Supplemental Material

Associative hallucinations result from stimulating left ventromedial temporal cortex

E. M. Aminoff*, Y. Li, J. A. Pyles, M. Ward, R. M. Richardson, A. Singh Ghuman

1. Materials and Methods

1.1 Patient Medical History

The Institutional Review Board of the University of Pittsburgh approved the experimental protocols. Written informed consent was obtained from the patient and separate video consent was also obtained.

The patient was a 19-year-old male college student, with a history of medically intractable epilepsy since the age of 13. The patient had right hand somatosensory-based seizure-related aura, consistent with supramarginal gyrus (somatosensory association cortex) onset, and spread into right arm somatomotor effects. Specifically, his aura began with right hand numbness, followed by right arm posturing and other right arm activity, followed by convulsive seizure activity.

Preoperative neuropsychological testing demonstrated his performance IQ to be in the average range. Furthermore, all cognitive skills were in the average range, including verbal and visual memory.

Ictal ECoG revealed that the patient's seizure onset zone comprised a portion of the lateral left supramarginal gyrus. After ECoG grid removal and all experimental studies reported here, the area subsequently was resected, and the patient has remained seizure free for 14 months (see Figure 2 in the Main Text). This was the only surgical epilepsy treatment for this patient.

1.2 Experimental Design

The data of this study was collected in two phases. The first phase was recording from the electrodes to determine whether any of the VTC electrodes were sensitive to the associative properties of the objects (contextual associative localizer). In a session after the ECoG recording session, for clinical purposes, EBS was administered to the patient while they performed a word naming and picture naming task. Resection of the supramarginal gyrus occurred after both these phases were completed. Details of both sessions are listed below.

1.2.1 Contextual Associative Localizer

1.2.1.1 Stimuli: Stimuli were photographs of objects in isolation presented against a grey background (see Fig 3). 84 objects were presented in the strong associative condition and 84 objects were presented in the weak associative condition. Stimuli have been used previously for localizing contextual associative processing and can be found at this website: https://faculty.biu.ac.il/~barlab/context_localizer.html (Bar & Aminoff, 2003).

1.2.1.2 Design and Procedure: Each image was presented for 900 ms with a 900 ms inter-trial interval, during which a fixation cross was presented at the center of the screen. There were two consecutive blocks in a session. A total of 168 images were presented in random, interleaved, order during a session, with 84 images in each block with a short (1-2 minute) break between blocks. The participant was instructed to press a button on a button box if the object shown was bigger than a shoebox, and a different button if not. All stimuli were presented on an LCD computer screen placed approximately 1.5 meters from participants' heads. Images subtended approximately 5 degrees of visual angle. Paradigms were programmed in Matlab™ using the Psychophysics Toolbox and custom written code.

1.2.1.3 Data preprocessing: Local field potential (LFP) data for the context localizer were collected at 1000 Hz using a Grapevine neural interface system (Ripple, LLC). They were subsequently band-pass filtered offline from 1-170 Hz using fifth order Butterworth filters in Matlab™, to remove slow and linear drift, and high frequency noise. The 50 Hz line noise and its harmonics were removed using discrete Fourier transform. To further reduce potential artifacts in the data, trials with peak amplitude 5 standard deviations away from the

mean across the rest of the trials or with absolute peak amplitude larger than 350 μV were eliminated. In addition, trials with a difference larger than 25 μV between consecutive sampling points were eliminated. These criteria resulted in the elimination of less than 1% of trials. Furthermore, no epileptiform activity was seen at any point during the recording session as assessed by a trained clinician.

1.2.1.4 Broadband gamma analysis: Time-frequency power spectra were calculated using a Fourier transform with a Hanning window taper calculated with a 200 ms sliding window and 2 Hz frequency step for each trial. The 40-150 Hz frequency window of interest was picked because lower frequencies dip into the beta frequency band, and at higher frequencies the signal-to-noise ratio declined due to the 1/frequency response of the brain. This range is generally consistent with previous reports using the broadband gamma activity (Hermes et al., 2012; Manning, Jacobs, Fried, & Kahana, 2009; Ray, Crone, Niebur, Franaszczuk, & Hsiao, 2008). A 250 ms time window in each trial (50 to 300 ms before stimulus onset) was used as baseline. The mean and variance of the power spectrum over the baseline at each frequency of interest were calculated across all trials for each electrode. The power spectrum of each trial was then normalized as z-scores using the mean and variance of the baseline. The area-under-curve (AUC) was calculated by the summation of the z-scores of the power spectrum density of the broadband gamma response over the 150 – 1500 ms time window after stimulus onset. An independent two-sample t-test was performed using the AUC of each trial.

1.2.2 Word Naming and Picture Naming during Electrical Brain Stimulation

1.2.2.1 Stimuli: The stimuli used for word naming during the electrode stimulation session were 60 7-letter words with 11.35 (10.60-13.67) mean log frequency, determined by the HAL Study used in the English Lexicon project (http://elexicon.wustl.edu/). The stimuli used during picture naming were 60 images taken from the Boston naming test. These images are well normed black-and-white line drawings of everyday concrete objects and animals (Kaplan, Goodglass, & Weintraub, 1983).

1.2.2.2 Design and Procedure: Bipolar electrical current during stimulation passed between adjacent electrode pairs. During the stimulation session pre-surgery, stimulation (1-5 mA) was alternatingly applied with sham stimulation while the patient overtly named words and pictures. Each stimulus trial began with a beep, followed by 750 ms of fixation and then the stimulus. The stimulus remained on the screen until it was named, after which an experimenter manually advanced to the next item. Stimulation length was between 3-5 seconds (stimulation was delivered manually), with 1-3 repetitions at each intensity from 1-5 mA (sometimes only 1 repetition at lower intensities, but always at least 2 repetitions 3 mA and above) with .5 mA steps, unless a cognitive effect was seen. In general, if a cognitive effect was seen at a site, the stimulation was repeated at that level one more time to confirm replicability of the effect, then the session proceeded at the next bipolar site. The word and picture stimuli were presented between 0-1000 ms after the onset of the EBS stimulation. In addition, a number of sham stimulation trials were delivered, where the stimulator sound was heard, but no current was delivered. The number of sham trials was not recorded. Critically, we consider the lower stimulation level trials and stimulation trials at other sites as the null, control trials, not these sham stimulation trials as they tended to be briefer than the true stimulation trials and therefore potentially noticeably different.

The word naming stimulation session occurred during a clinical language mapping session used to define eloquent regions for surgical planning. The language mapping session consisted of a total of 790 EBS bipolar stimulation trials between nearly every neighboring pair of contacts along the lateral grid and ventral temporal strip electrodes.

The picture naming session occurred immediately following this language mapping session to more carefully probe the nature of the phenomenon at the VTC site and test the study hypotheses. The picture naming session consisted of a total of 15 stimulation trials at the VTC site. For the picture naming session, after the first cognitive effect was seen at 5 mA, the patient did not wish to continue, as he was fatigued and hungry after the long word naming and picture naming sessions, thus only 1 trial of picture naming at 5 mA was acquired.

1.3 Visualization of electrode locations

Electrode locations were determined by co-registering the post-operative CT scan with the pre-operative, high resolution MRI structural using the method of Hermes *et al.*, 2010 (Hermes, Miller, Noordmans, Vansteensel, & Ramsey, 2010).

2. Results

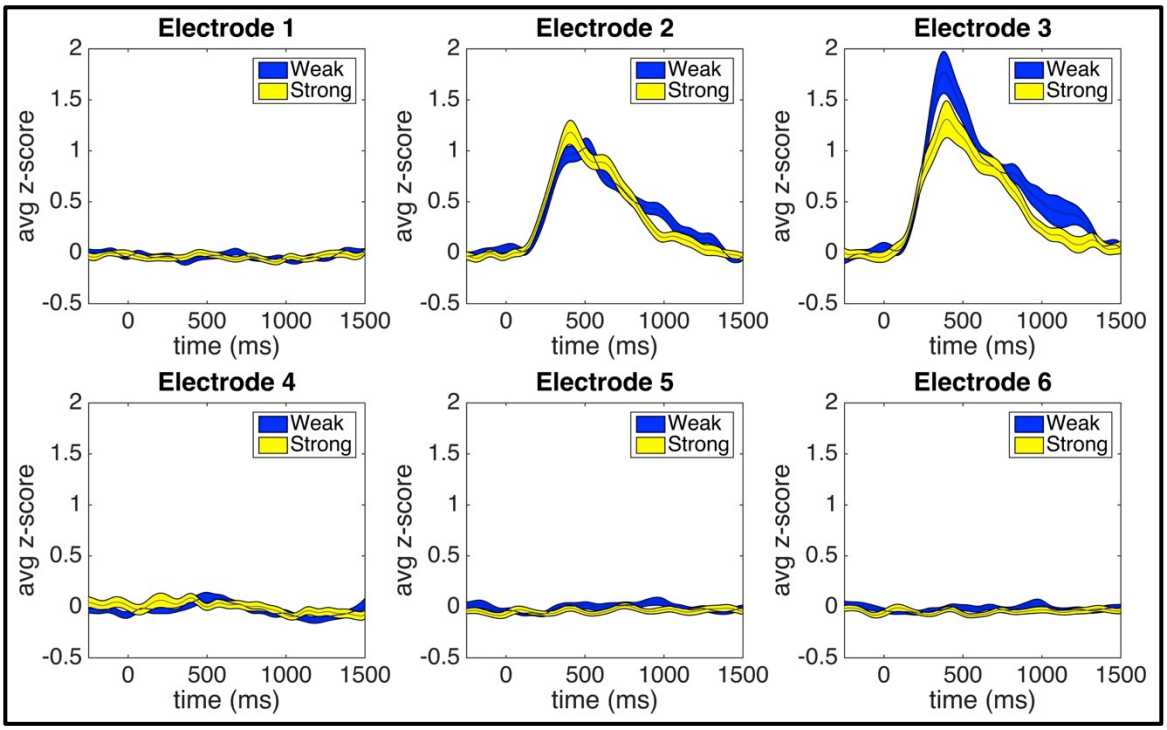

Figure S1: Broadband gamma activity for all VTC electrodes. Electrode 3 was the main electrode of interest falling within the medial fusiform (see Figure 1 in the Main Text). Bipolar stimulation between electrode 1 and electrode 2 was not possible as this caused the patient discomfort.

3. References

Bar, M., & Aminoff, E. (2003). Cortical analysis of visual context. *Neuron*, *38*(2), 347–358.

Hermes, D., Miller, K. J., Noordmans, H. J., Vansteensel, M. J., & Ramsey, N. F. (2010). Automated electrocorticographic electrode localization on individually rendered brain surfaces. *Journal of Neuroscience Methods*, *185*(2), 293–298.

Hermes, D., Miller, K. J., Vansteensel, M. J., Aarnoutse, E. J., Leijten, F. S. S., & Ramsey, N. F. (2012). Neurophysiologic correlates of fMRI in human motor cortex. *Human Brain Mapping*, *33*(7), 1689–1699.

Kaplan, E., Goodglass, H., & Weintraub, S. (1983). The boston naming test. Philadelphia: Lea & Febiger.

Manning, J. R., Jacobs, J., Fried, I., & Kahana, M. J. (2009). Broadband shifts in local field potential power spectra are correlated with single-neuron spiking in humans. *Journal of Neuroscience*, *29*(43), 13613–13620.

Ray, S., Crone, N. E., Niebur, E., Franaszczuk, P. J., & Hsiao, S. S. (2008). Neural correlates of high-gamma oscillations (60-200 Hz) in macaque local field potentials and their potential implications in electrocorticography. *Journal of Neuroscience*, *28*(45), 11526–11536.