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Stimulation of the human medial temporal lobe between learning and recall selectively enhances forgetting

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ABSTRACT

Background: Direct electrical stimulation applied to the human medial temporal lobe (MTL) typically disrupts performance on memory tasks, however, the mechanism underlying this effect is not known.
Objective: To study the effects of MTL stimulation on memory performance.
Methods: We studied the effects of MTL stimulation on memory in five patients undergoing invasive electrocorticographic monitoring during various phases of a memory task (encoding, distractor, recall).
Results: We found that MTL stimulation disrupted memory performance in a timing-dependent manner; we observed greater forgetting when applying stimulation during the delay between encoding and recall, compared to when it was applied during encoding or recall.
Conclusions: The results suggest that recall is most dependent on the MTL between learning and retrieval.

1. Introduction

Following in the tradition established by Wilder Penfield [1], cognitive neuroscientists have begun to use direct electrical stimulation (DES) to uncover the neural basis of human cognition. DES applies a voltage difference on the cortical surface or within the brain parenchyma, and provides a means of modulating local neural elements and their connections [2]. DES creates a short-lived (reversible) lesion, which is used clinically to demonstrate the behavioral function of specific brain regions [3]. Using this paradigm, researchers have shown that DES in the medial temporal lobe (MTL) frequently impairs memory performance [4–8]. However, the mechanism by which MTL DES impairs performance is not known.

Identifying the specific manner by which MTL DES impairs memory is an increasingly relevant area of research: both for memory theory and for clinical neuroscience. In particular, recent research has suggested that MTL stimulation can, under certain circumstances, enhance memory [9] and has led to the suggestion that electrical stimulation could be used to enhance memory in cases of pathological decreases in mnemonic function [10]. However, before clinical devices can be built to boost memory in the face of pathology, a better understanding of the precise effect of stimulation on memory is needed. A fundamental and unanswered question regarding the mechanistic action of MTL DES is whether it affects a specific mnemonic process or has a global effect on cognitive function.

Human memory function depends on a variety of cognitive processes that can grossly be divided into three categories: those related to stimulus encoding, maintenance, and retrieval. If MTL DES disrupts memory by altering a specific mnemonic processes, one would expect the effects of MTL DES on performance to be stage-dependent (i.e., to have differential effects based on whether

Abbreviations: DES (direct electrical stimulation), MTL (medial temporal lobe).

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it was applied during encoding, maintenance or retrieval). Alternatively, if MTL DES functioned by altering global cognitive function, one would expect MTL DES to have similar effects on memory performance regardless of the stage during which it was applied.

(*e.g.*, one's car keys) and contextual information (an integrated representation of external and internal features, such as the external environment and emotions, respectively), whereas retrieval involves a cued reinstatement of a previous contextual state. Alternatively, theories of working memory suggest that successful memory involves active maintenance of perceived stimuli or associations until time of test (e.g., by rehearsing a short list of items repeatedly). Both theoretical frameworks posit a distinct set of cognitive functions occur during encoding, delay and recall.

In this study, we leveraged the rare opportunity to study the mechanism by which MTL alters memory performance in patients undergoing invasive electrocortographic monitoring and brain stimulation. Patients performed a verbal memory task as we applied stimulation at eight left-sided medial temporal lobe electrode sites during various phases of the task (encoding, distractor interval, recall). Consistent with previous studies [5–7], we found that dominant MTL stimulation impairs memory performance. However, this disruptive effect was timing-dependent: we observed greater forgetting when stimulation was applied during the delay between encoding and recall, compared to when it was applied during encoding or recall. Performance on a distractor arithmetic task was not affected by stimulation. Our results suggest that MTL stimulation disrupts memory performance by selectively altering a cognitive process that occurs in between encoding and recall, and not by a global impairment of cognition. Possible mechanisms for this disruptive effect include enhanced contextual drift between encoding and recall ("contextual flushing;"), disruption of unconscious neural replay of past traces, or impaired conscious maintenance of recently encoded events.

2. Materials and methods

Five patients (age range 19 – 57; two women) with medication-resistant epilepsy underwent surgical procedures at Thomas Jefferson University in which subdural strip or depth electrodes were implanted to localize epileptogenic regions, including left medial temporal lobe sites, for possible surgical resection. All patients were left-language dominant, defined as right-handedness or evidence of left-language dominance on intracarotid sodium amytal injection or fMRI testing. Our research protocol was approved by the institutional review board and informed consent was obtained from the subjects.

Each patient participated in a free-recall task (see Fig. 1A). The task was developed using the python experiment-programming library [PyEPL; see Ref. [11]] and administered at the subject's bedside using a laptop computer. A fixation cross presented in the center of the screen for 10 s signaled the onset of each study list. Each item in the list was serially presented over a 6 s interval following which, subjects performed a minimum 10 s arithmetic distractor. They then recalled as many words as possible from the most recently presented list in a 10 s recall period. Lists comprised three words chosen randomly and without replacement from a pool of high-frequency nouns (http://memory.psych.upenn.edu/WordPools). In the case of one subject (subject three), we increased the list length to five words at a second electrode site given ceiling behavioral performance. All subjects completed at least 10 trials of each type at each electrode site.

A neuroradiologist experienced in neuroanatomical localizations identified bipolar pairs of electrodes within medial temporal lobe sites [12], which we used to administer DES. Electrodes were either circular 2.4 mm exposed diameter subdural contacts spaced

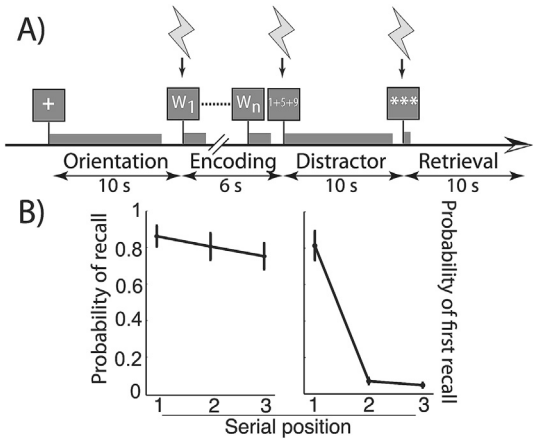

Fig. 1. A. Free-recall stimulation task. The schematic represents one trial of the free-recall task subjects performed. We applied five second stimulation pulses to the left MTL at variable phases of the experiment – encoding, arithmetic distractor, or recall period. **B. Sham stimulation probability of recall and probability of first recall by serial position**. During sham trials, both the probability of recall and the probability of first response were modulated by serial position (respectively, $MSE = 0.024$, $F_{2,23} = 5.28$, $p = 0.020$ and $MSE = 0.304$, $F_{2,23} = 50.8$, $p < 0.0001$). Subjects began recall with the first serial position more commonly than second or third word (respectively, $t_7 = 8.37$, $p < 0.0001$; $t_7 = 8.63$ and $p < 0.0001$). Error bars are centered at across-electrode mean and represent ± 1 SEM.

every 10 mm (Integra Lifesciences, N.J., U.S.A) or cylindrical 2.4 mm length, 1.2 mm diameter depth contacts spaced every 8 mm (Adtech, W.I., U.S.A.). A Grass S12 cortical stimulator (Natus, Rhode Island, U.S.A.) generated constant current, 50 Hz, biphasic square wave pulses of 300 μs per phase (*i.e.* each 20 ms period began with 600μs of stimulation), 5 s trains, at subafterdischarge threshold, which we administered to the medial temporal lobe synchronized to different phases of the memory task (see below). Prior to participating in the memory task, an epileptologist or neurosurgeon trained in direct cortical stimulation identified the afterdischarge threshold by slowly increasing current levels by 0.50 mA intervals until s/he identified afterdischarge potentials on the clinical recording system. We applied standard electroencephalogram definitions of afterdischarge potentials, which include various rhythmic spike or wave morphologies [13]. Amperage was decreased by 1 mA relative to the afterdischarge level for the memory experiment. The clinical recording system was monitored by a neurologist or neurosurgeon during the memory task. When afterdischarge potentials were present during the experiment, the task was paused for at least 2 min, the associated trial was discarded, and the amperage was decreased by 5–15%. Patients were tested for clinical symptoms during and after afterdischarge potentials to ensure no seizure had occurred.

There were four trial types: sham (no stimulation provided), or stimulation to the medial temporal lobe during the encoding interval (stimulation onset with the first item presentation), distractor interval (stimulation onset with the first math question), or the retrieval interval (stimulation onset with the "***" that represented the "GO" cue for retrieval). Trial type was ordered pseudorandomly and constrained such that successive series of eight trials included two of each timing condition. For the first four patients, stimulation was manually initiated by the clinician using a pre-determined stimulation schedule for that particular session, whereas for the last patient, stimulation was initiated automatically. We attempted to blind patients from the type of trial in the following ways: first, they were not able to see the monitors that were used by the clinician to monitor for after-discharges, second, when manual initiation of stimulation was used, a button was