasonable opportunity to advance the field before embarking on clinical trials with patient populations specifically targeted for cognitive relief, such as patients with Alzheimer's disease. At the same time, stimulation in epilepsy patients mandates caution, as it may cause seizures. It is thus encouraging, and perhaps surprising, that the protocol used by Miller *et al.* did not induce any seizures or untoward effects despite prolonged stimulation at currents around 7 mA.

What, then, does the future hold for the burgeoning field of neuromodulation? In embarking upon modulation of the human nervous system we are encouraged by the results of DBS in movement disorders, and driven by the pressing need arising from severe disorders of the nervous system which devastate cognitive and emotional life, such as major depression, OCD and dementia. Yet there is a significant gap between basic understanding of cognitive mechanisms and the results obtained by stimulation. The 2014 Nobel Prize in Physiology or Medicine recognized the discovery of basic cellular mechanisms underlying spatial navigation in rodents, namely the intricate system of place cells in the hippocampus and grid cells in entorhinal cortex. These findings were extended to humans in studies carried out in epilepsy patients implanted with depth electrodes (Ekstrom *et al.*, 2003; Jacobs *et al.*, 2013). Yet precisely how massive stimulation of the fornix at 7 mA affects these intricate networks remains a mystery. This is a knowledge gap that has not been adequately addressed, even in rodents.

The distance from simple one-way stimulation affecting cognitive variables, to clinically applicable devices that will treat neurological cognitive disorders and which may have an influence on disease course and quality of life is therefore daunting. Such devices will likely need to use closed-loop strategies with patterned stimulation, controlled by brain signals and behavioural feedback. The opportunity to conduct studies in patients already implanted with brain electrodes, such as those with severe epilepsy undergoing surgical evaluation (as in the study by Miller *et al.*), or patients undergoing awake DBS procedures, may be an important step towards achieving this goal.

Itzhak Fried MD, PhD.
Department of Neurological Surgery
David Geffen School of Medicine, UCLA,
Los Angeles, CA, USA

Correspondence to: Itzhak Fried,
E-mail: ifried@mednet.ucla.edu

doi:10.1093/brain/awv121

References

Alivisatos AP, Chun M, Church G, Greenspan R, Roukes ML, Yuste R. Thye brain activity map and the challenge of connectomics. Neuron 2012; 74: 970–4.

Ekstrom AD, Kahana MJ, Caplan JB, Fields TA, Isham EA, Newman EL, et al. Cellular networks underlying human spatial navigation. Nature 2003; 425: 184–7.

Hamani C, McAndrews MP, Cohn M, Oh M, Zumsteg D, Shapiro CM, et al. Memory Enhancement induced by hypothalamic/fornix deep brain stimulation. Ann Neurol 2008; 63: 119–23.

Jacobs J, Weidemann CT, Miller JF, Solway A, Burke JF, Wei X, et al. Direct recordings of grid-like neuronal activity in human spatial navigation. Nat Neurosci 2013; 16: 1188–90.

Laxton AW, Tang-Wai DF, McAndrews MP, Zumsteg D, Wennberg R, Keren R, et al. A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. Ann Neurol 2010; 68: 521–34.

Miller J, Sweet J, Bailey C, Munyon C, Luders H, Fastenau P. Visual-spatial memory may be enhanced with theta burst deep brain stimulation of the fornix: a preliminary investigation with four cases. Brain 2015; 107: 7054–59.

Miranda RA, Casebeer WB, Hein AM, Judy JW, Krotkov EP, Laabs TL, et al. DARPA-funded efforts in the development of novel brain-computers interface technologies. J Neurosci Methods 2015; 244: 52–67.

Smith GS, Laxton AW, Tang-Wai DF, McAndrews MP, Diaconescu AO, Workman CI, et al. Increased cerebral metabolism after 1 year of deep brain stimulation in Alzheimer disease. Arch Neurol 2012; 69: 1141–8.

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: 502–10.