



Published in final edited form as:

N Engl J Med. 2019 August 22; 381(8): 783–785. doi:10.1056/NEJMc1905240.

Fornix-Region Deep Brain Stimulation–Induced Memory Flashbacks in Alzheimer’s Disease

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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To the Editor:

In a randomized trial involving 42 patients, we assessed deep brain stimulation targeting the fornix to improve cognition in patients with Alzheimer's disease (ClinicalTrials.gov number, NCT01608061; the protocol for the trial is available with the published article¹). Although the primary trial outcome of improvement on cognitive scales was negative, we encountered a phenomenon of flashback-like cognitive experiences that occurred during initial programming of the stimulator (before randomization) in some of the patients in the trial, which may inform the understanding of human memory.

For deep brain stimulation of the fornix in these patients we used the Medtronic lead model 3387, which contains four contacts spanning 10.5 mm, arranged linearly. Stimulation was administered 2 weeks after implantation. Each contact was stimulated, and the voltage was gradually increased from 0 to 10 V or until the onset of side effects. A total of 20 patients (48%) spontaneously reported having vivid experiences of ostensible previous events in their lives. For example, a patient described an entire experience of being inebriated while drinking a margarita at a resort in Aruba. Another patient experienced a sense of satiety after recalling the taste of eating sardines on his front porch 20 years earlier. Details of the experiences in all 42 patients in the trial are provided in the Supplementary Appendix, available with the full text of this letter at [NEJM.org](https://www.nejm.org).

A total of 85 unique memory recollections were described by these 20 patients. A total of 12 patients had 29 memory experiences with elaborate spatiotemporal details. Six patients reported having ancillary experiences involving emotions, smells, or ambient temperatures. The experiences became more robust as stimulation voltage increased. For example, a patient's recollection at 7-V stimulation evolved from a generic notion of "helping a guy find something on his property" to, at 10-V stimulation, remembering "that this event occurred at night around Halloween" (Fig. 1). With increasing stimulation voltages, in many patients these reports were accompanied by very uncomfortable sensory or autonomic effects that precluded stimulation with higher voltages.

The occurrence of memory flashbacks did not correlate at the patient or group level with the trial outcomes of changes on cognitive testing, total brain volume, or hippocampal volume. There was no relationship at the group level between the development of memory flashbacks and the side of hippocampal stimulation.

These flashbacks are consistent with the iconic reports by Penfield and Perot and others of complex "experiential phenomena" with cortical electrical stimulation.^{2,3} In our trial, the regions that were stimulated included the fornix, anterior commissure, subcallosum

(subcallosal region of the corpus callosum), and precommissural archicortex (inner and inferior portion of the subcallosal area). The fornix is part of a circuit that processes episodic memory (autobiographic events) and semantic memory (ideas and concepts). The subcallosal area is involved in memories with emotional and spatial properties. Brain maps that have been obtained with the use of diffusion tensor imaging in patients with Alzheimer's disease have shown lower numbers of tracts in the fornix and greater numbers of subcallosal tracts than were observed in controls without Alzheimer's disease.⁴ On the basis of localization data from tractographic studies (three-dimensional modeling of nerve tracts) involving our patients, we found that most memory flashbacks (87%) were associated with the dorsal brain contacts that probably stimulated both the fornix and the subcallosal area.

The memory flashbacks from brain stimulation in our trial may provide information regarding the neuroanatomical substrates and pathways of memory encoding and retrieval. Future studies of brain stimulation could further correlate stimulated recollections with results on tractography and functional imaging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Supported by a grant (R01AG042165) from the National Institute on Aging and by the Federal Economic Development Agency for Southern Ontario, Medtronic, and Functional Neuromodulation.

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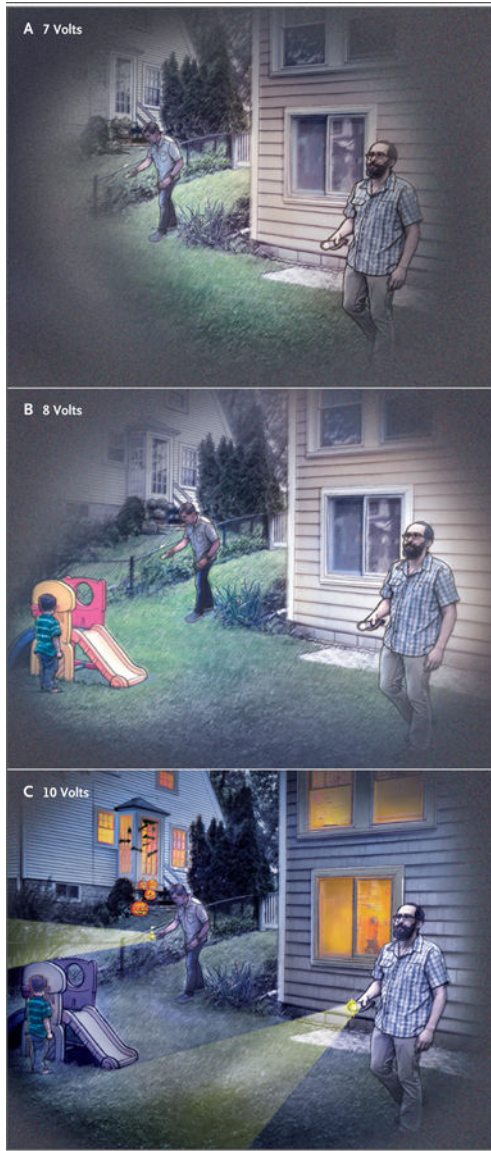


Figure 1. Increase in Detail and Clarity of Memory Flashbacks with Increases in Stimulation Voltage.

Memory experiences became more robust as the voltage of deep brain stimulation increased. For example, one patient’s recollection at 7-V stimulation evolved from a generic notion of “helping a guy find something on his property” to, at 8-V stimulation, remembering “helping the man’s son,” to at 10-V stimulation, also recalling “that this event occurred at night around Halloween.”