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Review

Repeated stimuli elicit diminished high-gamma electrocorticographic responses

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ABSTRACT

In the phenomenon of repetition suppression (RS), when a person views a stimulus, the neural activity involved in processing that item is relatively diminished if that stimulus had been previously viewed. Previous noninvasive imaging studies mapped the prevalence of RS for different stimulus types to identify brain regions involved in representing a range of cognitive information. However, these noninvasive findings are challenging to interpret because they do not provide information on how RS relates to the brain's electrophysiological activity. We examined the electrophysiological basis of RS directly using brain recordings from implanted electrocorticographic (ECoG) electrodes in neurosurgical patients. Patients performed a memory task during ECoG recording and we identified high-gamma signals (65–128 Hz) that distinguished the neuronal representation of specific memory items. We then compared the neural representation of each item between novel and repeated viewings. This revealed the presence of RS, in which the neuronal representation of a repeated item had a significantly decreased amplitude and duration compared with novel stimuli. Furthermore, the magnitude of RS was greatest for the stimuli that initially elicited the largest activation at each site. These results have implications for understanding the neural basis of RS and human memory by showing that individual cortical sites exhibit the largest RS for the stimuli that they most actively represent.

Contents

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1. Introduction

The phenomenon of repetition suppression (RS) is a powerful technique for mapping the functional roles of neurons across different brain areas. In RS, the brain areas that activate when a person views an item generally show a diminished response when a person later sees an identical or similar stimulus. By identifying the areas that exhibit RS across different types of stimuli, researchers have obtained rich insights into the neural basis of various human neuronal processes, including perception, memory, and reasoning (Grill-Spector et al., 2006). Research has used RS to reveal detailed information regarding the types of neuronal processes that occur in different brain areas, such as the findings that perceptual memory information is represented in sensory regions (Tootell et al., 1998) and that abstract stimulus properties are coded by neurons in temporal and frontal cortices (Henson et al., 2004). Further, the magnitude of RS predicts the strength of a person's memory on a trial-by-trial basis (Maccotta and Buckner, 2004) and shows the involvement of different brain regions in distinct memory processes (Gonsalves et al., 2005). Although RS is not a perfect measure of neuronal coding (Sawamura et al., 2006), obtaining a more detailed understanding of RS is likely to shed light on the fundamental nature of human memory and cognition and is considered a key goal of cognitive neuroscience (Weiner and Grill-Spector, 2012).

The phenomenon of RS has been studied with various methods, including scalp electroencephalography (Conrad et al., 2007; Gruber and Matthias, 2005; Gruber et al., 2006; McDonald et al., 2010; Sambeth et al., 2004; Van Strien et al., 2007), magnetoencephalography (Dale et al., 2000; Friese et al., 2012; Gonsalves et al., 2005; McDonald et al., 2010; Noguchi et al., 2004; Vidyasagar et al., 2010), electrocorticography (Hermes et al., 2012; McDonald et al., 2010; Puce et al., 1999), and single-cell recordings (De Baene and Vogels, 2010; Kaliukhovich and Vogels, 2011; Sawamura et al., 2006; Sobotka and Ringo, 1996). Nevertheless, the vast majority of research on RS in humans uses fMRI (Harris and Aguirre, 2010; Henson et al., 2000b; Henson et al., 2004; James and Gauthier, 2006; Larsson and Smith, 2012; Maccotta and Buckner, 2004; Malach, 2012; Sayres and Grill-Spector, 2006). Various neural models have been proposed to explain how the RS observed with fMRI is related to the brain's electrical activity (Grill-Spector et al., 2006). These models differ in terms of how they attribute RS to changes in the amplitude, timing, and identities of the neurons that are active when viewing a repeated item. Distinguishing between these theories is further complicated by uncertainty regarding the relation between the fMRI blood-oxygenation signal and underlying neuronal activity (Ekstrom, 2010; Logothetis et al., 2001). Thus, researchers suggested that direct electrophysiological recordings could help to explain RS more fully (Gotts et al., 2012).

We studied RS using direct electrocorticographic (ECoG) brain recordings from neurosurgical patients performing a working-memory task. The high-frequency component of these ECoG signals correlates with neuronal spiking (Manning et al., 2009; Miller et al., 2009). These high-frequency signals have revealed neural assemblies that distinguish particular stimuli during cognitive tasks (Blakely et al., 2008; Jacobs and Kahana, 2009; Pasley et al., 2012; Pei et al., 2011). We thus used ECoG to examine RS in detail in humans by comparing the neural representations of individual stimuli between the viewing of novel and repeated items. With this stimulus-based approach, our findings demonstrate that RS is specific to the high-gamma band (65–128z) of ECoG signals and, further, that the neuronal assemblies with the largest initial activations are the ones that exhibit the most RS.

2. Methods

2.1. Patients

We analyzed data from 25 patients who were undergoing invasive seizure monitoring for drug-resistant epilepsy (Jacobs and Kahana, 2010). Throughout ECoG monitoring, patients volunteered to participate in our memory task in free time between clinical procedures on a bedside laptop computer. Each patient participated in between one and five testing sessions. The research protocol was approved by Institutional Review Boards at the Hospital at the University of Pennsylvania (Philadelphia, PA) and the Thomas Jefferson University Hospital (Philadelphia, PA). Informed consent was obtained from each patient or their legal guardians.

2.2. Task

Patients performed the Sternberg working-memory task (Sternberg, 1966); each session lasted about 45 min and contained multiple trials. This is a new dataset that is distinct from the one reported by Jacobs and Kahana (2009). Each trial consisted of three phases: encoding, maintenance and response (Fig. 1A). In the encoding phase, patients were first presented a fixation cross and then a list of three uppercase letters were displayed sequentially on a computer screen. Each single letter stimulus remained on the screen for 700 ms and was followed by a blank screen for 275–350 ms (uniformly distributed). Each character had a visual field size of ~10°, although this varied according to where the subject positioned the laptop on their hospital tray. Patients were instructed to closely attend to each stimulus presentation and to silently hold the identity of each item in memory. After all three list items were presented, the patient attempted to remember all the presented items during a maintenance period. Last, in the response phase, a cue item appeared on the screen, and patients pressed a key to indicate whether the cue item was present or absent in the just-seen list (a target or lure, respectively). Exactly half of the cue items were targets and half were lures, with the order randomized. After the response, a feedback message appeared on the screen, indicating whether the response was correct. Individual patients participated in different numbers of task sessions according to their time and interest.

On average, each patient performed 335 trials across all sessions (~167 repeats), for a total of 1005 letter presentations. The letters used in this task were one of 8 consonants; vowels were excluded to prevent patients from using mnemonic strategies to remember each list (e.g., remembering the entire list as an easily pronounceable word-like sound). Half the trials had three different list items and half the trials had a repeat. In lists with repeats, the position of the non-repeat item was uniformly distributed across the three list positions.

2.3. Data analysis

We analyzed brain signals related to viewing each stimulus by measuring the amplitude of ECoG activity in the 800 s after each item onset. These measurements included all oscillatory activity after item onset, ignoring the signal's phase, in contrast to some previous studies that measured RS with ERP techniques (Anderson et al., 2008; Gilbert et al., 2010) that measure only the portion of the signal that is phase- and time-locked to each stimulus appearance (Fell et al., 2004; Hanslmayr et al., 2007; Jacobs et al., 2006; Yeung et al., 2004). For each electrode, we filtered ECoG activity in five frequency bands: theta (4–8z), alpha (8–16 Hz), beta (16–30 Hz), low gamma (30–65z) and high gamma (65–128z). We then computed the ECoG amplitude in each band with the Hilbert transform (Bruns, 2004; Freeman, 2007) and smoothed it with a 50-ms boxcar filter. We calculated the mean amplitude for each band in each of 8 consecutive 100-ms time intervals after each letter appearance (Fig. 1B).

Our next goal was to identify electrodes that recorded ECoG activity related to processing the identity of each viewed letter (Jacobs and Kahana, 2009). To do this, we used a one-way ANOVA to test whether the amplitude of ECoG activity at each electrode, time bin, and frequency band significantly varied ($p < 0.01$) between presentations of each individual letter (Fig. 1C). For each electrode measuring letter-related ECoG activity, we then separately ranked the individual

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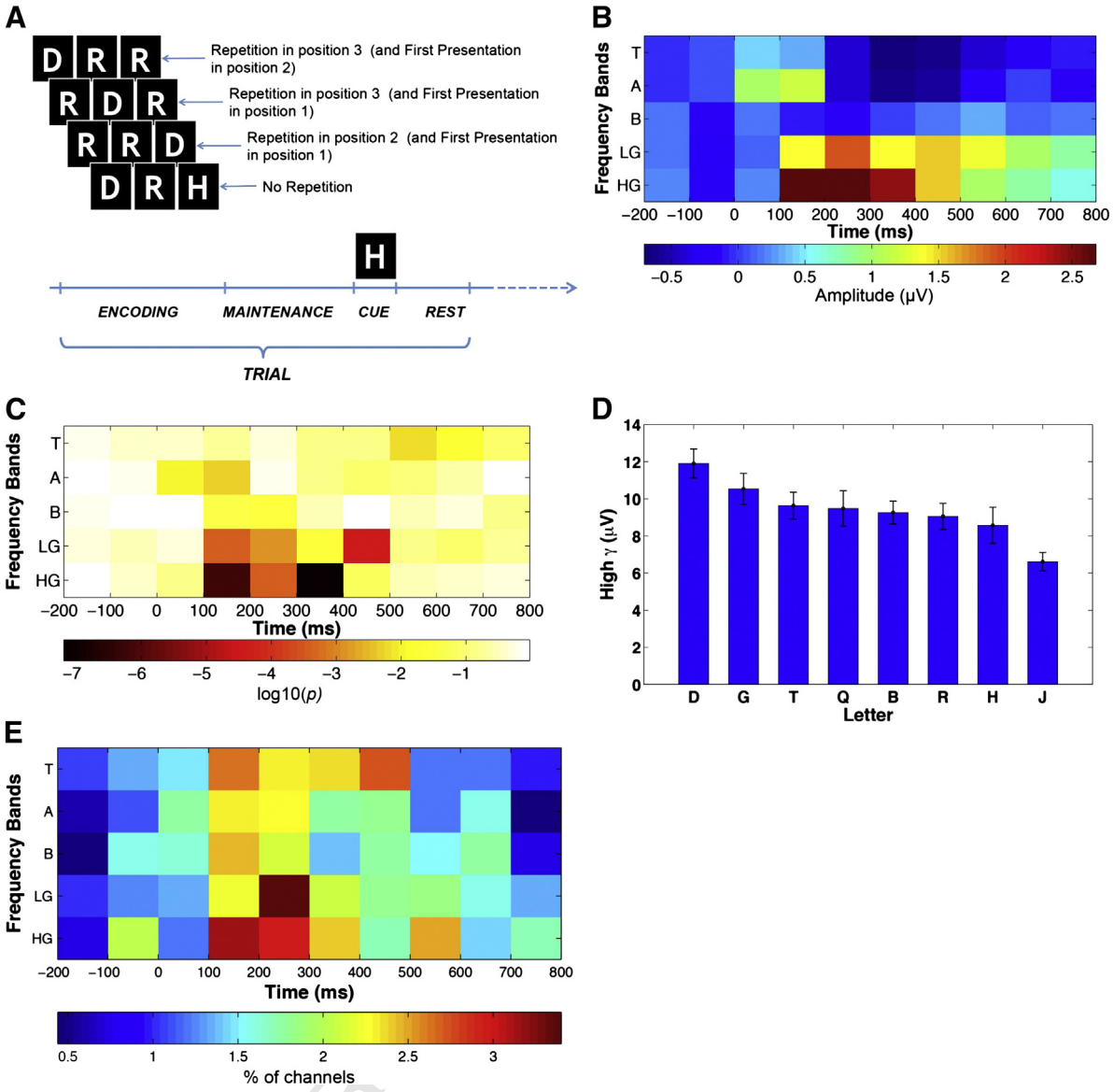

Fig. 1. (A): Schematic representation of Sternberg task with repetitions. Each trial consisted of an encoding period, during which a list of three letters was presented, and a maintenance period, followed by a cue. The participant's task was to identify whether the cue appeared in the just-presented list. (B): The amplitude of neuronal activity at one electrode following letter onset. The amplitude of activity at each timepoint and frequency is normalized related to letter onset (sample electrode from patient 15's left Brodmann area 19). (C): Analysis of letter-related ECoG activity at this same electrode; color indicates *log10*(p) from an ANOVA. (D): Detail of letter-related activity at this same electrode. The bars show the mean unnormalized high-gamma amplitude for each letter at 100–400 s. Error bars represent 95% confidence intervals. (E): Time–frequency distribution of the percentage of electrodes exhibiting letter-related activity across the entire dataset.

letters according to the mean response magnitude at 100–400 s (Fig. 1D), with rank 1 corresponding to the largest response at that electrode and rank 8 corresponding to the smallest. We also identified the electrodes that activated generally during memory encoding without exhibiting letter-related activity, by comparing the amplitude of ECoG activity after stimulus onset with the activity in the 200-ms prestimulus baseline (t test, $p < 0.05$).

Next we were interested in identifying ECoG activity related to stimulus repetition. We labeled each stimulus presentation according to whether that item was a repeat or new item within that list. To test for effects of repetition, we employed a four-way ANOVA at each frequency band. The ANOVA factors were the following: *Repeated item* (whether the stimulus was a novel or repeat presentation) *Rank* (the rank of the viewed letter), *List position* (the serial position of the item in the presented list), and *Electrode* (individual ECoG electrodes). *List position* and *Electrode* were random factors and others were fixed. In our analysis of RS that ignored stimulus-related activity, we used a three-way ANOVA that omitted the factor *Rank*. In addition to the ANOVA, we conducted post-hoc tests to identify individual electrodes exhibiting RS by using paired t tests to compare the mean responses across the first two ranks between novel and repeated presentations ($\alpha = 0.05$). Repeats appear only in the second or third list positions, unlike novel items, which can also appear in the beginning of each list. Thus, a potential issue is that a neural signal that varies with list position (e.g. Azizian and Polich, 2007; Sederberg et al., 2006; Serruya et al., in press) could incorrectly appear as a correlate of repetition. We corrected for this potential issue in our statistics with the factor *List position* and in our plots by normalizing each ECoG response relative to the mean response from that same list position for non-repeat items. However, there was no significant effect of *List position* in the high gamma band ($p = 0.9$), which suggests that any relevant position effects were minimal in this dataset.

To assess the timecourse of RS, we computed the amplitude timecourse of each electrode's responses to repeat and novel items

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and measured several temporal features of its shape (Fig. 3A). The measurements are *Onset time*, which is the latency from stimulus onset until the response reaches 75% of its peak increase; *Peak time*, the latency (in ms) from stimulus onset until the peak ECoG response; and *Duration*, the length of time from response onset until its subsequent drop 75% of the way back from its peak to its baseline. All response shape measurements were computed separately for novel and repeat items.

We also examined repetition-related changes in event-related potentials (ERPs) by computing the time-locked ECoG voltage signal at each electrode and using *t* tests to compare this signal between repeats and novel items. ECoG signals were low-pass filtered below 30z and then ERPs were computed at the sites that actively exhibited elevated high-gamma activity during the task.

3. Results

We recorded activity from a total of 2262 electrodes implanted in 25 epilepsy patients who performed a working-memory task in free time between clinical procedures. In each trial of the task, the patient memorized a list of three letters, each of which either contained three different items or had one item repeated. Our data analyses sought to characterize neural patterns that differentiated between the processing of novel and repeat items.

3.1. Behavioral data

First, we assessed patients' task performance by measuring their reaction times responding to the memory probes after each list. Overall, patients responded more rapidly to lists containing a repeated item (1393 s) compared to those that contained three different items (1589 s; $p < 0.05$, *t* test).

3.2. Stimulus-based analysis of repetition suppression

Earlier work showed that a prominent feature of human ECoG recordings was the presence of neuronal patterns that distinguished individual items that were encoded into memory (Jacobs and Kahana, 2009). Here utilized these ECoG measurements of individual stimulus representations to characterize the neuronal basis of repetition suppression (RS). Our strategy was to first identify the ECoG representations of particular stimuli and then to measure changes in these signals when stimuli were repeated.

To identify the ECoG signals that encoded stimulus-related information, at each electrode we performed a one-way ANOVA comparing neuronal responses after the patient viewed different letters in the task's encoding phase. As seen previously, many individual electrodes exhibited increased high-gamma amplitude after each letter appeared on the screen (Fig. 1B; Crone et al., 1998). For each electrode, we used a separate series of ANOVAs to test whether the amplitude of this activity significantly varied according to the identity of the letter that the person viewed (Jacobs and Kahana, 2009). Fig. 1C illustrates the results of the ANOVA at an example electrode that exhibited significant letter-related activity in the high-gamma band at 100–400 s. This site exhibited the largest amplitude of high-gamma activity when the person viewed the letter "D", and had a smaller response for other letters, like "J" (Fig. 1D).

Across the entire dataset, significant letter-related ECoG activity (ANOVA *p*'s < 0.01) was most prevalent in the high-gamma band 100–400 s after stimulus onset (Fig. 1E), where 50 electrodes exhibited activity that differed significantly between individual letters, consistent with previous work (Jacobs and Kahana, 2009). Our next analyses focused on high-gamma activity in this frequency band and time interval (see below for analyses of other frequencies). For each electrode that exhibited significant stimulus-related high-gamma activity, we separately ranked each individual letter according to the magnitude of its response. For example, at the electrode in Fig. 1D the letter "D" was ranked first because it elicited the strongest high-gamma amplitude (11.9 μV) and letter "J" was ranked last (6.6 μV).

Next, we tested whether the high-gamma representations of individual items changed with repetition, by aggregating across all electrodes that exhibited significant letter-related activity (see Section 2). For this purpose, the most critical features of the ANOVA were the factors *Repetition* and *Rank*, and their interaction. We did not observe a significant main effect of *Repetition* ($p > 0.7$). However, we did observe a significant *Repetition* × *Rank* interaction ($p < 0.001$). This significant interaction showed that high-gamma ECoG activity exhibited RS, but that the magnitude of this effect varied according to the letter's rank. To illustrate this pattern, Fig. 2A shows the mean difference in high-gamma amplitude between novel and repeated items, computed seperately for each letter rank. RS is strongest and statistically robust for stimuli with ranks 1 and 2, and this phenomenon diminished for letters with lower ranks.

This phenomenon of RS in high-gamma ECoG activity was also clearly visible at individual electrodes (Figs. 2C–H). Of the 50 electrodes that exhibited significant high-gamma stimulus-related activity, 17 exhibited significant RS and only 1 exhibited response enhancement (see Table 1).

3.3. Timing analysis

ECoG recordings measure aggregate neuronal activity with a high temporal resolution (K. Miller et al., 2012). This allowed us to measure the detailed timecourse of human RS. For each electrode, we computed the detailed timecourse of the mean high-gamma response amplitude to first and repeated stimuli. We then measured the shape of each electrode's response by measuring each response's *Onset time*, *Peak Time*, and *Duration* (see Fig. 3).

We compared these measurements between first and repeat presentations of each item. Overall, the initial response times to first presentations were significantly shorter than responses to repeated items (*Onset time*: $p < 0.05$, paired *t* test) and had longer *Durations* ($p < 0.05$). The latency of the peak response was also significantly faster for first presentations than repeats (*Time to Peak*: $p < 0.05$, *t* test).

4. Analysis of repetition effects at other frequencies

We tested for RS at other frequencies in addition to the high-gamma band (van Gerven et al., in press). As for high gamma, for each other frequency band we identified the electrodes that exhibited stimulus-related ECoG activity. We then used the same ANOVA framework to test for RS at the population level by testing for a interaction between factors *Repetition* and *Rank* at each band. Besides high-gamma, the only band where significant RS appeared was the 4–8-Hz theta frequency range ($p = 0.001$; all other bands: *p*'s > 0.5). However, when we analyzed each electrode individually, we found that theta stimulus-related RS was less robust compared with the high-gamma band. Only 3 electrodes exhibited theta RS total, which is significantly less than the 17 that exhibited high-gamma RS ($p < 0.002$, χ^2 test).

We also tested for broader patterns of RS beyond the electrodes that exhibited stimulus-related activity. This approach is common in fMRI and EEG studies, where individual stimulus representations are not generally observed (Grill-Spector et al., 2006). We identified all electrodes that exhibited increased high-gamma activity during stimulus viewing. Then we performed an ANOVA at each frequency band to identify significant repetition-related changes in ECoG amplitude. This analysis did not reveal significant RS at any band (all *p*'s > 0.9 for factor *Repetition*, uncorrected). In addition to this population analysis, we tested for RS at the level of individual electrodes, by comparing the counts of electrodes at each band that exhibited RS compared with enhancement. This electrode-count analysis also did not identify significant RS at any frequency (*p*'s > 0.1, uncorrected binomial tests).

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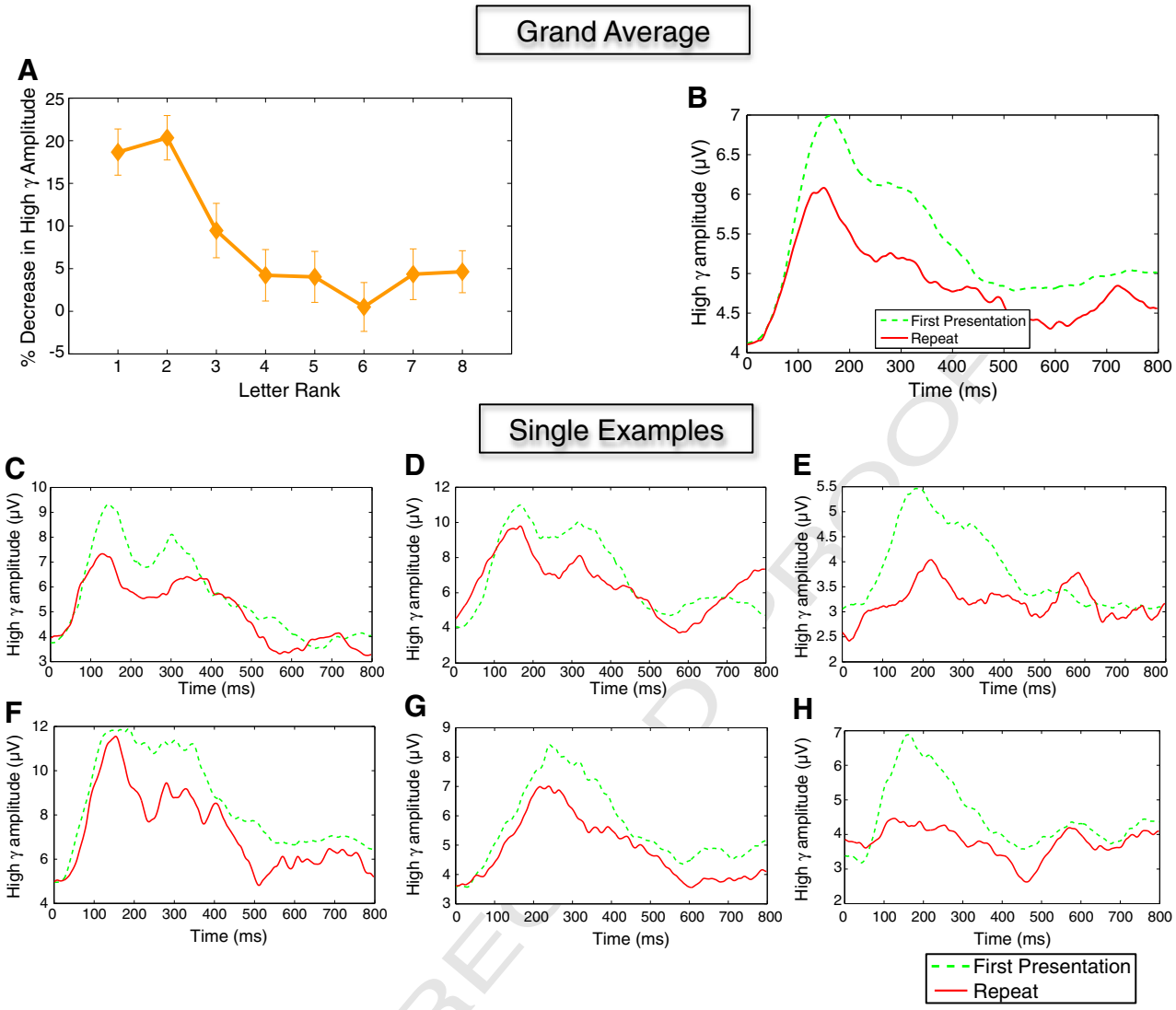

Fig. 2. Examples of repetition suppression in human electrocorticographic data. Grand Average — (A): Mean difference for high-gamma amplitude between first and repeat presentations for each letter rank, averaged across the dataset. (B): Comparison of average unnormalized high-gamma amplitude time courses between first and repeat presentations. The averages were obtained including all electrodes exhibiting significant repetition suppression and considering only the two highest ranked letters. Single Electrode Examples — Comparison of time courses between first and repeat presentation in single electrodes exhibiting significant repetition suppression at 100–400 s window. Only the two highest ranked letters were included. (C): Sample electrode from patient 4's right Brodmann area 18. (D): Sample electrode from patient 4's right Brodmann area 19. (E): Sample electrode from patient 11's right Brodmann area 19. (F): Sample electrode from patient 15's left Brodmann area 19. (G–H): Sample electrodes from patient 18's left Brodmann area 19.

5. ERP analysis of repetition suppression

In addition to measuring the amplitude of ECoG signals, a different literature has probed human brain signals by assessing event-related potentials (ERPs), which are the subsets of brain signals that are phase-locked to external events (Yeung et al., 2004). We computed ERPs following the onset of each stimulus and compared these ERPs between the viewing of novel and repeated items.

Many individual electrodes exhibited significant ERP changes for viewing repeat items. Fig. 4A shows one electrode that exhibits this effect, by displaying a larger negative ERP fluctuation at ~200 s for repetitions compared with viewing novel items. A similar pattern was also evident across the population of electrodes (Fig. 4B), whereby many individual electrodes had significantly more negative voltage for viewing repetitions compared with novel items. Together these findings are consistent with prior work suggesting increased phase synchrony for repetitions (Gotts et al., 2012), as phase synchrony often manifests as ERP fluctuations (Yeung et al., 2004).

6. Discussion

We conducted a large-scale analysis of RS using human ECoG data and identified novel neural changes related to viewing repeated stimuli, including stimulus specificity and timing changes. Seventeen ECoG electrodes (out of 50) exhibited high-gamma RS. Only one electrode showed enhancement ($p < 0.001$, binomial test). This pattern is generally consistent with the findings from previous studies that reliably demonstrate suppressed neural activity with repeated activations via fMRI and other techniques (Buckner et al., 1998; Dale et al., 2000; Grill-Spector and Malach, 2001; Henson et al., 2000b; Hermes et al., 2012; Miller and Desimone, 1994; Puce et al., 1999; Sambeth et al., 2004; Swick and Knight, 1997; Wiggs and Martin, 1998). Although these studies used a variety of experimental paradigms and their methodological details differ greatly, the consistent pattern of RS is one that we replicate.

ECoG data measure human brain activity with a higher spatial and temporal resolution than other human neuroimaging techniques. Here,

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Table 1
Summary dataset and high-gamma ECoG repetition effects. Each row describes for one patient, indicating the testing location (TJ, Thomas Jefferson University Hospital, Philadelphia, USA; UP, University of Pennsylvania Hospital, Philadelphia, USA), handedness, and the counts of electrodes with letter-specific activity, repetition-related suppression and enhancement. Electrode counts are reported overall, as well as separately for temporal and occipital cortices.

			Temporal				Occipital				Overall			
Patient #	Location	Handedness	Total	Letter-specific	Repetition suppression	Repetition enhancement	Total	Letter-specific	Repetition suppression	Repetition enhancement	Total	Letter-specific	Repetition suppression	Repetition enhancement
1	TJ	R	40	0	0	0	2	0	0	0	78	0	0	0
2	TJ	R	11	0	0	0	0	0	0	0	63	0	0	0
3	TJ	R	43	0	0	0	4	0	0	0	160	0	0	0
4	TJ	R	57	1	0	0	6	6	3	0	98	7	3	0
5	TJ	R	60	0	0	0	6	4	0	0	90	4	0	0
6	TJ	R	44	0	0	0	1	0	0	0	90	2	0	0
7	TJ	R	39	0	0	0	2	0	0	0	106	0	0	0
8	TJ	R	1	0	0	0	0	0	0	0	138	0	0	0
9	TJ	R	38	0	0	0	0	0	0	0	62	1	0	0
10	TJ	R	43	1	0	0	0	0	0	0	120	1	0	0
11	TJ	R	67	2	2	0	15	6	2	0	110	8	4	0
12	TJ	R	29	0	0	0	4	3	0	0	96	3	0	0
13	TJ	R	53	1	0	0	8	1	0	0	99	2	0	0
14	TJ	R	20	0	0	0	14	6	1	1	48	6	1	1
15	TJ	R	57	2	1	0	12	3	3	0	96	5	4	0
16	TJ	R	43	0	0	0	7	1	0	0	72	1	0	0
17	TJ	R	54	0	0	0	14	6	2	0	150	8	3	0
18	UP	R	42	0	0	0	2	2	2	0	80	2	2	0
19	UP	L	12	0	0	0	0	0	0	0	86	0	0	0
20	UP	R	30	0	0	0	0	0	0	0	78	0	0	0
21	UP	R	28	0	0	0	5	0	0	0	36	0	0	0
22	UP	L	28	0	0	0	2	0	0	0	86	0	0	0
23	UP	L	10	0	0	0	0	0	0	0	74	0	0	0
24	UP	R	35	0	0	0	0	0	0	0	78	0	0	0
25	UP	R	25	0	0	0	0	0	0	0	68	0	0	0
All patients			909	7	3	0	104	38	13	1	2262	50	17	1

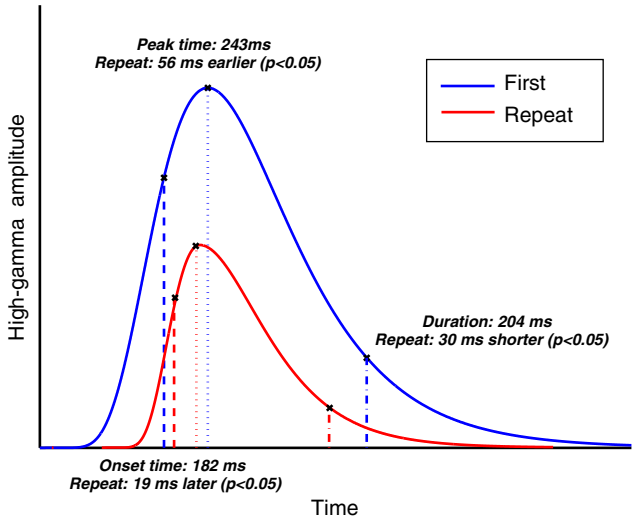

Fig. 3. Representation of our analyses examining repetition-related changes in the shape of the high-gamma responses to initial and repeat stimulus presentations.

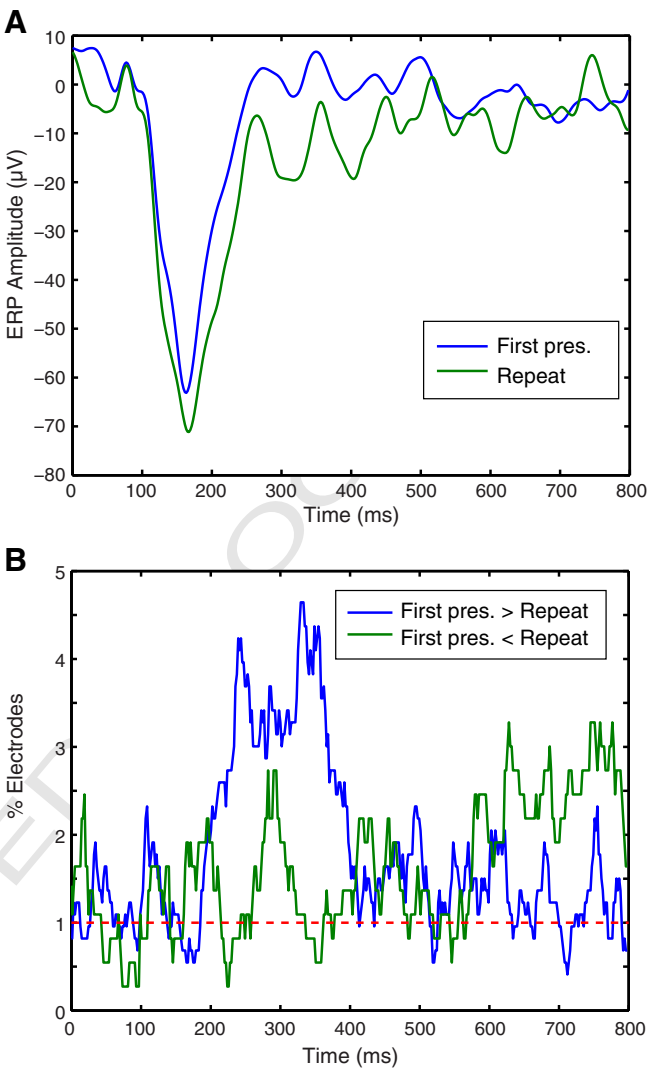

Fig. 4. Event-related potential (ERP) analysis of repetition suppression. A. Example electrode showing a large negative ERP component after stimulus onset. This component was significantly larger for viewing repeated items. B. Population analysis of repetition-related changes in ERPs. Plot indicates the percentage of electrodes that exhibited significant differences in ERPs between the initial viewing of stimuli compared with repetitions. Blue line indicates electrodes with more positive voltage for initial viewings, Green indicates electrodes with more positive voltage for repetitions. Red dashed line indicates the chance level of significant RS patterns.

we found that RS was most apparent in the high-gamma band of these signals. Previous research showed that ECoG high-gamma activity is caused by a broadband signal (Miller et al., 2007) that correlates with neuronal spiking (Manning et al., 2009; Miller et al., 2009). This link between high-gamma activity and neuronal spiking, in conjunction with our finding of high-gamma RS, suggests that RS manifests neurally as decreased neuronal activity. By showing that RS also appears with high-gamma ECoG, it strengthens the evidence that fMRI can be used to noninvasively estimate neuronal activity and is informative for understanding the complex interrelation between spiking, the fMRI BOLD signal, and oscillatory activity (Ekstrom, 2010; Logothetis et al., 2001). However, to the extent that high-gamma ECoG activity may additionally relate to neuronal synchrony (Ray et al., 2008), an important area of future work is to assess repetition-related changes in synchronous spike timing.

The most novel feature of our study was that we were able to separately measure RS for the neural representations of individual stimuli. Many prior studies of RS aggregated across large cortical regions that showed category-level neuronal responses. This category-wide approach is logical in fMRI and scalp EEG data where large-scale category responses are the dominant cognitive pattern. The spatial blurring inherent in noninvasive brain data largely precludes differentiating between local neuronal populations. Here we were motivated by our prior finding that ECoG signals reveal stimulus-related neural patterns (Jacobs and Kahana, 2009) and this allowed us to study human RS for individual exemplars within a category. This stimulus-based approach was vital for our finding that RS is largest for the stimuli that caused the largest activations at each electrode.

Although RS is most often observed with noninvasive brain measurements, researchers continue to discuss the implications of these measurements for the firing of individual neurons (for reviews, see Grill-Spector et al., 2006; Gotts et al., 2012). We did not directly record individual action potentials, but our ECoG findings nonetheless shed some light on these issues. We observed repetition-related decreases in the duration of high-gamma ECoG responses (Fig. 3). This duration change is consistent with one prediction of the *Facilitation* model of RS (Grill-Spector et al., 2006; Henson and Rugg, 2003; James and Gauthier, 2006; Sobotka and Ringo, 1996) which proposed that repetition caused a decrease in the latency or duration of the neural response. We also observed a significantly later onset time for repeats compared with novel stimuli, which appears to contradict a different prediction of the facilitation model. The Facilitation model was created to explain perceptual-priming data, which is very different from our memory task. However, this onset time difference is nonetheless very relevant for its predictions because the effect happens at such an early latency that is unlikely to be caused by top-down memory processes.

A recent model proposed that the RS observed with fMRI is fundamentally caused by increased low-frequency oscillatory synchronization for repeat items (Gotts et al., 2012). This theory suggests that low-frequency activity improves neuronal efficiency by enhancing the precision of spike timing, thus reducing the total number of action potentials required to perform the task. We tested for changes in low-frequency amplitude for repeated items, but did not observe repetition-related enhancement, both across the entire population of electrodes and for the subset of electrodes that exhibited stimulus-related activity. However, we did identify significant changes in evoked ECoG signals for repetitions, consistent with prior work (Anderson et al., 2008; Gilbert et al., 2010). Evoked ERP patterns can result from either amplitude or phase changes (Fell et al., 2004; Hanslmayr et al., 2007; Yeung et al., 2004). Thus, together these findings generally support the view that there is increased phase synchrony for repetitions but no low-frequency amplitude changes (Gotts et al., 2012).

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Across the brain, the overall prevalence of RS in our study is lower than that found in some prior fMRI studies. This may be a result of the letter stimuli we used. Stimulus-related ECoG activity for letters is most often observed in visual regions and the patients in our study had electrodes placed in these areas fairly infrequently (Jacobs and Kahana, 2009). Because our analysis of RS is predicated on first observing stimulus-related activity at a particular site, it is likely that a future study could identify a greater prevalence of RS in ECoG signals by using a more diverse stimulus set and having more comprehensive electrode coverage. It is also possible that the prevalence of RS we observed was impacted by the fact that our dataset only included a single stimulus category (letters), and, thus, we could only characterize stimulus-level RS, as in primate single-neuron recordings (Miller and Desimone, 1994), rather than also measuring RS at the category level.

The phenomenon of RS has become a core neuroimaging method that is used in many studies to compare the nature of neuronal representations and computational schemes across widespread brain areas and behaviors. The vast majority of these studies are conducted with fMRI. Our findings help provide an electrophysiological basis for RS by showing that this activity is prominent in the high-gamma band of ECoG and is thus likely correlated with mean neuronal spiking rates (Manning et al., 2009). An important task going forward is to test for electrophysiological differences in RS across stimuli, brain areas, and tasks, as the detailed properties of RS are likely to vary as a function of the type of item being viewed and how it is processed behaviorally (Epstein et al., 2008; Henson et al., 2000a). Our observation that RS is largest for stimuli that elicit the largest neuronal activations has implications for our fundamental understanding of the neural basis of memory by suggesting that individual cortical sites participate in representing only a subset of stimuli. This implies that we are likely to create increasingly detailed insights into the neural basis of human memory with high-resolution recording methods that can measure precise stimulus-related neural patterns, such as high-field fMRI (Yacoub et al., 2008), fMRI with custom pulse sequences or coils (Grill-Spector et al., 2006), and direct brain recordings like ECoG or single-neuron recordings (Engel et al., 2005; Jacobs and Kahana, 2010).

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