Explaining How Brain Stimulation Can Evoke Memories

Joshua Jacobs[1]*, Bradley Lega[2]*, and Christopher Anderson[2]

Abstract

■ An unexplained phenomenon in neuroscience is the discovery that electrical stimulation in temporal neocortex can cause neurosurgical patients to spontaneously experience memory retrieval. Here we provide the first detailed examination of the neural basis of stimulation-induced memory retrieval by probing brain activity in a patient who reliably recalled memories of his high school (HS) after stimulation at a site in his left temporal lobe. After stimulation, this patient performed a customized memory task in which he was prompted to retrieve information from HS and non-HS topics. At the one site where stimulation evoked HS memories, remembering HS information caused a distinctive pattern of neural activity compared with retrieving non-HS information. Together, these findings suggest that the patient had a cluster of neurons in his temporal lobe that help represent the "high school-ness" of the current cognitive state. We believe that stimulation here evoked HS memories because it altered local neural activity in a way that partially mimicked the normal brain state for HS memories. More broadly, our findings suggest that brain stimulation can evoke memories by recreating neural patterns from normal cognition. ■

INTRODUCTION

Over 70 years ago, Wilder Penfield began a series of pioneering studies examining human behavior using the application of electrical stimulation to the neocortex during awake neurosurgeries. By comparing how stimulation at different locations affected behavior, he identified brain regions that support different types of movement, perception, and language (Penfield & Boldrey, 1937). Less frequently, he also reported that stimulation at sites in the temporal lobe caused patients to recall what they believed were old memories, such as one patient who recalled images of a circus traveling at night (Penfield & Perot, 1963). These findings were a breakthrough for two reasons: They demonstrated that electrical brain stimulation could artificially induce retrieval of complex memories, and they indicated that the temporal lobe played a unique role in memory because this was the main neocortical area where stimulation induced memory recall. The discovery that cortical stimulation could elicit memories prompted a number of fruitful experimental investigations (Selimbeyoglu & Parvizi, 2010; Ojemann, 1991; Gloor, Olivier, Quesney, Andermann, & Horowitz, 1982; Halgren, Walter, Cherlow, & Crandall, 1978) and inspired scientists to propose theories of how the brain stores memories and how these memories are activated by stimulation (Gloor, 1990; Penfield, 1958; Jackson, 1879).

In spite of such an auspicious beginning for research on this phenomenon, several barriers have stunted progress toward understanding how brain stimulation induces memory retrieval. The topic is difficult to study because only a small set of neurosurgical patients undergo direct temporal lobe stimulation and because improvements in noninvasive brain imaging have reduced the need for stimulation (Spencer, 1994). Of those that undergo stimulation mapping, only 8% report memory recalls (Penfield & Perot, 1963). However, the largest hurdle for understanding why stimulation at particular areas causes memory retrieval is that scientists have not had precise information on neural activity at these sites during normal memory function without stimulation.

Here we describe results from a patient who underwent cortical stimulation and also performed a customized memory task during electrocorticographic (ECoG) monitoring. Because electrodes were not moved between stimulation and the memory task, this situation provided the unique opportunity to examine neuronal activity during normal cognition at a site where stimulation induced memory recall. Stimulation at a site in the left ventral-temporal cortex (lateral occipito-temporal gyrus) caused the patient to spontaneously recall memories of his high school (HS). We encourage the reader to view these events via the Supplemental Movie available at http://jacobslab.biomed.drexel.edu/stimulation/. Taking advantage of this finding, we designed the first experiment that examined the neural basis of stimulation-induced memory retrieval by analyzing activity at the stimulation site during normal memory processing without stimulation. We found that, at the same site where stimulation elicited HS memories, there was less neuronal activity for retrievals of HS-related information compared with the larger activity that appeared when retrieving non-HS information. The type of stimulation that we used temporarily inhibits neuronal

[1]Drexel University, [2]Hospital of the University of Pennsylvania, Philadelphia, PA

*These authors contributed equally to the study.

activity (Logothetis et al., 2010; Chkhenkeli et al., 2004; Kinoshita et al., 2004). Thus, our findings suggest that ECoG electrical stimulation can evoke memories when it inhibits local neuronal spiking in a way that mimics the neural activity that appears when a memory is retrieved normally.

METHODS

Patient

A right-handed male patient in his thirties with drug-resistant epilepsy was surgically implanted with ECoG electrodes to identify epileptiform brain regions for potential resection. He had suffered simple partial, complex partial, and secondarily generalized convulsions since age 5. Clinically, his seizures typically started with a vague sense of deja vu, but not vivid memories (nothing related to his HS). MRI scans did not reveal any lesions, but scalp recordings suggested temporal lobe onset (potentially bilateral). Preoperative testing revealed normal scores on memory and IQ tests without any major localizing or lateralizing findings. The patient was treated with levetiracetam, oxcarbazepine, and pregabalin as an outpatient, but these were withdrawn during our stimulation and cognitive testing sessions.

The ECoG electrodes were strips that were placed on the surface of widespread cortical regions, including bilateral temporal lobes, left occipital cortex, right frontal cortex, and left parietal cortex (see Supplementary Figure S1 available on-line at http://jacobslab.biomed.drexel.edu/stimulation/). Each electrode was manufactured by Ad-Tech Medical Instrument Corporation and had a 4-mm conductive surface. The electrodes remained implanted for 4 weeks while the patient was connected to a clinical recording system and waited for epileptiform activity that would guide doctors in potential resective surgery. This recording system (Grass-Telefactor Corp., West Warwick, RI) measured ECoG activity with a 512-Hz sampling rate. During this monitoring interval, in free time between clinical interactions the patient performed cognitive tasks on a bedside laptop computer (Jacobs & Kahana, 2010; Jerbi et al., 2009). All testing and data collection (including anonymized video) was approved by the University of Pennsylvania's Institutional Review Board.

During ECoG monitoring, the patient did not experience his typical seizures. Two short focal epileptiform runs were captured (one right temporal and one left temporal), but they were not useful for resection planning and did not occur near the times of our testing sessions. Because a single seizure focus could not be clearly identified, the electrodes were eventually explanted without resective surgery. Overall, we have no reason to believe the patient's neurological characteristics affected our research findings.

Stimulation

During ECoG monitoring, the patient underwent a routine preoperative functional stimulation mapping procedure to identify areas eloquent for motor and speech function, as well as a research procedure to identify sites involved in memory encoding (for the Methods and Results of this experimental procedure, see the Supplemental Material available at http://jacobslab.biomed.drexel.edu/stimulation/). This research procedure attempted to use electrical stimulation to modulate memory performance, and 11 stimulation sites were chosen because they exhibited ECoG activity related to memory formation (Sederberg, Kahana, Howard, Donner, & Madsen, 2003). Stimulations were conducted with a Grass Technologies S88 device. The site described in the text was the only location where stimulation caused an unusual behavior; no stimulations caused significant modulations in memory performance. In the first stimulation session when HS memories were evoked, stimulations consisted of 300-μsec biphasic pulses at 50 Hz for a duration of 1 sec. In the second, the stimulations were 600-μsec biphasic pulses at 50 Hz for 2.8 sec.

HS Memory Task

During normal ECoG recording without stimulation, the patient performed a remote memory task that we designed to identify potential neural activity related to HS. This task asked the patient to recall and visualize the answers to questions from various categories (Figure 2A), including information related to his HS. There were 32 questions, eight from each of four categories: HS person, HS nonperson, non-HS person, and non-HS nonperson. Questions were chosen by the authors without having specific knowledge of any of the patient's HS experience. All person-related questions were included as controls because the electrode of interest was located near face-responsive cortical regions (Kanwisher, McDermott, & Chun, 1997). All of the HS questions concerned autobiographical information. Of the non-HS person questions, five concerned autobiographical information and the other three queried nonautobiographical information (the nonautobiographical questions are numbered 17, 23, and 24 in Supplementary Table 1, available on-line). The non-HS nonperson questions were nonautobiographical queries of geographical locations, which were selected as a control group because the electrode of interest was near regions that have been implicated in spatial processing (Epstein & Kanwisher, 1998).

In each trial, the patient viewed a single question. Each question appeared at the center of the laptop computer screen, and the patient was instructed to press a key after reading it (Figure 2B). Then the computer screen went blank, and the patient was asked to silently visualize the answer with his eyes closed. The computer emitted a tone after 3800–4200 msec (uniformly distributed) to indicate that the visualization period was over and that the patient should open his eyes. Then three fixation crosses appeared on the screen and the patient spoke the answer aloud. The patient could pause briefly before pressing a key to advance to the next trial. The task consisted 10 blocks, and we encouraged the patient to take a several-minute

break between blocks. Within each block the patient viewed all 32 questions in a random order. Across the entire 134-min session, each individual question was viewed 10 times for 320 total trials. After the second block of trials, the task paused and the patient was asked to rate each question on a 1–5 scale as to how well he could retrieve and visualize its answer.

Data Analysis

We analyzed ECoG recordings during the task to identify distinctive patterns of neuronal activity that appeared when the patient recalled or visualized HS stimuli. First, we measured the amplitude of ECoG activity after each question using bandpass filters and the Hilbert transform. To analyze ECoG activity related to memory retrieval, we computed the amplitude of activity at each electrode in six frequency bands: 2–4, 4–8, 8–16, 16–30, 30–55, and 65–150 Hz ("high gamma"); for each of 20 consecutive 50-msec intervals after question onset. To visualize these patterns (Figure 3C), we computed the instantaneous high-gamma activity over time, smoothing with a 100-msec boxcar filter. When measuring ECoG power spectra (Figure 6A, B), we used Morlet wavelets with center frequencies of $2^{x/8}$ for $x \in 8, \ldots, 64$ (Wave Number 6) and "whitened" the power spectra by subtracting away the overall $1/f$ power spectrum (Manning, Jacobs, Fried, & Kahana, 2009).

We used a general linear model to identify phase-amplitude coupling (PAC) between the phase of low-frequency oscillations and the amplitude of high-frequency activity (Figure 6C). To measure the magnitude of this coupling, at each pair of frequencies we computed the r^2 from a circular–linear regression that modeled how the amplitude of high-frequency activity varied with the phase of a low-frequency oscillation (Penny, Duzel, Miller, & Ojemann, 2008; Fisher, 1993). In this procedure, rather than using phase (a circular number) in the regression directly, we took the sine and cosine of the phase to create two new independent linear variables that were regressed against the high-frequency amplitude. To assess whether individual categories of stimuli were distinguished by increased high-gamma activity at specific theta phases, we used a three-way ANOVA with two fixed factors, HS and person (two levels each), and one random factor, phase (four levels, corresponding to 90° phase bins centered at 0°, 90°, 180°, and 270°). When statistically comparing phase-coupled activity across conditions (Figure 6E, F), we computed a single mean amplitude at each phase bin for each trial to ensure independence of observations.

RESULTS

Electrical Stimulation

Our study was motivated by a surprising occurrence during electrical stimulation of Electrode 17 in this patient's left ventral temporal lobe (Figure 1). During bipolar stimulation between this electrode and the one immediately lateral to it, the patient noted that he spontaneously experienced thoughts of his HS. Here, he exclaimed, "I'm, like, remembering stuff from, like, high school…. Why is this suddenly popping in my head?" Similar experiences had never been observed before, during, or after this patient's spontaneous seizures. This phenomenon seemed to be similar to classic descriptions of "experiential" phenomena after direct temporal lobe stimulation (Ojemann, 1991; Gloor et al., 1982; Halgren et al., 1978; Penfield, 1938). Stimulation at this site first caused the patient to experience memories of HS during pretesting with an 8-mA current. A few minutes later, the patient attempted to perform a task as we stimulated this site at 5 mA, but it again caused the patient to recall HS memories and we stopped the task.

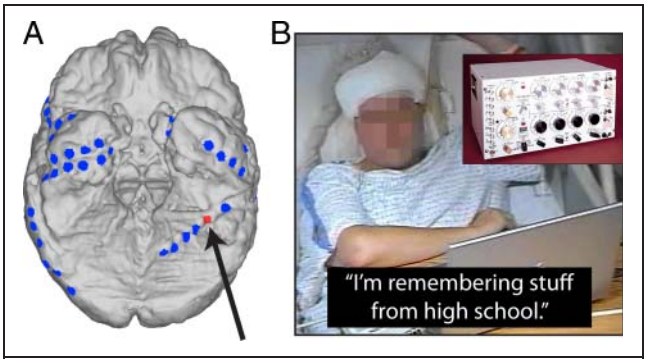

Figure 1. Stimulation induces retrieval of HS memories. (A) A three-dimensional reconstruction of this patient's brain surface generated from preoperative magnetic resonance images. The position of each recording electrode is plotted as a colored dot on a ventral view of the patient's brain surface (dots not to scale). (B) Anonymized image of the patient during ECoG monitoring. When we stimulated one electrode in the patient's left ventral temporal lobe, the patient reliably reported that he recalled memories related to his HS. The electrode where stimulation elicited HS memories is colored red and marked with an arrow in A. This site was labeled Electrode 17 in our recording montage.

In a separate session 14 days later, we again found that stimulation of this electrode caused the patient to spontaneously remember his HS. Stimulation-induced retrieval of HS memories occurred twice in this second session, at currents of 6 and 4 mA, both times with stimulation between Electrode 17 and the one immediately medial to it. We encourage the reader to view the Supplementary Movie for details of the patient's HS-related experiences during stimulation (available on-line at http://jacobslab.biomed.drexel.edu/stimulation/). Besides this site, stimulations at other locations did not elicit memory retrieval or other unusual cognitive phenomena.

Neuronal Activity Related to Retrieving HS Memories

Our ECoG stimulations and recordings used a common set of electrodes that were implanted at fixed locations

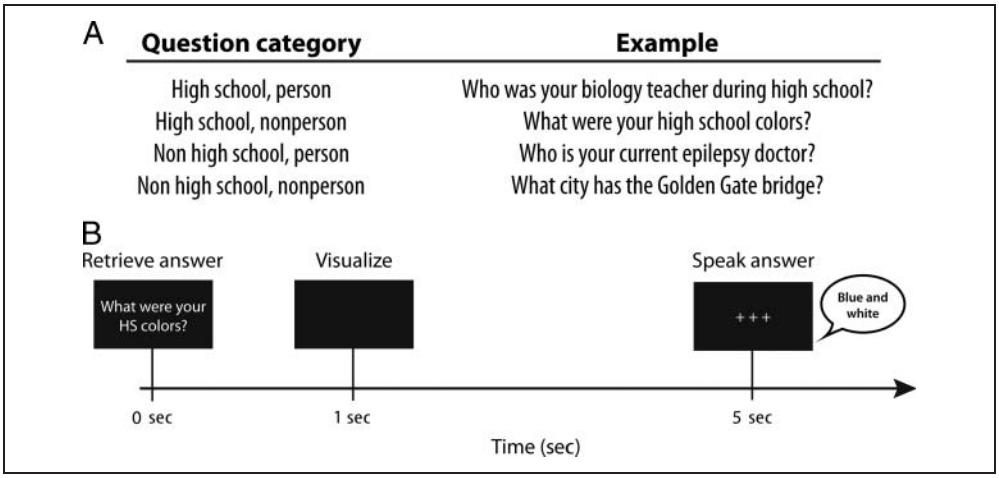

Figure 2. The custom memory task we designed to examine the neural representation of HS memories in this patient. (A) The four categories of questions during the memory task. (B) A timeline of the retrieval, visualization, and vocalization phases of each task trial.

throughout the patient's monitoring. This afforded us the unique opportunity to examine neural activity at the stimulation site during normal cognition. We hypothesized that by recording normal brain activity here, it could reveal a distinctive neural pattern that would explain why stimulation caused memory retrieval.

Following the stimulation sessions, the patient participated in our custom-designed HS memory task (Figure 2). Our data analyses from this task sought to identify distinctive patterns of neuronal activity related to processing HS information. We computed the amplitude of ECoG activity at each electrode for each of various frequency bands and time intervals after each question appeared on the screen. Then we tested whether the amplitude of neuronal activity in each band varied according to whether HS or non-HS questions were viewed. Across all electrodes, viewing HS questions elicited a distinctive pattern of neuronal activity that was significant at only one site—the same electrode (Electrode 17) where stimulation elicited HS memories (Figure 3A). We examined activity at this site in more detail and found that the contrast between viewing HS and non-HS questions was reflected neurally by changes in the amplitude of activity in the high-gamma band (65–150 Hz) from ~350 to ~450 msec after the question appeared ($p < 10^{-6}$, t test; Figure 3B). Figure 3C details the timecourse of the neuronal activity at this site, revealing that both HS and non-HS stimuli caused an increase in the amplitude of high-gamma activity after question onset. The magnitude of this increase was larger for non-HS questions than HS questions, resulting in an attenuation of high-gamma ECoG activity for retrieving HS information. The pattern was unaffected by whether the patient answered questions about people or nonpeople (Figure 3D).

High-gamma ECoG activity is caused by a broadband signal that is highly correlated with the rate of local neuronal spiking (Ray & Maunsell, 2011; Jacobs, Manning, & Kahana, 2010; Manning et al., 2009; Miller, Sorensen, Ojemann, & den Nijs, 2009). Thus, the lower high-gamma amplitude for HS questions suggests that the population of neurons at this site was less active when the patient retrieved HS memories. More broadly, these findings suggest that neurons at this site are part of a network that represents the concept "high school" in this patient's brain.

We considered the hypothesis that apparent HS-related neuronal activity could result from other interquestion differences, such as HS questions being more difficult. By asking the patient to rate each question according to how difficult it was to visualize its answer (Supplementary Table 1, available on-line), we found that HS questions had slightly lower visualizability ($p = .03$) and RTs ($p = .11$) than non-HS questions. We used a multivariate linear model to distinguish which of these factors (HS/non-HS, visualizability, RT, and their interactions) best predicted the observed neuronal activity. This analysis indicates that the distinctive activity at this site was most closely related to the concept of HS, as the HS factor was the only significant predictor of neuronal activity ($p = .02$), unlike visualizability or RT (ps $> .3$).

Given the distinctive HS-related high-gamma activity that appeared at this electrode, we conducted follow-up analyses to characterize the functional role of the cortex at this site. First, we characterized neural responses to individual stimuli within each of the four categories, inspired by recent studies showing detailed neural correlates of individual brain states (Jacobs & Kahana, 2009; Kriegeskorte, Formisano, Sorger, & Goebel, 2007). To do this, we tested for differences in the amplitude of neuronal activity for individual questions within each category using four one-way ANOVAs. We computed the mean amplitude of high-gamma ECoG activity 300–450 msec after each question appearance. For three of the categories (all except HS people) this signal differed significantly (ps $< .01$) across individual questions in that category (Figure 4). For example, in the HS nonpeople category, there was an especially large activation for the question "Who was your main rival high school, if you had to pick one?" This suggests that there is a hierarchy of neuronal responses at this site, with some neurons representing information about specific memories (Jacobs & Kahana, 2009), in addition to

coarser neural activity that distinguishes HS and non-HS information.

Previous work reported specific cortical regions that play a role in representing autobiographical memories (Cabeza & St. Jacques, 2007; Svoboda, McKinnon, & Levine, 2006; Gilboa, Winocur, Grady, Hevenor, & Moscovitch, 2004; Piefke, Weiss, Zilles, Markowitsch, & Fink, 2003; Fink et al., 1996). Thus, we considered that the HS-related activity we observed could be a part of a broader cortical network that represents autobiographical information in general. To test whether activity at this location represented general autobiographical information, we scrutinized neural responses to the questions from the non-HS people category, which included both autobiographical and nonautobiographical queries. Across these questions, we observed significantly attenuated activity for autobiographical information compared with nonautobiographical information ($p < .001$, t test). This suggests that the cortical networks that represent autobiographical and HS information in this person overlap or are related. However, we confirmed that the HS and autobiographical effects at this site are at least partially independent, as we still observed significantly lower high-gamma activity for HS information compared with non-HS information when we restricted the comparison with only include autobiographical questions ($p < .02$, t test).

We also conducted an ERP analysis of this site (Luck, 2005). ERPs for all question types exhibited a P400 response (Figure 5A), similar to previous recordings in the human ventral-temporal lobe (Nobre, Allison, & McCarthy, 1994). However, unlike the high-gamma patterns described above, the ERP did not distinguish between HS and non-HS memories (Figure 5B; Bonferroni-corrected ps $> .05$). The fact that we did not observe an ERP effect is not necessarily surprising, as other recent ECoG studies also reported that ERPs and high-gamma activity respond in complementary ways (Engell & McCarthy, 2010; Vidal et al., 2010).

Analysis of Memory Visualization

In addition to examining neural activity when the patient retrieved each question's answer, we also analyzed the visualization phase of each trial. This analysis was motivated by recent studies suggesting that visualizing information would elicit neuronal activity similar to the patterns observed when the information was initially processed

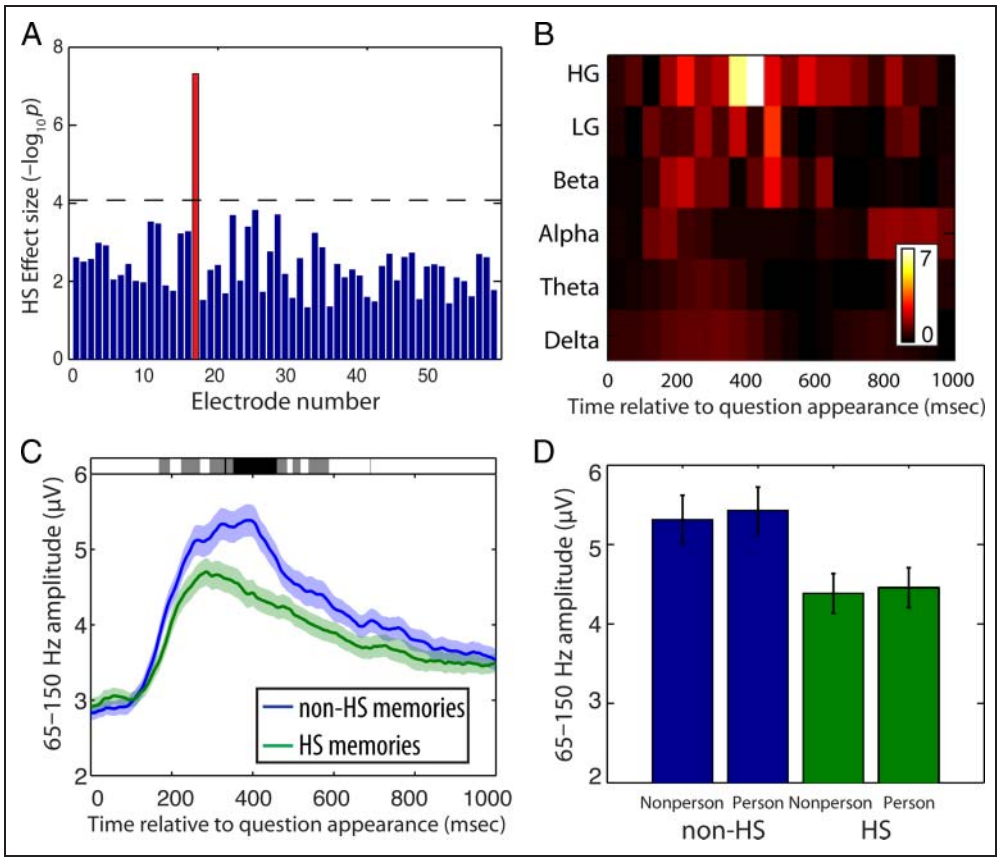

Figure 3. HS-related ECoG activity. (A) The significance of the difference in ECoG amplitude between HS and non-HS stimuli at each electrode ($-\log_{10}(p)$). The bar for each electrode is computed by identifying the minimum p value across two-sided t tests that were performed at each frequency band and time interval between HS and non-HS stimuli. Red bar indicates Electrode 17. Dotted line indicates the significance threshold ($p < .01$; Bonferroni-corrected). (B) Significance of HS-related power changes at Electrode 17 for various frequency ranges and time intervals. HG denotes the 65–150 Hz "high gamma" band; LG denotes the 30–55 Hz "low gamma" band. The color at each point indicates the $-\log_{10}$ p value from a t test comparing the amplitude of activity between answering questions on HS and non-HS topics. (C) Timecourse of the activity at this site after stimulus onset. Shaded regions indicate 95% confidence intervals, computed across the different presentations of questions from each category. Gray shading at top indicates differences at $p < .001$; black shading denotes $p < 10^{-6}$. (D) The mean amplitude of high-gamma activity 350–450 msec after question onset for each stimulus category. Error bars indicate 95% confidence intervals.

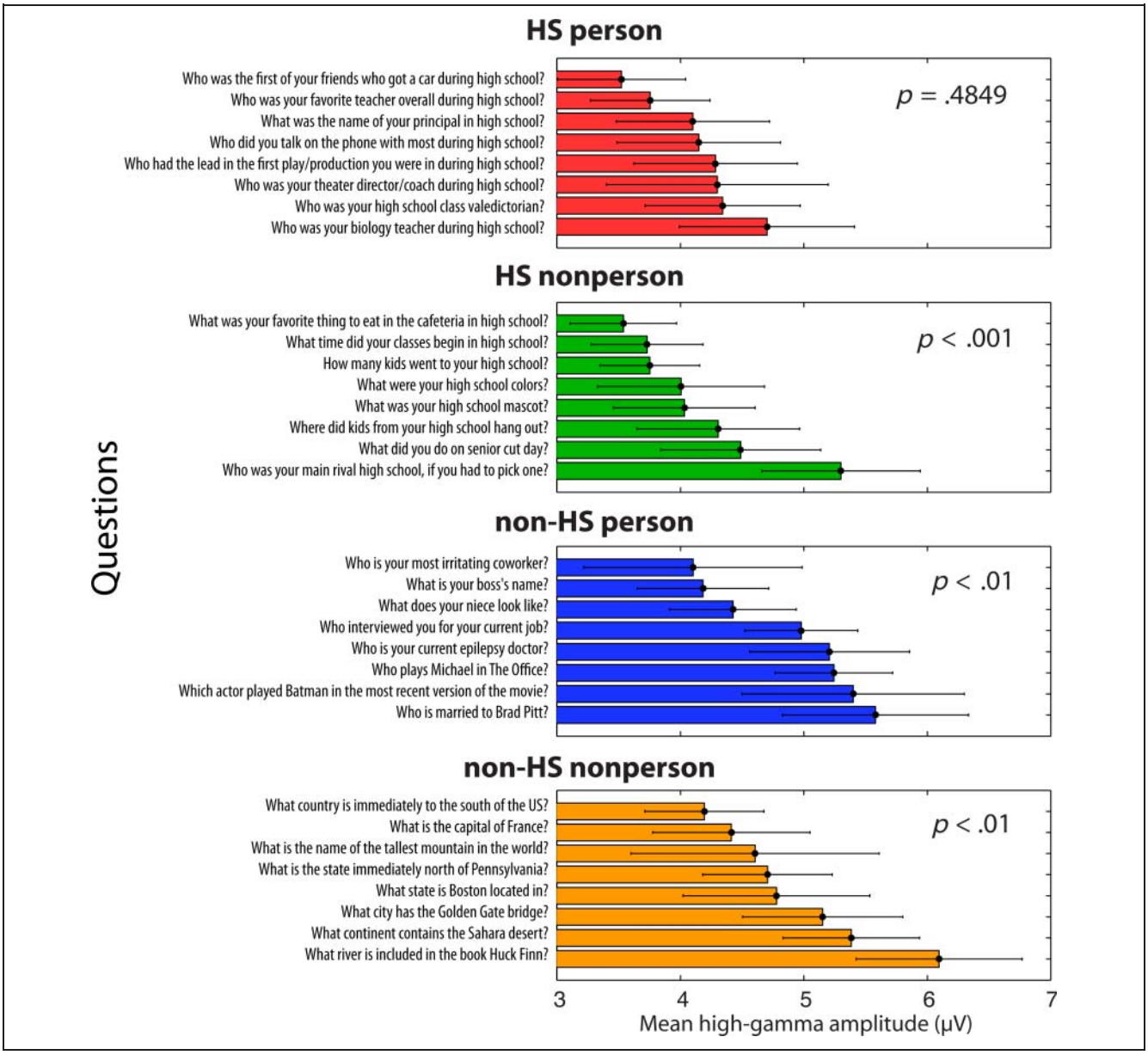

Figure 4. High-gamma activity for individual questions. Graphs depict the amplitudes of high-gamma responses at Electrode 17 to individual questions from different categories. Labels on the left side of plot indicate the text of each question; error bars denote 95% confidence intervals (computed across the 10 times each question was presented). The *p* value inside each plot comes from a one-way ANOVA comparing the responses within each group.

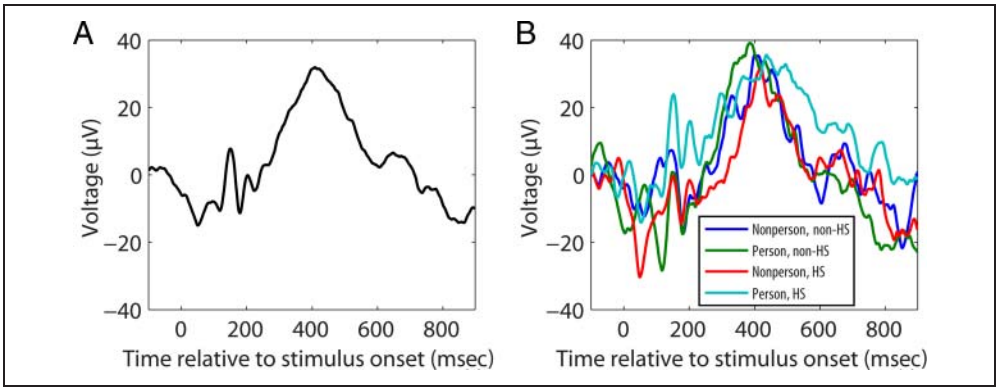

Figure 5. ERP analysis at the site where stimulation induced retrieval of HS information. (A) Mean ERP computed after the presentation of all questions. The signal was baseline-corrected relative to the 100-msec period preceding question onset. (B) ERPs computed separately for the presentations of questions from each category. There were no significant differences between the ERPs for these groups.

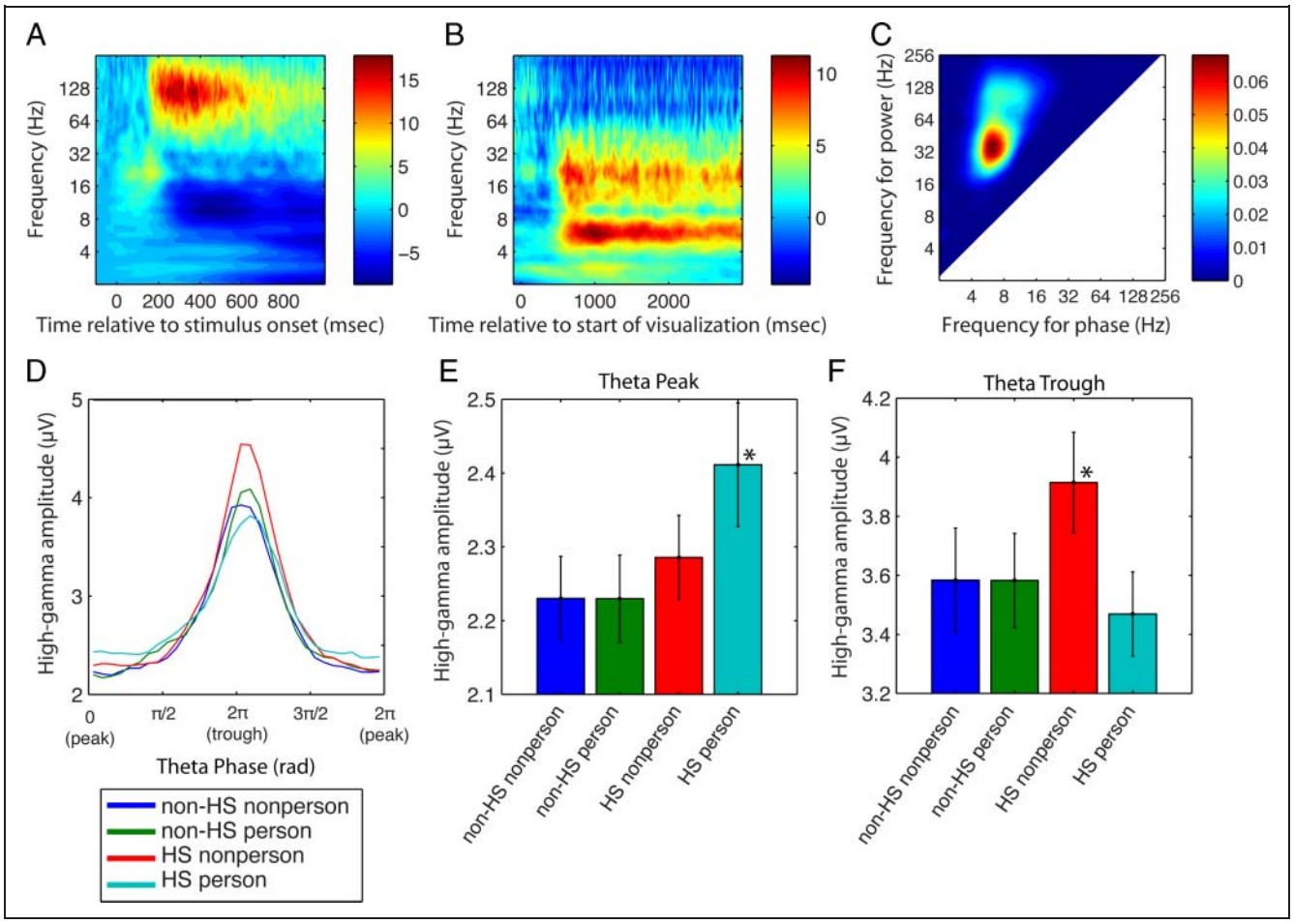

Figure 6. Neuronal activity related to stimulus visualization. (A) The mean power spectrum after viewing each question during the memory retrieval interval. The color at each point indicates the power change (decibels) relative to the mean power in the baseline period (the 100 msec before stimulus onset). (B) Mean power spectrum during the visualization of each question's answer. (C) Analysis of PAC. Color at each location indicates the magnitude of coupling (r^2) from a circular–linear regression where low-frequency phase is used to predict the amplitude of high-frequency activity. (D) The amplitude of high-gamma activity during visualization for each question category, as a function of theta (4–8 Hz) phase. (E) High-gamma activity during visualization at the peak phase of theta (0° ± 45°). Asterisks denote groups with significant elevations (post hoc t tests, ps < .01). Error bars denote 95% confidence intervals computed across trials. (F) High-gamma activity during visualization at the theta trough (180° ± 45°).

(Harrison & Tong, 2009; Polyn, Natu, Cohen, & Norman, 2005).

Whereas memory retrieval was characterized by elevated high-gamma activity at this site (Figure 6A), during visualization there were prominent theta (4–8 Hz) and beta (20–30 Hz) oscillations (Figure 6B). The amplitude of theta and beta activity did not vary with the stimulus category (ps > .05). We examined whether these visualization-related oscillations were involved in PAC, a phenomenon where the amplitude of a high-frequency signal dynamically varies with the phase of a slower oscillation (Voytek et al., 2010; Sirota et al., 2008; Tort et al., 2008; Canolty et al., 2006; Lakatos et al., 2005; Mormann et al., 2005). We measured PAC by using a linear model to identify the variation (r^2) in the amplitude of high-frequency activity that could be explained by the phase of a slower oscillation (Penny et al., 2008; Fisher, 1993). Figure 6C depicts the results of our PAC analyses across widespread frequencies, showing that during stimulus visualization there was PAC between theta oscillations and two higher-frequency signals: one at ~40 Hz ("low gamma") and the other at ~100 Hz ("high gamma").

We examined whether the detailed patterning of PAC varied with the category of the visualized stimulus, in line with predictions of theoretical models suggesting that oscillatory phase coupling is involved in memory maintenance (Buzsáki, 2005; Jensen & Lisman, 2005). For each question category, we computed the amplitude of high-frequency activity at four theta phase bins (peak, trough, ascending, and descending). Overall, the amplitude of high-gamma activity was elevated at the theta trough for all categories, consistent with previous work (Canolty et al., 2006). However, at particular theta phases, the amplitude of high-gamma activity varied with the category of the visualized memory (fixed-effect ANOVA, $p < .005$; Figure 6D); this effect was absent for low gamma ($p > .1$).

This result was driven by two patterns: At the theta peak, neural activity was greater when the patient visualized HS person memories (Figure 6E; $p < 10^{-4}$, post hoc t test) and at the trough activity was elevated for HS nonperson memories (Figure 6F; $p < .005$). Thus, activity at this site represented HS-related information both during memory retrieval and visualization, but the nature of these coding schemes differed.

DISCUSSION

In spite of decades of work (Selimbeyoglu & Parvizi, 2010; Gloor, 1990; Halgren et al., 1978; Penfield, 1938), we still have not gained a solid understanding of why brain stimulation causes some patients to experience spontaneous memory recall. Here, by recording normal brain activity at a site where stimulation caused memory retrieval, it revealed for the first time a distinctive neural pattern that helps explain this phenomenon mechanistically.

At a site where stimulation caused retrieval of HS memories, we observed that there was less high-gamma ECoG activity for remembering HS information compared with other categories during normal cognition in the absence of stimulation. High-gamma activity is a robust correlate of neuronal spiking, as demonstrated by recent work showing that both of these signals are related to broadband ECoG activity (Jacobs et al., 2010; Manning et al., 2009; Miller et al., 2007, 2009). Thus, the lower level of high-gamma activity at this site indicates that the population of neurons here are less active when the patient normally retrieves HS memories.

Unlike microelectrodes, the clinical ECoG electrodes that we used record the aggregate activity of $\sim 5 \times 10^5$ neurons (Miller et al., 2009). The fact that we are able to observe HS-related neuronal activity with this type of electrode suggests that this patient has a contiguous group of neurons at this ventral-temporal location that are part of a network that encodes the "high school-ness" of a memory. More broadly, this suggests that other neurons in the human temporal lobe may be clustered spatially such that nearby neurons respond to similar abstract categories. In this way, our findings extend recent studies identifying distinct category-specific cortical regions, such as those responding to faces, places, animals, or tools (Dahl, Logothetis, & Kayser, 2009; Mitchell et al., 2008; Beauchamp, Argall, Bodurka, Duyn, & Martin, 2004; Martin & Chao, 2001; Epstein & Kanwisher, 1998; Kanwisher et al., 1997). However, unlike these regions, which are generally consistent across individuals (Tsao, Moeller, & Freiwald, 2008; Epstein & Kanwisher, 1998; Kanwisher et al., 1997), it is unlikely that all humans have HS patches of cortex, as many developed and well-functioning humans are unaware of this concept. Instead, it seems likely that neurons representing abstract information like HS develop this responsiveness through experience.

An important broader issue is understanding how a patch of neurons that encodes HS-related information fits into the larger-scale organization of the human brain. One possibility is that the HS region borders areas that encode memories from nearby periods, such as elementary school or college. We could not examine this issue in this patient because of time constraints. However, we did find that neurons in this same region also participate more generally in representing autobiographical memories (Cabeza & St. Jacques, 2007; Fink et al., 1996). This suggests that the HS patch in this patient may be part of a hierarchy, being situated near or among cells that represent various types of autobiographical information more generally.

We hypothesize that electrical stimulation at a site can evoke a memory if normal recordings from that area reveal distinctive neural activity when retrieving that memory compared with others. This interpretation is consistent with the data reported here and with current knowledge about the electrophysiology of brain stimulation. The type of ECoG stimulation that we used is generally thought to inhibit local activity (Kinoshita et al., 2004; Dostrovsky et al., 2000) via activation of inhibitory interneurons (Logothetis et al., 2010). Thus, our findings suggest that ECoG stimulation causes memory retrieval by causing a pattern of inhibition that is similar to the attenuated activity that appears at that area when the memory is retrieved normally. Observing a lower level of activity for a particular class of stimulus might be considered surprising, based on the common observations of individual neurons that increase their firing for particular stimuli or categories (e.g., Quiroga, Reddy, Kreiman, Koch, & Fried, 2005; Tovee, Rolls, Treves, & Bellis, 1993). However, this type of pattern has been repeatedly observed in larger-scale brain recordings that measure entire neuronal populations, such as functional imaging (Shmuel, Augath, Oeltermann, & Logothetis, 2006) or local field potentials (Lachaux et al., 2008; Freeman & Schneider, 1982).

During normal memory retrieval, this patient's "HS patch" exhibited increased activity compared with the baseline for all questions, but the magnitude of this increase was significantly smaller for HS questions. One potential explanation for this pattern is that there are distinct populations of neurons at this site (Figure 7), including one that is specifically inhibited when representing the concept of HS ("HS−") as well as others that activate for retrieval of various memories. The recording electrode could have measured the average activity of both populations and thus recorded less overall high-gamma activity for HS questions. Following this model, stimulation could have elicited HS memories because it inhibited various cells including the HS subpopulation. However, additional work is necessary to test this model by revealing how individual memories are represented at the scale of individual neurons.

In our interpretation, stimulation at Electrode 17 caused this patient to experience HS memory retrieval because it partially replicated a neural pattern that was normally present during recall of HS information. Gloor (1990) hypothesized that stimulation-induced memory retrieval occurs because the stimulation creates a local pattern of

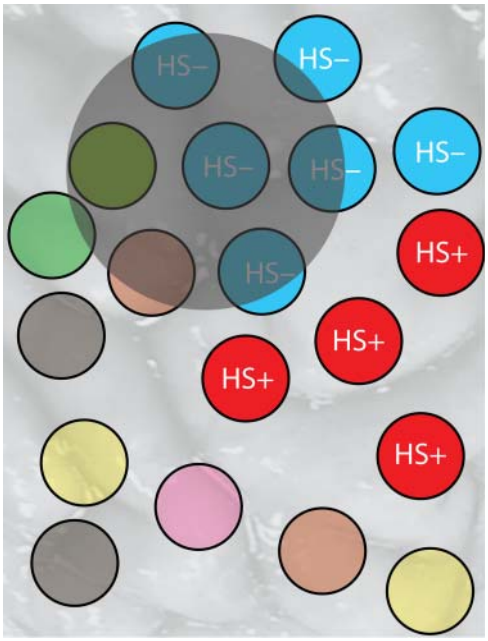

Figure 7. Illustration of a hypothetical organization of the cortex where stimulation evoked memories of HS. When the patient recalls HS memories, individual cortical columns (small circles) may exhibit decreased ("HS−"; blue) or increased ("HS+"; red) activity. The small unlabeled circles represent columns where neuronal activity does not specifically encode HS-related information but may activate for various other memories. The electrode where we observed HS-related ECoG activity is represented by the large shaded circle, which overlies several HS− columns.

activation that is filled in by activity at other brain sites, leading to a global state that approximates the brain state of a remote memory. Our data support Gloor's theory by revealing that there can be a robust correspondence between activity at the stimulation site during normal cognition and the neural correlate of the memory evoked when that location is stimulated. We note that our interpretation and that of Gloor contradict Penfield's general view on stimulation-induced memory retrieval. Penfield generally argued that there was no relation between the location of the stimulated cortex and the content of the spontaneously recalled memory. Instead, he suggested that the details of a memory elicited by stimulation were random: "The experience that appears…when stimulation is begun…seems to depend on chance. It may be recent or it may come from childhood many years before." (Penfield, 1958). To the contrary, our findings show that, at least in some cases, there is a correspondence between activity at the stimulation site during normal cognition and the properties of the memory that is evoked when that location is stimulated. Consistent with our interpretation, we note that some of Penfield's case reports did describe instances where repeated stimulations at one site elicited the same memory (Penfield, 1975).

Although our findings showed that stimulation at this site was sufficient to evoke HS memories, we do not believe that this is necessarily the only cortical region where neurons in this patient store HS memories or, more generally, that memories are stored solely at individual cortical locations. Previous research clearly showed that stimulation at widespread brain regions can cause memory retrieval, including both neocortical and limbic structures (Barbeau et al., 2005; Bartolomei et al., 2004; Gloor et al., 1982; Halgren et al., 1978). Consistent with this, we believe that various memories are stored throughout distributed brain networks. We note that unlike some previous studies (Bartolomei et al., 2004; Penfield & Perot, 1963; Jackson, 1879), we observed that HS memory retrieval occurred without after-discharges. More work is necessary to understand the potential involvement of afterdischarges in stimulation-related memory retrieval.

Unlike the retrieval interval, during visualization we observed robust theta and beta oscillations. This was not entirely unexpected because previous studies implicated these oscillations in memory maintenance (Kopell, Whittington, & Kramer, 2011; Engel & Fries, 2010; Lee, Simpson, Logothetis, & Rainer, 2005; Raghavachari et al., 2001). However, we were surprised to find that the HS person and HS nonperson categories were represented by increased neuronal activity at different theta phases (Figure 6). Neuronal oscillations have been shown to enhance information coding by revealing oscillatory phases when spikes are most informative (Fries, 2009; Jacobs, Kahana, Ekstrom, & Fried, 2007; Lakatos et al., 2005; Lee et al., 2005) and to help represent order information with different oscillatory phases representing positions in a sequence (Siegel, Warden, & Miller, 2009; Jensen & Lisman, 2005). However, our results are the first to suggest that activity at a neocortical site occurred at separate phases for different stimulus categories.

Conclusion

In conclusion, we found a detailed correspondence between the activity at a cortical region during normal memory retrieval and the behavioral effect of electrically stimulating that site. Our findings offer an explanation for the neuronal basis of stimulation-induced memory recall by indicating that stimulation induces memory retrieval by artificially reinstating brain patterns from normal cognition. An additional novel finding we made is identifying a patch of cortex where neurons encode information about an abstract concept (i.e., "high school"). A challenge for future researchers is to map how abstract information is represented in the human brain more generally and determine whether this coding follows spatial organizational schemes analogous to the ones observed in sensory regions (Van Essen & Maunsell, 1983; Penfield & Boldrey, 1937).

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Reprint requests should be sent to Dr. Joshua Jacobs, School of Biomedical Engineering, Science and Health Systems, Drexel University, Philadelphia, PA 19104, or via e-mail: Joshua.Jacobs@drexel.edu or Dr. Bradley Lega, Department of Neurosurgery, University of Pennsylvania, Philadelphia, PA 19104, or via e-mail: Bradley.Lega@uphs.upenn.edu.

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