

## Case Report

# Auras localized to the temporal lobe disrupt verbal memory and learning – Causal evidence from direct electrical stimulation of the hippocampus

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## ABSTRACT

Auras (focal aware seizure; FAS) are subjective ictal events with retained consciousness. Epileptiform activities can disrupt cognitive tasks, but studies are limited to seizures with impaired awareness. As a proof of concept, we examined the cognitive effects of direct electrical stimulation to the left hippocampus which induced a habitual FAS in a patient with left mesial temporal lobe epilepsy. During the induced habitual FAS, verbal memory performance declined significantly as compared to pre-stimulation testing. Tasks measuring auditory working memory and psychomotor processing speed were not affected by the stimulation. The study confirms that FAS can impair episodic verbal memory and learning.

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## 1. Introduction

Epileptic auras (revised nomenclature focal aware seizures-FAS) are subjective ictal events experienced by patients at the onset of a seizure and are usually brief, lasting for a few seconds to a minute. The International Classification of Epileptic Seizures in 1981 defined aura as “that portion of the seizure which occurs before consciousness is lost and for which memory is retained afterward” [1]. FAS are scored less on seizure severity scales and are reported to be less disabling. Suppression of FAS typically requires higher doses of anti-seizure medications at the expense of increased adverse effects. Hence aggressive treatment to suppress FAS is seldom practiced. Driving is prohibited legally in many countries when patients experience focal seizures with impaired awareness (FIA) while having FAS is wrongly perceived to be protective against motor vehicle accidents [2]. Overall, in comparison to FAS, FIA significantly impacts quality of life [3].

A growing body of literature suggests paroxysmal epileptiform activities can disrupt specific cognitive tasks [4,5]. Most of these studies include testing of cognition during the interictal or postictal period in

patients with intracranial EEG recordings [5]. Spontaneous FAS are brief, commonly progress into FIA or rapidly generalizes and typically does not provide adequate time for more sophisticated cognitive testing. A FAS reproducibly and reliably induced by stimulation, on the other hand, can facilitate more sophisticated testing of cognitive tasks. In the present study, we tested this question by using direct electrical stimulation of the hippocampus that induced the habitual FAS in a patient with left mesial temporal lobe epilepsy. We hypothesized that electrical stimulation resulting in habitual FAS would further result in the selective disruption of verbal learning and memory function.

## 2. Case report

A 28-year-old right handed woman with known drug-resistant focal epilepsy was referred to our epilepsy center for possible epilepsy surgery. Her seizure semiology included feelings of déjà vu and “thoughts that get stuck in my mind” (FAS) that could progress to loss of awareness (FIA). The FAS could be present 3–5 times a week while FIA was less frequent (1 per week).

A 3 Tesla MRI of the brain was negative for any structural abnormality, fluorodeoxyglucose PET scan was positive for subtle hypometabolism over the left anterior temporal region, and magnetoencephalography (MEG) showed clusters of epileptiform spikes over the left anterior temporal region.

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The preoperative neuropsychological evaluation described impairment of expressive language, episodic memory, and complex psychomotor processing speed.

The scalp EEG was suggestive of left mesial temporal onset seizures, and the consensus in the patient management conference was to perform stereo-EEG investigation (SEEG) to rule out mimics of mesial temporal onset epilepsy. Anatomical targets for SEEG included left anterior and posterior hippocampus, uncus, amygdala, anterior and midcingulate, anterior insula, orbitofrontal, and basal temporal region. The SEEG recordings occurred over a 15-day span. Seven electroclinical seizures with semiology of aura and automatism were localized to the left hippocampus and uncus. Based on functional MRI and intracarotid methohexital sodium procedure (Wada test) the left hemisphere was conclusive to be speech/language dominant, and the risk of memory decline following left anterior temporal lobectomy was estimated to be high.

Extraoperative direct cortical stimulation (DCS) for functional mapping is a standard procedure performed before epilepsy resective surgery, and in this patient, hippocampal stimulation was performed to investigate if transient suppression of hippocampal neural activity impairs verbal memory.

DCS was performed in two different sessions over the last two days of intracranial EEG investigation after restarting of anti-seizure medications. Stimulation was performed in a bipolar fashion with parameters (50 Hz, pulse width 500  $\mu$ s, train duration 5 s, current between 1 and 4 mA).

The neuropsychologist (RM) administered a brief battery of cognitive tests on the first day while the patient was not stimulated and then repeated the tests on the second day while hippocampal DCS was performed (results presented in Table 1). The test battery included the Trail tests from the Delis–Kaplan Executive Function System (assessing aspects of visual attention, processing speed, flexibility), Digit Span Test (assessing aspects of auditory attention, working memory), and the California Verbal Learning Test (CVLT-2) (assessing episodic verbal memory and learning). These results were compared with presurgical cognitive test results.

Intracranial EEG with simultaneous video recording was obtained throughout the testings. Stimulation of left anterior and posterior hippocampus separately at 2 mA induced electroclinical seizures that lasted 50–70 s (Fig. 1A). During the seizure, the patient reported feeling nausea and *deja vu*, and fluently communicated the time, place, and person correctly. Verbal memory and language were evaluated at the bedside with instructions to name three objects that were displayed and the patient was asked to recollect them after the seizure. The patient was able to follow the motor command “lift your left arm.”

Postictally, the patient, failed to recall the three objects, was unable to recall being tested but was oriented and attentive (Fig. 1B). Time–frequency analysis (spectrogram) of pre-processed EEG during an induced seizure with bandwidth 1–100 Hz showed increased power up to high gamma (100 Hz) in hippocampus and beta range (20 Hz) in ipsilateral orbitofrontal channels (Fig. 1C).

Cognitive testing occurred during the hippocampal stimulation. The patient displayed a significant drop in verbal memory performance while, psychomotor processing speed, auditory attention, and working memory remained unchanged (Table 1).

Given the potential risk of memory decline following dominant anterior temporal lobectomy, the patient opted for hippocampal responsive neurostimulation therapy. The retrospective study has approval from the institutional review board.

### 3. Discussion

The brain's ability to learn and remember involves a complex dynamic process that is essential for everyday survival and adaptation to the environment. Central to the cellular mechanism of learning and memory is synaptic plasticity – a process that is significantly affected by repeated seizure activity. Several studies have aimed at analyzing the extent of acute cognitive impairment by epileptiform discharges or seizures, and the results are variable depending on seizure subtypes, cognitive tasks, and the timing of behavioral assessment [5]. Here we have demonstrated that FAS localized to the dominant hippocampus can impair selective cognition (i.e., verbal memory) by disrupting its function. The underlying mechanism of epileptiform discharges disrupting cognition is an active area of research.

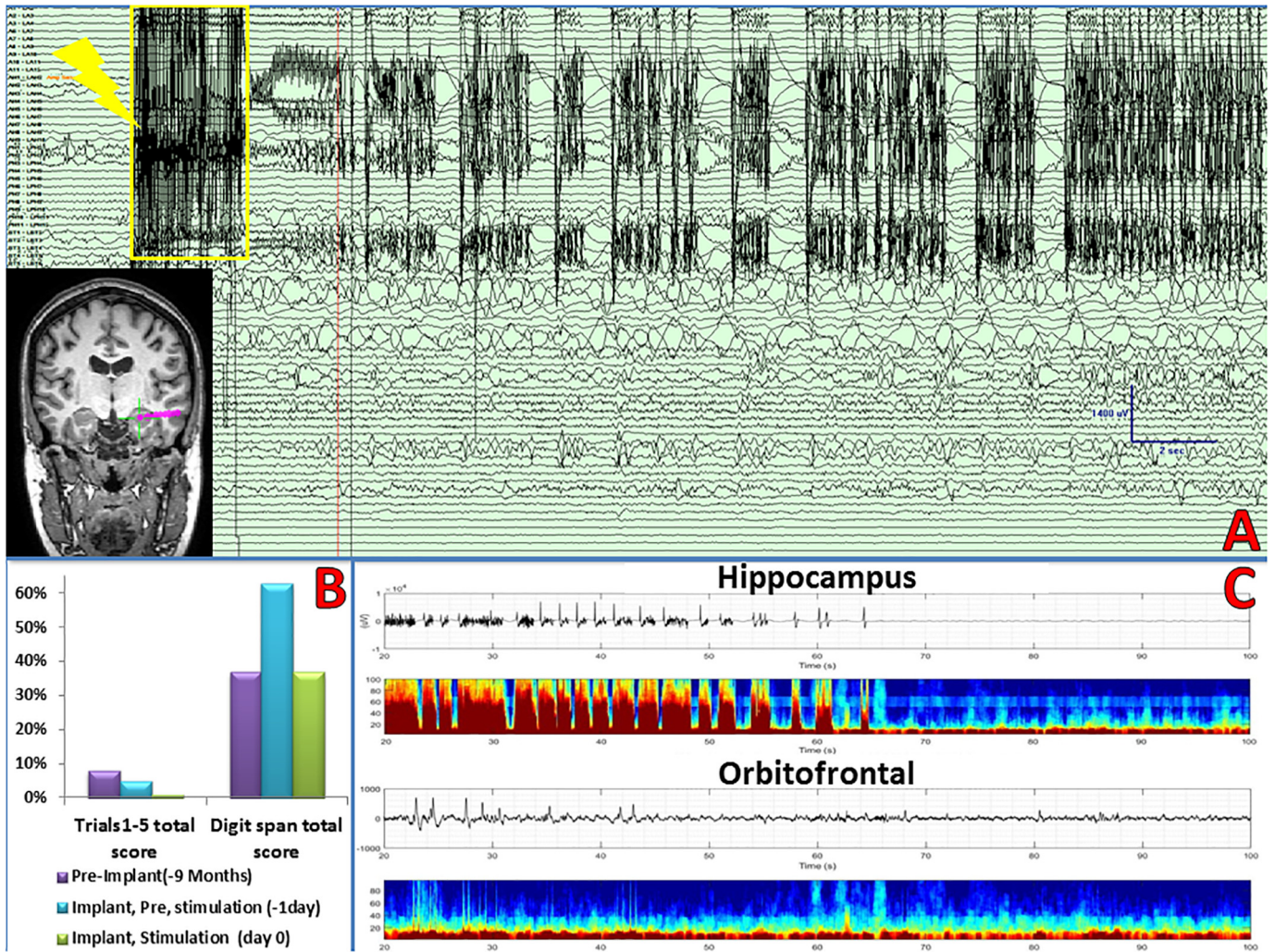
The effects of direct cortical stimulation in memory are variable and depend on multiple factors including acute versus chronic stimulation, site of stimulation and the stimulation parameters [6]. Improvement in verbal memory was demonstrated with chronic hippocampal stimulation delivered in response to seizures and epileptiform activities using a responsive neurostimulation device (RNS) [7]. Studies with acute hippocampal stimulation have shown positive and negative effects on memory depending on stimulation frequencies (1–50 Hz versus > 100 Hz) and site of stimulation (hippocampal versus fornix stimulation) [8–11]. Note that the stimulation in these studies did not induce a seizure, unlike our study. Evaluating consciousness during a seizure is challenging and hence differentiating FA from FIA at the bedside is not always reliable. This is one of the limitations of the study.

**Table 1**  
Serial cognitive testings performed at nine months before stereo EEG implantation and after implantation but with and without cortical stimulation.

Tests performed	Pre-implant (–9 months)	Implant, pre-stimulation (–1 day)	Implant, stimulation (day 0)
CVLT-2			
Trials 1–5 total score	42 words (8%)	39 words (5%)	21 words (<1%) <sup>a</sup>
Trial B	8 words (69%)	6 words (31%)	04 (7%)
Short delayed free recall	10/16 words (31%)	10/16 (31%)	0
Short delayed cued recall	11 words (16%)	11 (16%)	00 (5 intrusion errors)
Long delayed free recall	11 words (31%)	05 (1%)	0
Long delayed cued recall	12 words (31%)	07 (1%)	01 (5 intrusion errors)
Recognition discriminability	3.4 (50%) 2.2 (2%)	0.4 (<1%)	
Recognition hits	15/16 correct (31%)	15 (31%)	13 (2%)
False positive error	01 (50%) 08 (1%)	22 (<1%)	
Digit span total score	27 (37%)	30 (63%)	27 (37%)
DKEFS trial tests (represents time to completion of task, higher #s indicate slower completion rate)			
Visual scanning speed	17" (75%)	20" (50%)	20" (50%)
Number sequencing	20" (84%)	20" (84%)	21" (75%)
Letting sequencing	24" (75%)	31" (37%)	30" (50%)
Number–letter sequencing	97" (16%)	82" (37%)	66" (50%)
Motor tracing speed	19" (75%)	20" (75%)	21" (75%)

CVLT-2: California Verbal Learning Test; DKEFS: Delis–Kaplan Executive Function System; % indicates percentile performance relative to normative sample.

<sup>a</sup> Indicates task administered during seizure induced by electrical stimulation of hippocampus.



**Fig. 1.** A: Intracranial EEG with recordings from left amygdala–hippocampus, orbitofrontal, insula and lateral temporal regions. Electrical stimulation artifact (highlighted) in hippocampal channels followed by an induced seizure. Co-registered MRI to demonstrate the orthogonal trajectory of left hippocampal depth electrode. B: Serial cognitive test performances in percentile. C: Spectrogram (1–100 Hz) showing seizure in the hippocampal channel and spread to orbitofrontal regions.

## Conclusion

We examined the cognitive effects of direct electrical stimulation to the left hippocampus which induced a habitual FAS in a patient with left mesial temporal lobe epilepsy. During the induced habitual FAS, verbal memory performance declined significantly as compared to prestimulation testing. Tasks measuring auditory working memory and psychomotor processing speed were not affected by the stimulation. The study confirms that FAS can impair episodic verbal memory and learning.

## Ethics

Extraoperative direct cortical stimulation is routinely performed in clinical practice. The patient was informed about the procedure and verbal consent was obtained before performing stimulation. The retrospective case study has approval from the institutional review board. The privacy right of the subject is observed.

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## References

- [1] Proposal for revised clinical and electroencephalographic classification of epileptic seizures From the Commission on Classification and Terminology of the International League Against Epilepsy, *Epilepsia* 1981;22:489–501.
- [2] Punia V, Farooque P, Chen W, et al. Epileptic auras and their role in driving safety in people with epilepsy. *Epilepsia* 2015;56:e182–5.
- [3] Bautista RE, Glen ET. Seizure severity is associated with quality of life independent of seizure frequency. *Epilepsy Behav* 2009;16:325–9.
- [4] Aldenkamp AP, Arends J, de la Parra NM, Migchelbrink EJ. The cognitive impact of epileptiform EEG discharges and short epileptic seizures: relationship to characteristics of the cognitive tasks. *Epilepsy Behav* 2010;17:205–9.
- [5] Coleshill SG, Binnie CD, Morris RG, et al. Material-specific recognition memory deficits elicited by unilateral hippocampal electrical stimulation. *J Neurosci* 2004;24:1612–6.
- [6] Meisenhelter S, Jobst BC. Neurostimulation for memory enhancement in epilepsy. *Curr Neurol Neurosci Rep* 2018;18:30.
- [7] Loring DW, Kapur R, Meador KJ, Morrell MJ. Differential neuropsychological outcomes following targeted responsive neurostimulation for partial-onset epilepsy. *Epilepsia* 2015;56:1836–44.
- [8] Jacobs J, Miller J, Lee SA, et al. Direct electrical stimulation of the human entorhinal region and hippocampus impairs memory. *Neuron* 2016;92:983–90.
- [9] Ezzyat Y, Kragel JE, Burke JF, et al. Direct brain stimulation modulates encoding states and memory performance in humans. *Curr Biol* 2017;27:1251–8.
- [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;138:1833–42.
- [11] Koubeissi MZ, Kahrman E, Syed TU, Miller J, Durand DM. Low-frequency electrical stimulation of a fiber tract in temporal lobe epilepsy. *Ann Neurol* 2013;74:223–31.