



Like a Circle in a Spiral: Stimulating the Windmills of Your Mind

Memory Enhancement and Deep-Brain Stimulation of the Entorhinal Area.

Suthana N, Haneef Z, Stern J, Mukamel R, Behnke E, Knowlton B, Fried I. *N Engl J Med* 2012;366(6):502–510.

BACKGROUND: The medial temporal structures, including the hippocampus and the entorhinal cortex, are critical for the ability to transform daily experience into lasting memories. We tested the hypothesis that deep-brain stimulation of the hippocampus or entorhinal cortex alters memory performance. **METHODS:** We implanted intracranial depth electrodes in seven subjects to identify seizure-onset zones for subsequent epilepsy surgery. The subjects completed a spatial learning task during which they learned destinations within virtual environments. During half the learning trials, focal electrical stimulation was given below the threshold that elicits an afterdischarge (i.e., a neuronal discharge that occurs after termination of the stimulus). **RESULTS:** Entorhinal stimulation applied while the subjects learned locations of landmarks enhanced their subsequent memory of these locations: the subjects reached these landmarks more quickly and by shorter routes, as compared with locations learned without stimulation. Entorhinal stimulation also resulted in a resetting of the phase of the theta rhythm, as shown on the hippocampal electroencephalogram. Direct hippocampal stimulation was not effective. In this small series, no adverse events associated with the procedure were observed. **CONCLUSIONS:** Stimulation of the entorhinal region enhanced memory of spatial information when applied during learning. (Funded by the National Institutes of Health and the Dana Foundation.).

Commentary

The entorhinal cortex stands out among the myriad of mysterious and elegant brain structures as a relay station between the neocortical parahippocampus and the more primal memory-encoding, seizure-producing hippocampus. It seems to have not six neocortical layers or three archicortical layers, but arguably five to eight layers with one atrophied layer (layer IV, the lamina densa) and a complex layer V with three distinct layered cell types (A, B, and C). Therefore, the entorhinal cortex combines a near sum of the neocortical and archicortical layers as it sorts input from the amygdala, olfactory bulb, septal nuclei, hippocampus, and parahippocampus (not a complete list) and delivers output to the dentate gyrus and hippocampus (1). Its proper functioning is critical for episodic memory, and it certainly mediates the formation of memories of navigational landmarks, via input from the parahippocampal cortex, which itself houses the processing of spatial relationships and the contextual information of experiences (2).

The entorhinal cortex is a critical hub for memory formation and is invariably one of the first areas of pathology in Alzheimer disease, showing neuronal loss and atrophy (3). If there was ever a single site important for memory functioning, this would be it. What if its function could be enhanced?

The investigators of the article at hand appear to have found a way. Based on evidence that there are site-specific brain areas in which stimulation can improve neurologic and psychiatric disease, and rodent experiments in which stimulation to analogous structures produced physiologic potential changes in the dentate, including long-lasting potentiation (4), it was undertaken to stimulate the entorhinal cortex and hippocampus in humans in order to assess the effect on memory function. A key feature of this experiment was the surrogate marker for enhanced memory encoding, the resetting of the hippocampal theta rhythm, which was measured as an increase in hippocampal theta power associated with stimulation versus nonstimulation conditions.

Intractable epilepsy patients were studied who already had hippocampal and/or entorhinal depth electrodes placed for localization of seizure onset for subsequent epilepsy surgery. The stimulation parameters used were already known to be subthreshold for afterdischarges based on pretesting of the stimulation sites. Overall, seven patients were studied: six underwent stimulation in the entorhinal cortex and five in the hippocampus. Four of the subjects were stimulated at both sites, which logically would be the only approach to determine a site-specific differential effect on memory function. It should be noted that memory enhancement by hippocampal stimulation would not be expected, since two previous human experiments (cited by the authors) showed memory deficits produced by such (5, 6). The memory test used was a complex virtual navigational task, that of delivering passengers



to stores, which took an average of 15 seconds to complete and was presented in groups of six stores per trial in a block. The store order was randomized, but a specific store presentation was either stimulated or nonstimulated within a subject. Further, each store was eventually equally associated with stimulation and nonstimulation conditions across subjects. Four trial blocks were performed, the first three in a stimulated condition and the fourth without stimulation.

The grouped results indeed showed reduction in excess path length with entorhinal stimulation compared with hippocampal stimulation, as well as shorter latency to complete the task. Most interesting is the fourth trial, performed without stimulation. This fourth trial results imply that memory retention is improved by stimulation of the entorhinal cortex, and not the hippocampus; path length and latency were both significantly decreased in the trial after entorhinal cortical stimulation versus nonstimulation. While hippocampal stimulation during the trials seemed to enhance memory, there was no difference in performance in the fourth nonstimulated trial.

The site-specific benefit of stimulating the entorhinal cortex versus the hippocampus is not well supported by results in the subjects who underwent stimulation of both sites. In the fourth trial (retention), three out of the four showed memory improvement with both entorhinal and hippocampal stimulation, and in two subjects the latency was clearly shorter with hippocampal versus entorhinal stimulation. Could laterality of the stimulation have played a role in the results? With enough power, laterality of stimulation may further elucidate the findings. The authors comment that this could be a factor; however, the laterality of the stimulation in the study subjects is not provided.

The implications of these results for neurologic disease are marvelous. For patients with hypoxic hippocampal injury, would entorhinal stimulation promote cognitive recovery? Can the remaining mesial temporal lobe memory function be enhanced by stimulation after temporal lobectomy in epilepsy patients? Could this be an on-demand stimulation for persons with minimal cognitive impairment who need to learn a new task? Or, for the most looming problem, could this be a way to mitigate the profound memory deficits that are the hallmark of Alzheimer disease? Obviously, this work needs to be repeated

and expanded upon greatly before clinical applications can be contemplated. The stimulation parameters used were thought to be safe, based on previous work, but are they optimal? Are all types of memory tasks amenable to improvement by stimulation? While navigational tasks are extremely relevant to daily life, what about autobiographical memory, remembering loved ones faces or the words to a Michel Legrand song? The provocative results herein must be considered preliminary and will hopefully “stimulate” similar investigations to first confirm and clarify the site specificity, which is the claim put forth in the current work, and to move toward validation of the increased hippocampal theta rhythm power as a marker for enhanced memory.

Note: lyrics to “The Windmills of Your Mind” are by Alan Bergman and Marilyn Bergman and music is by Michel Legrand.

by Cynthia L. Harden, MD

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