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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.

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

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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 (65–128 Hz) of ECoG signals and that the neuronal assemblies with the largest initial activations are the ones that exhibit the most RS.

Methods

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 one to 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.

Task

Patients performed the Sternberg working-memory task (Sternberg, 1966); each session lasted about 45 minutes 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 with 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.

Data analysis

We analyzed brain signals related to viewing each stimulus by measuring the amplitude of ECoG activity in the 800 ms 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 (4–8 Hz), alpha (8–16 Hz), beta (16–30 Hz), low gamma (30–65 Hz) and high gamma (65–128 Hz). 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 letters according to the mean response magnitude at 100–400 ms (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 200ms 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 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