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Citation	Gifford, Gordon W. III, Katherine A. MacLean, Marc D. Hauser, and Yale E. Cohen. 2005. The neurophysiology of functionally meaningful categories: Macaque ventrolateral prefrontal cortex plays a critical role in spontaneous categorization of species-specific vocalizations. <i>Journal of Cognitive Neuroscience</i> 17(9): 1471-1482.
Published Version	doi:10.1162/0898929054985464
Accessed	February 18, 2015 7:08:23 AM EST
Citable Link	http://nrs.harvard.edu/urn-3:HUL.InstRepos:3554390
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The Neurophysiology of Functionally Meaningful Categories: Macaque Ventrolateral Prefrontal Cortex Plays a Critical Role in Spontaneous Categorization of Species-Specific Vocalizations

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Abstract

■ Neurophysiological studies in nonhuman primates have demonstrated that the prefrontal cortex (PFC) plays a critical role in the acquisition of learned categories following training. What is presently unclear is whether this cortical area also plays a role in spontaneous recognition and discrimination of natural categories. Here, we explore this possibility by recording from neurons in the PFC while rhesus listen to species-specific vocalizations that vary in terms of their social function and acoustic morphology. We found that ventral prefrontal cortex (vPFC) activity, on average, did not differentiate between food

calls that were associated with the same functional category, despite having different acoustic properties. In contrast, vPFC activity differentiated between food calls associated with different functional classes and specifically, information about the quality and motivational value of the food. These results suggest that the vPFC is involved in the categorization of socially meaningful signals, thereby both extending its previously conceived role in the acquisition of learned categories and showing the significance of using natural categorical distinctions in the study of neural mechanisms. ■

INTRODUCTION

Categorization is a natural and adaptive process seen in all animals. Although nature presents significant variation, animals typically ignore some sources of variation, while attending to others in the service of guiding adaptive responses. For example, when a person speaks, the voice carries information about sex, age, emotion, and semantic content. For any given situation, we may decide, consciously or not, to attend to a more limited range of such information. If the speaker is alarmed and is yelling “Fire!,” the sex and age of the speaker may carry no meaning at the time although such information is available for discrimination.

Much is known about the neurophysiology of categorization in humans and nonhuman primates (Miller, Freedman, & Wallis, 2002; Miller & Cohen, 2001). However, in attempting to use nonhuman primates as models for understanding human categorization, there are at least two gaps in our present knowledge. First, most physiologically linked categorization studies involve extensive training and often, the use of artificial categories (e.g., dogs vs. cats, Freedman, Riesenhuber, Poggio, & Miller, 2001; number discrimination of dots, Nieder,

Freedman, & Miller, 2002). These studies, although fundamental in terms of their articulation of key aspects of the categorization process, raise interesting questions about the extent to which the same neurophysiological circuits are engaged when animals spontaneously classify exemplars from more natural and biologically meaningful categories. Second, although there is a long history of neurophysiological work on primates using natural categories such as faces and vocalizations (Rolls, 2004; Ghazanfar, 2003), most of these studies have focused on how particular perceptual features are or are not involved in categorization as opposed to how higher-order mechanisms might be involved in the process of discrimination and classification. In other words, some forms of classification are relatively detached from the raw perceptual inputs and potentially entail more abstract concepts (Nieder et al., 2002; Sawamura, Shima, & Tanji, 2002).

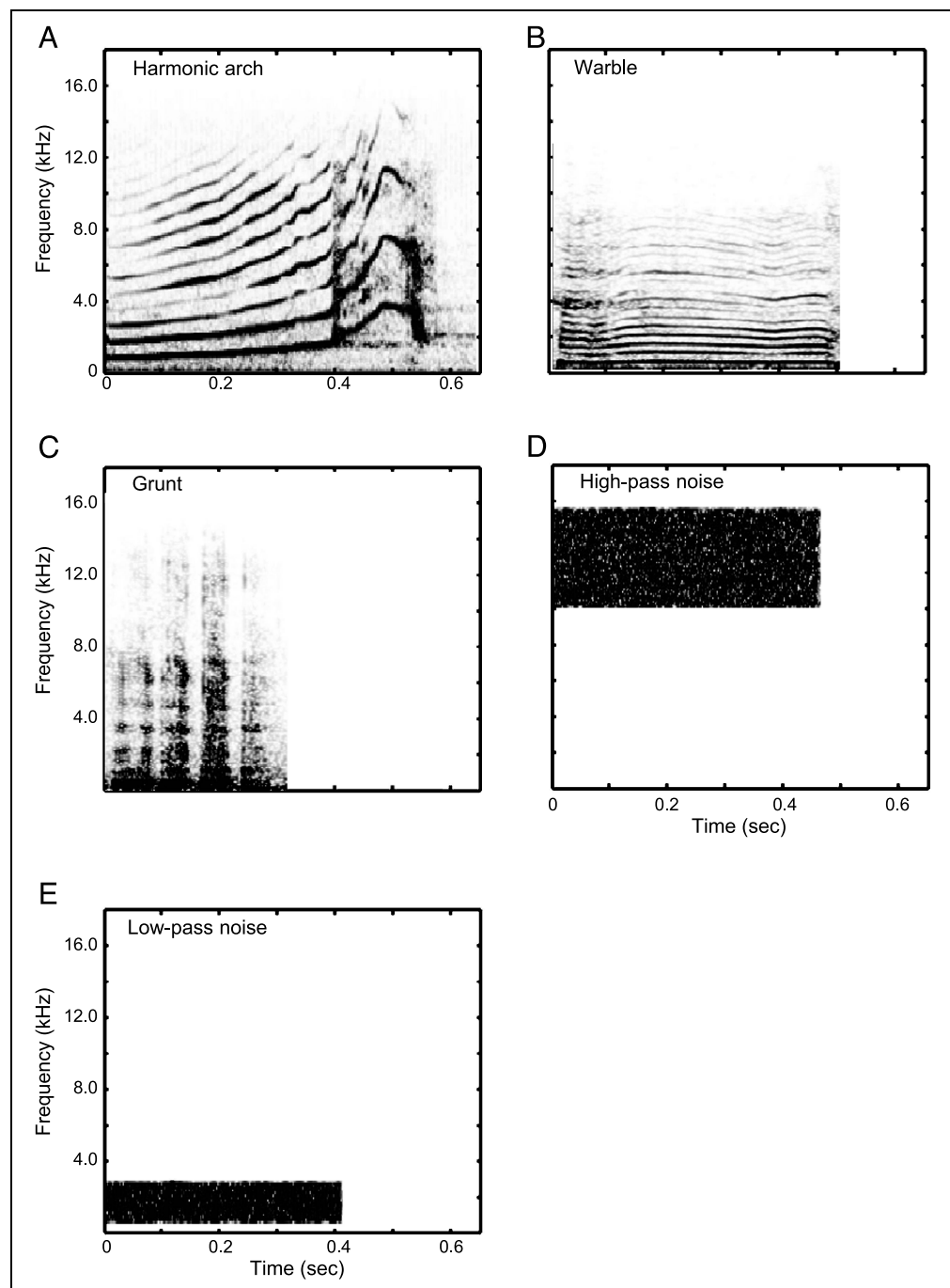
To begin to fill these gaps, we designed a series of neurophysiological experiments with rhesus macaques (*Macaca mulatta*) that extends prior work at both the neural and behavioral levels. At the neural level, we targeted the prefrontal cortex (PFC) due to its involvement in categorization following training and especially, its capacity to discriminate among relatively abstract categories (Reber, Gitelman, Parrish, & Mesulam, 2003;

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Miller et al., 2002; Strange, Henson, Friston, & Dolan, 2000). At the behavioral level, we targeted a class of species-specific vocalizations (SSVs) produced in the context of food. These calls are acoustically variable and prior work in both the field and laboratory reveals that rhesus discriminate between them on the basis of relatively abstract categories as opposed to raw perceptual features. Specifically, rhesus categorize food-related calls (Hauser & Marler, 1993a, 1993b) on the basis of differences in their function (Gifford, Hauser, & Cohen, 2003; Hauser, 1998). “Harmonic arches” and “warbles,” despite having different acoustic properties (Figure 1A

and B), are categorized by rhesus as being functionally equivalent as both transmit information about the discovery of rare, high-quality foods. In contrast, “grunts,” which have different acoustic properties than harmonic arches and warbles, belong to a different functional category than harmonic arches/warbles as they transmit information about the discovery of common, low-quality foods (Figure 1C). As noted by several investigators working on primate semantically significant vocalizations, evidence in favor of encoding functionally referential information about external objects and events (e.g., food quality) in no way denies the encoding of

Figure 1. Stimulus spectrograms. Spectrographic representations of exemplars of SSV (A–C) and band-pass noise (D, E).



affective information. In the case of food-associated calls, this is undoubtedly the case, and prior work suggests that call rate may encode information about the motivational state of the caller (Hauser, 2000).

In order to explore the role of the PFC in “spontaneous categorization,” as opposed to its involvement in categorization following training, we modeled this neurophysiological study on our previous behavioral studies (Gifford et al., 2003; Hauser, 1998) that probed how monkeys spontaneously categorize food calls. The goal of this study was to assess the extent to which the PFC represents the relatively abstract distinctions between these food calls. The particular cortical locus of our study was the ventral prefrontal cortex (vPFC). We focused on the vPFC because it receives input from regions of the auditory cortex (Hackett, Stepniewska, & Kaas, 1999; Romanski, Bates, & Goldman-Rakic, 1999; Romanski, Tian, et al., 1999) that respond to the unique acoustic features of rhesus vocalizations (Tian, Reser, Durham, Kustov, & Rauschecker, 2001).

We found that vPFC activity, on average, did not differentiate between food calls that were associated with the same functional category, despite having different acoustic properties. In contrast, vPFC activity differentiated between food calls associated with different functional classes. These results provide the first evidence that in the absence of (laboratory-based operant) training, the PFC is involved in the recognition and discrimination of natural categories, and that the vPFC specifically is an important processing stage in the representation of meaningful vocalizations.

RESULTS

We recorded from 97 vPFC neurons in two rhesus monkeys. Of these 97 neurons, 71 were defined as “auditory” if they had a mean firing rate that was significantly different (t test, $p < .05$) during auditory-stimulus presentation than the 500-msec period prior to auditory-stimulus presentation. Activity from 53 of these vPFC neurons were recorded when monkeys listened to food SSVs presented in two different contexts (see Methods for more details). During the “repetitive-presentation” context, we presented a single SSV multiple times followed by a single presentation of a “test” SSV exemplar. The relationship between the “repeated” and test exemplar was varied so that we could test whether vPFC neurons code transitions between (1) SSVs that belong to the same acoustic class, (2) SSVs that belong to different acoustic classes but transmit the same food-quality information, or (3) SSVs that belong to different acoustic classes and transmit different types of food-quality information. During the “random-presentation” context, the test and repeated SSV exemplars were presented in random order interleaved between presentations of other auditory stimuli, and

trials of a saccade task. Of the vPFC neurons tested using SSVs as the repeated and test exemplars, the responses of 32 vPFC neurons were recorded during all three transitions of the repetitive-presentation context and the corresponding random-presentation context. Of the remaining 21 neurons, 11 were tested with transitions between grunts and harmonic arches. Ten neurons were tested with transitions between warbles and harmonic arches. As a control, an additional 18 vPFC neurons were recorded when band-pass noise was the repeated and test exemplars during both the repetitive-presentation context and the corresponding random-presentation context.

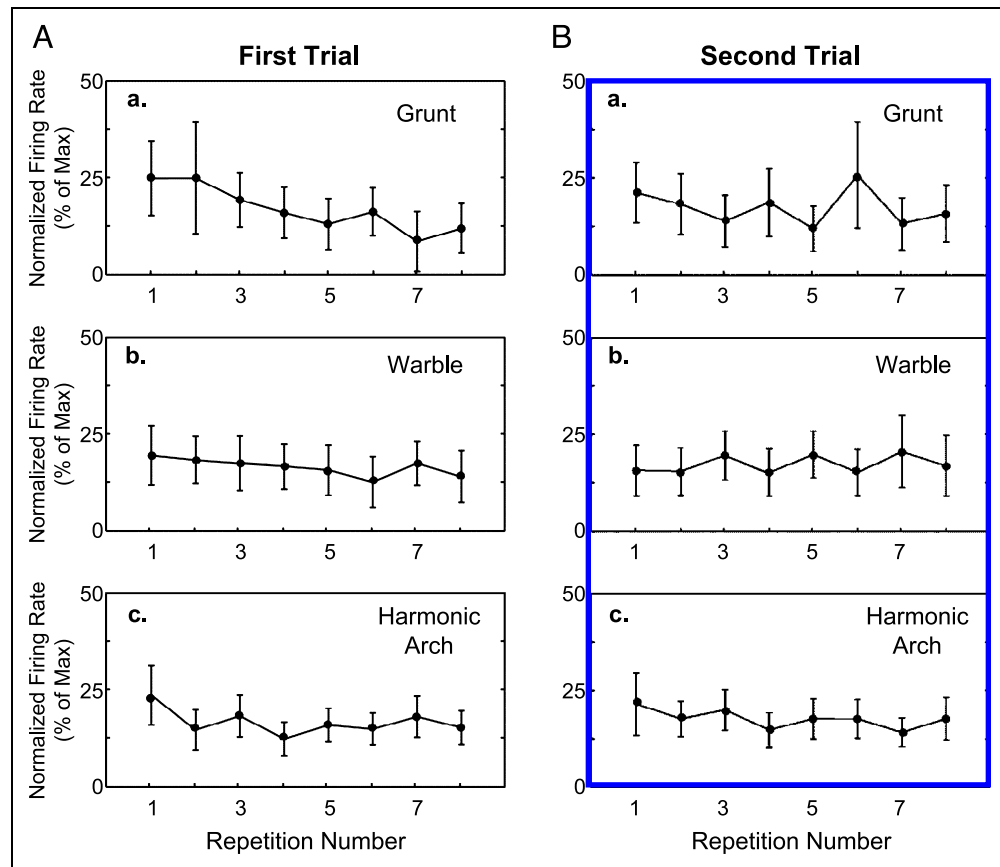
vPFC Responses to the Repeated SSV Exemplars during the Repetitive-presentation Context

In a first series of analyses, we tested whether, at a population level, vPFC activity was systematically modulated by subsequent presentations of the repeated exemplar during the repetitive-presentation context (see Methods). The results of this analysis are shown in Figure 2. The plots in Figure 2A were generated from data collected during the first trial of the repetitive-presentation context. For each of these plots, a repeated-measures ANOVA indicated that the population firing rate did not reliably change ($p > .05$) as a function of repetition number. When we analyzed the data generated during the second trial of the repetitive-presentation context (Figure 2B), we also found that the population firing rate did not reliably change (repeated-measures ANOVA, $p > .05$) with repetition number.

vPFC Responses to the Test SSV Exemplars during the Repetitive-presentation Context

vPFC neurons were not modulated by transitions between SSVs that transmitted the same food-quality information. However, they were modulated by transitions between SSVs that transmitted different types of food-quality information. The time-varying population responses are shown in Figure 3. When both SSVs belonged to the same acoustic class, and thus, transmitted the same food-quality information, the population response was not modulated preferentially by transitions from the repeated SSV to the test SSV (Figure 3A). The population response when both the repeated and test SSV exemplars were harmonic arches is shown in Figure 3Aa, when both were grunts in Figure 3Ab, and when both were warbles in Figure 3Ac. Specifically, the population response was not reliably different ($p > .05$) during the 300-msec interval that followed onset of the test SSV in the repetitive-presentation context than during the comparable period that followed onset of the identical exemplar in the random-presentation context.

Figure 2. Population firing rates of the repeated exemplars during the repetitive-presentation context. The different panels represent data collected in response to different food SSVs; the data are organized independently of the test exemplar. Each panel plots the population firing rate as a function of repetition number. The plots in A were generated from data collected during the first trial of the repetitive-presentation context, whereas those in B were generated from data collected during the second trial. The error bars reflect ± 1 standard error of the mean.



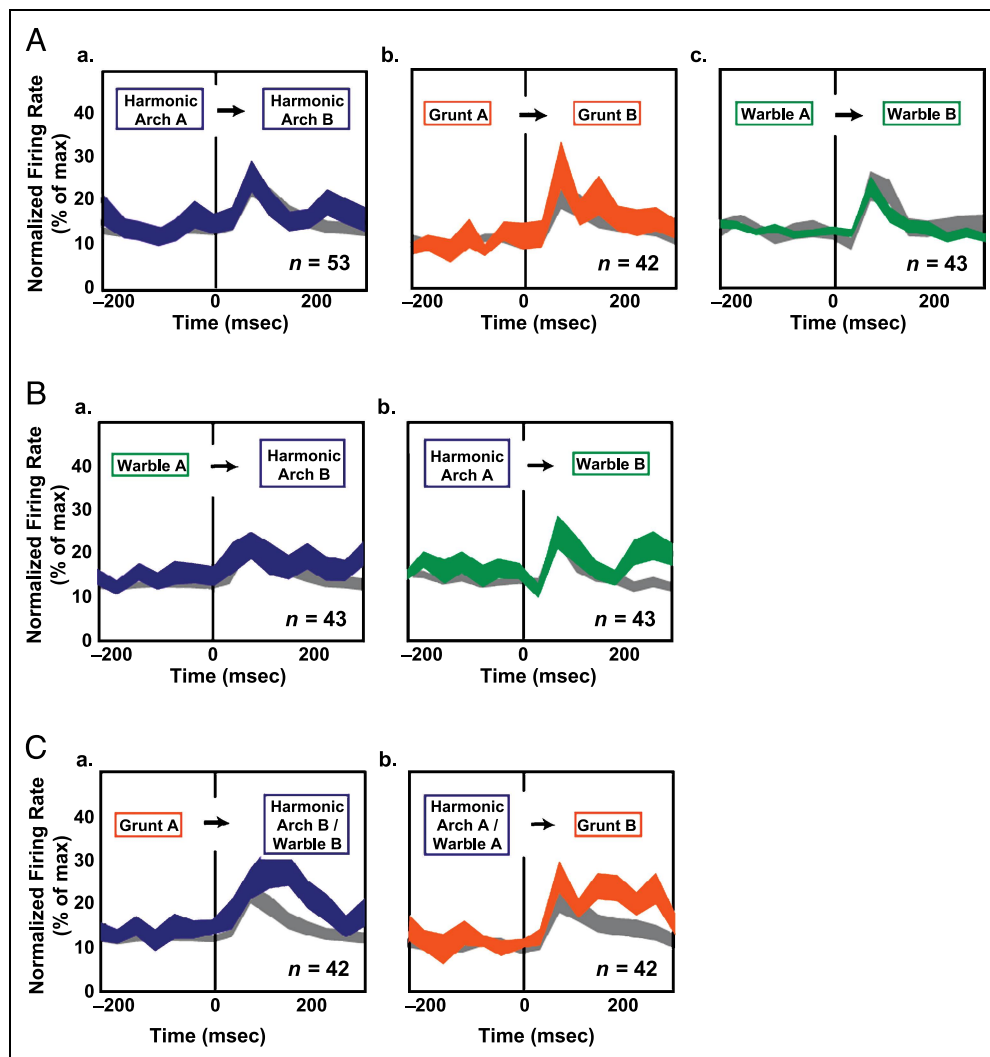
Similarly, the population response was not modulated by transitions from the repeated SSV to the test SSV when the two SSVs belonged to acoustically distinctive acoustic classes but transmitted the same food-quality information (Figure 3B). In these contrasts, the repeated SSV was a warble exemplar and the test SSV was a harmonic-arch exemplar (Figure 3Ba) or the repeated SSV was a harmonic-arch exemplar and the test SSV was a warble exemplar (Figure 3Bb). vPFC activity, on average, was not reliably different ($p > .05$) during the 300-msec interval that followed onset of the test SSV than during the comparable period that followed onset of the identical exemplar when it was presented during the random-presentation context.

However, a different pattern emerged when the repeated and test SSVs transmitted different types of food-quality information (Figure 3C). The population response when the repeated SSV exemplar was a grunt and the test exemplar was a harmonic arch or warble is shown in Figure 3Ca. Figure 3Cb shows, in contrast, the population response when the repeated exemplar was a harmonic arch or warble and the test exemplar was a grunt. For both of these conditions, the population response was significantly higher ($p < .05$) than the population response to the identical SSV during the 300-msec interval of the random-presentation context.

A second, independent analysis, which did *not* use the aforementioned population-response methodology (see Methods; Figures 2 and 3), produced a comparable result. In this analysis, on a neuron-by-neuron basis, we calculated the firing rate (number of action potentials divided by SSV duration) in response to the single presentation of the test exemplar during the repetitive-presentation context. Next, the firing rate values in response to the multiple presentations of the test exemplar during the random-presentation context were calculated. The extent to which the firing rate during the repetitive-presentation context deviated from the mean (and standard deviation) of the firing rate values during the random-presentation context was expressed as a z-score.

Figure 4 shows the distribution of z-scores for the population of recorded neurons as a function of the repeated and test exemplar. As can be seen, when the repeated and test exemplar transmitted the same food-quality information, independent of whether they originated from the same (Figure 4A) or different acoustic classes (Figure 4B), the mean z-score value was not reliably different from zero ($p > .05$). In contrast, when the repeated and test exemplar transmitted different types of food-quality information (Figure 4C), the mean z-score value was significantly greater than zero ($p < .05$).

Figure 3. Population response of vPFC activity to transitions between SSV exemplars during the repetitive-presentation context. (A) The population response to a test SSV that belonged to the same acoustic class as the repeated SSV. (B) The population response to a test SSV belonged to a different acoustic class and transmitted the same food-quality information as the repeated SSV. (C) The population response to a test SSV that transmitted different types of food-quality information as the repeated SSV. The thick colored line in each panel represents the population response to a test SSV during the repetitive-presentation context and the thick gray line in each panel represents the population response to the same test SSV during the random-presentation context. The thicknesses of the two lines indicate activity ranging two standard errors from the mean response for the population. All data are aligned relative to onset of the test SSV; the vertical black line indicates stimulus onset. In each panel's schematic, the repeated SSV exemplar is denoted by an *A* and the test SSV exemplar is denoted by a *B*.



vPFC Responses to the Test Noise Exemplars

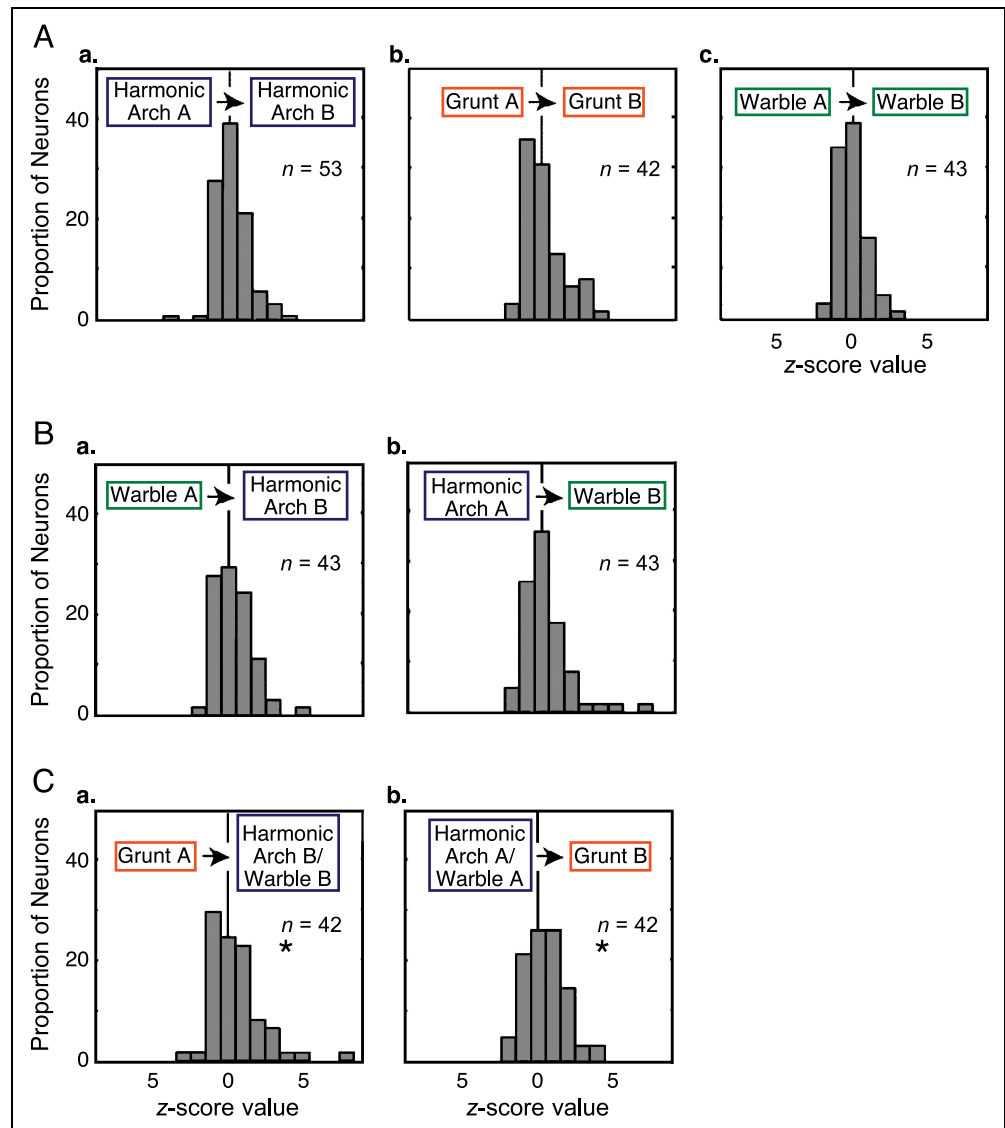
To further eliminate the possibility that vPFC neurons are simply modulated by transitions between stimuli that belong to different acoustic classes (Ulanovsky, Las, & Nelken, 2003), we examined how an additional 18 vPFC neurons were modulated by transitions between high-pass and low-pass noise exemplars. The advantage of these two classes of artificial auditory stimuli is that, although acoustically distinct, they do not transmit any meaningful different information to rhesus monkeys (Gifford et al., 2003). For these conditions, during the 300-msec interval that followed onset of the test noise-burst exemplar, the population response to the test exemplar during the repetitive-presentation context was not reliably different ($p > .05$) than the response to the test stimulus during the random-presentation context (Figure 5A and B). Also, a *z*-score analysis analogous to that described above (data not shown) indicated that for transitions between high-pass or low-pass noise ex-

emplars, the mean *z*-score value was not reliably different than zero ($p > .05$).

DISCUSSION

vPFC neurons were modulated preferentially by transitions between SSVs that transmitted meaningfully different types of information about food quality. vPFC neurons were not modulated preferentially by transitions between SSVs that were acoustically distinct nor were they modulated preferentially by artificial stimuli with different bandwidths. These properties suggest that the vPFC may be involved in those higher-order computations that underlie the spontaneous categorization of natural categories and not simple perceptual feature extraction. Below, we discuss an alternative interpretation of our results, the role that affect may play in the modulation of vPFC activity, and speculate on the role of the vPFC in acoustic categorization, including

Figure 4. Population histograms of the z-score values of firing rate. In each panel's schematic, the repeated SSV exemplar is denoted by an *A* and the test SSV exemplar is denoted by a *B*. The solid black line in each panel indicates a z-score of 0. Panels with asterisks indicate distributions with mean values that are significantly ($p < .05$) different than zero.



monkey vocalizations more specifically, and human speech more generally.

Potential Alternative Interpretation

One potential interpretation of our study is that vPFC neurons are simply modulated preferentially by the low-probability occurrence of the test exemplars during the repetitive-presentation context. Indeed, human electrophysiological studies using the “mismatch negativity” response (Näätänen, 1992) and a recent single-unit study (Ulanovsky et al., 2003) have demonstrated that low-probability auditory stimuli evoke stronger responses than commonly presented stimuli.

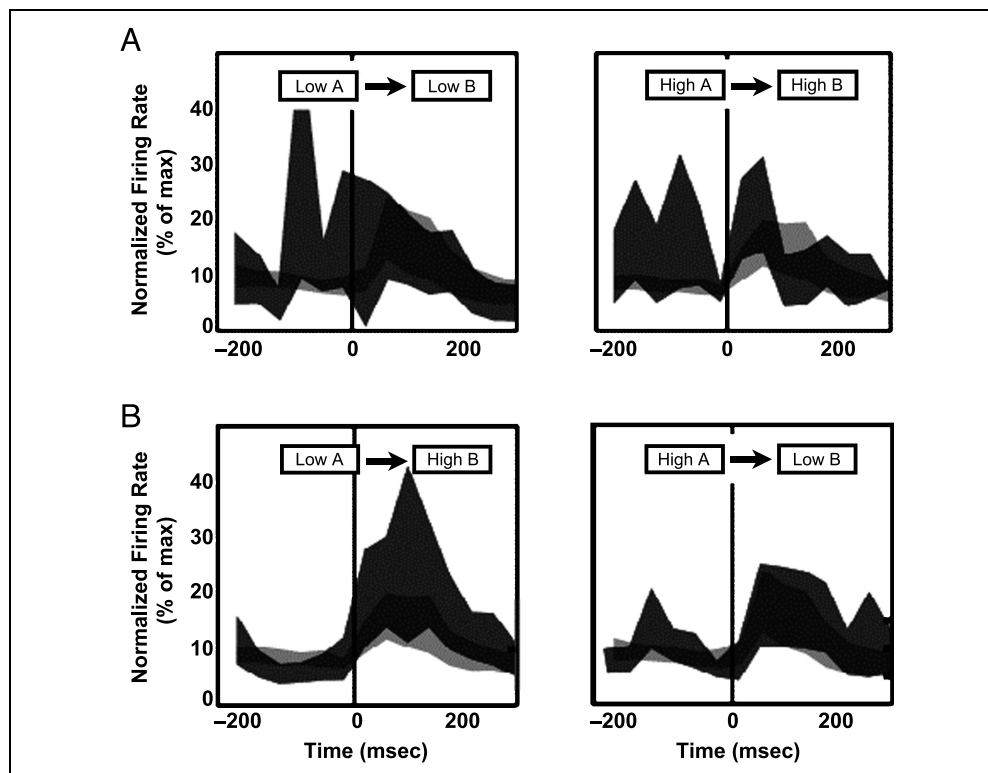
Our data do not provide support for this interpretation. First, if vPFC neurons were simply modulated by low-probability stimuli, then we would expect that vPFC activity would be preferentially modulated by any of the test exemplars that were presented during the

repetitive-presentation context. We did not, however, observe this pattern of response. Instead, we only observed preferential modulation when the repeated and test exemplars reflected a transition between meaningfully different categories: between harmonic arches/warbles and grunts or the reverse. Also, when we presented low-pass and high-pass noise as the repeated or test exemplars, vPFC activity was not preferentially modulated despite large differences in their acoustic properties; the lack of effect here is presumably because these two classes of stimuli do not belong to meaningfully different categories (Gifford et al., 2003).

Role of Affect in Modulating vPFC Activity

It is important to consider the role that the affective qualities of the food calls may play in modulating vPFC activity. Because harmonic arches and warbles are produced when rhesus encounter rare, high-quality food,

Figure 5. Population response of vPFC activity to transitions between noise test exemplars during the repetitive-presentation context. (A) The population response to a test noise exemplar that belonged to the same acoustic class as the repeated noise exemplar. (B) The population response to a test noise exemplar that belonged to a different acoustic class as the repeated noise exemplar. Same format as Figure 2 except that the thick black line in each panel represents the population response to a test noise exemplar during the repetitive-presentation context and the thick gray line in each panel represents the population response to a test noise exemplar during the random-presentation context. The thicknesses of the two lines indicate activity ranging two standard errors from the mean response for the population.



these vocalizations transmit information about relatively high affective state (Hauser & Marler, 1993a). Grunts, on the other hand, are produced when rhesus encounter common, low-quality food items (as well as other nonfood contexts) and transmit information about a relatively lower affective state. Further, when rhesus are waiting to gain access to food, those individuals that call at the highest rates tend to gain access first, and there is some evidence that as individuals approach and then consume a rare high-quality food item, such as coconut, there is a transition from grunts and coos to warbles and harmonic arches if they produce more than one call type (Hauser, 2000). Consequently, our neurophysiological results may reflect the role of the vPFC in the categorization of food-quality information, the categorization of affective state, or some combination of these two factors (Hauser, 1998; Marler, Evans, & Hauser, 1992).

Although affect may play a significant role in modulating vPFC activity, three points of evidence argue against it being the factor that is singly coded by vPFC neurons. First, the pattern of activity of the repeated exemplars during the repetitive-presentation context does not support this interpretation. If vPFC neurons only reflect the perception of the caller's affective state, we would predict that the magnitude of the vPFC response should decrease with subsequent presentations of the repeated exemplar as the affective component associated with the vocalization decreases with

repeated presentations. However, as can be seen in Figure 2, vPFC activity does not reliably decline with subsequent presentations but instead remains constant.

Second, our behavioral measures (Gifford et al., 2003; Hauser, 1998) do not correspond with the neurophysiological measures reported here. In our behavioral studies, we found that after rhesus habituated to repeated presentations of a harmonic arch (warble), habituation transferred to a test grunt or to a test warble (harmonic arch). However, following habituation to a grunt, habituation did not transfer when a test harmonic arch (warble) was presented. This asymmetric response profile was interpreted to suggest that rhesus discriminate between vocalizations based not only on the food-quality information transmitted by the vocalizations, but also on the *relative* affective qualities of this information.

The pattern observed from behavioral studies does not match our neurophysiological measures. Indeed, although vPFC neurons were preferentially modulated by SSVs that transmitted different types of information about food quality, there was no evidence that vPFC activity was differentially modulated by the relative affect of the repeated and test exemplars. Indeed, the magnitude and direction of the effect was the same regardless of whether the transition was between grunts (low-quality food) and harmonic arches/warbles (high-quality food) or between harmonic arches/warbles and grunts (Figure 3C).

Finally, indirect evidence against this affect hypothesis originates from a recent functional imaging study with rhesus monkeys (Gil-da-Costa et al., 2004). In that study, functional brain images were obtained from rhesus monkeys while they listened passively to vocalizations and other control auditory stimuli. Activity that was correlated with the relative affect of a vocalization was seen in the ventromedial prefrontal cortex and other limbic and paralimbic areas. Notably, the authors did not report affective-related activity in the vPFC.

Although we suggest that the most parsimonious interpretation of our study is that vPFC neurons are involved in categorizing the food-quality information that is transmitted by SSVs, we cannot entirely rule out an affective component completely; nor is this likely to be the case given that rhesus are indeed highly motivated by the discovery of food. Indeed, both affective and semantic components of the signal are inexorably linked. Future field studies are required to gain a fuller understanding of the function of harmonic arches, warbles, and grunts in the socioecology of rhesus, and to decompose the acoustic morphology of these signals into features that code for affect and those that code for their putative referent. Furthermore, it is important for future neurophysiological studies to collect behavioral or psychophysiological (e.g., galvanic skin responses) data that can be correlated with affective state. Finally, it will be important to record from limbic areas and other cortical areas involved in coding socially relevant signals, such as the superior temporal sulcus (Puce & Perrett, 2003), in order to further probe how affective and functionally referential information are processed in different cortical areas.

The Role of the vPFC in Vocalization and Language Processing

We propose that the vPFC is a component of the neural circuitry involved in the categorization of socially meaningful signals. This proposed role is consistent with previous hypotheses regarding this region's role in vocalization processing (Jürgens, 2002; Deacon, 1992). Indeed, previous work has suggested that the vPFC does not play a critical role in the automatic production of vocalizations. Instead, it has been suggested that the vPFC plays a prominent role in more abstract rule-based processes associated with classifying vocal signals. For instance, the vPFC might contribute to the production of "purposeful" vocalizations or perhaps to the contextually dependent inhibition of vocalization production.

How might this study relate to humans and language processing? The vPFC lies in the inferior convexity of the frontal lobe (see Figure 6C) and overlaps with Brodmann's area 45 (Romanski & Goldman-Rakic, 2002; Romanski, Bates, et al., 1999; Romanski, Tian, et al., 1999). In humans, area 45 overlaps with Broca's area,

which is traditionally thought to be involved in the motor control of speech. Recent studies, though, suggest that this cortical region may also be involved in other non-motor aspects of language processing involving computational and semantic analyses. For instance, human functional imaging studies have demonstrated that this region is activated during semantic processing and syntactic working memory (Amunts et al., 2004; Fiebach, Schleewsky, Lohmann, Von Cramon, & Friederici, 2004; Muller & Basho, 2004; Price, 1998; Demb et al., 1995). The vPFC has also been implicated in the maintenance and retrieval of abstract rules (Bunge, Kahn, Wallis, Miller, & Wagner, 2003) and the prefrontal cortex, in general, plays an important role in categorization (Reber et al., 2003; Strange et al., 2000). Given the nature of our findings, we suggest that the vPFC in macaques may represent a homologous structure (Romanski & Goldman-Rakic, 2002).

METHODS

Subjects

Two female rhesus monkeys were used in these experiments. All surgical, training, and recording were approved by the Dartmouth Institutional Animal Care and Use Committee. Neither monkey had been trained to make behavioral responses to auditory stimuli.

Experimental Setup

Behavioral training and recording sessions were conducted in a darkened room with sound-attenuating walls. The walls and floor of the room were covered with anechoic foam insulation (Sonomatt, Auralex, Indianapolis, IN). While inside the room, the monkeys were seated in a primate chair and placed in front of a stimulus array. The primate chair was placed in the center of a 1.5-m diameter, two-dimensional, magnetic coil (Riverbend Instruments, Birmingham, AL) that was part of a system monitoring the monkeys' eye position (Judge, Richmond, & Chu, 1980) at a rate of 1.0 kHz.

The stimulus array contained eight light-emitting diodes (LEDs). The LEDs were arranged in a circle centered on a "central" LED. The central LED was mounted and centered on the face of a speaker (Pyle, PLX32). Relative to the monkey's position in the room and the central LED, the other eight LEDs formed a circle with a radius of 12°. The central speaker-LED combination was in front, and at the eye level, of the monkeys.

Auditory Stimuli

We presented SSVs, band-pass noise, or ripple noise. To facilitate comparison with our behavioral data (Gifford et al., 2003; Hauser, 1998), we limited the SSVs and band-pass noise to those used in these behavioral studies.

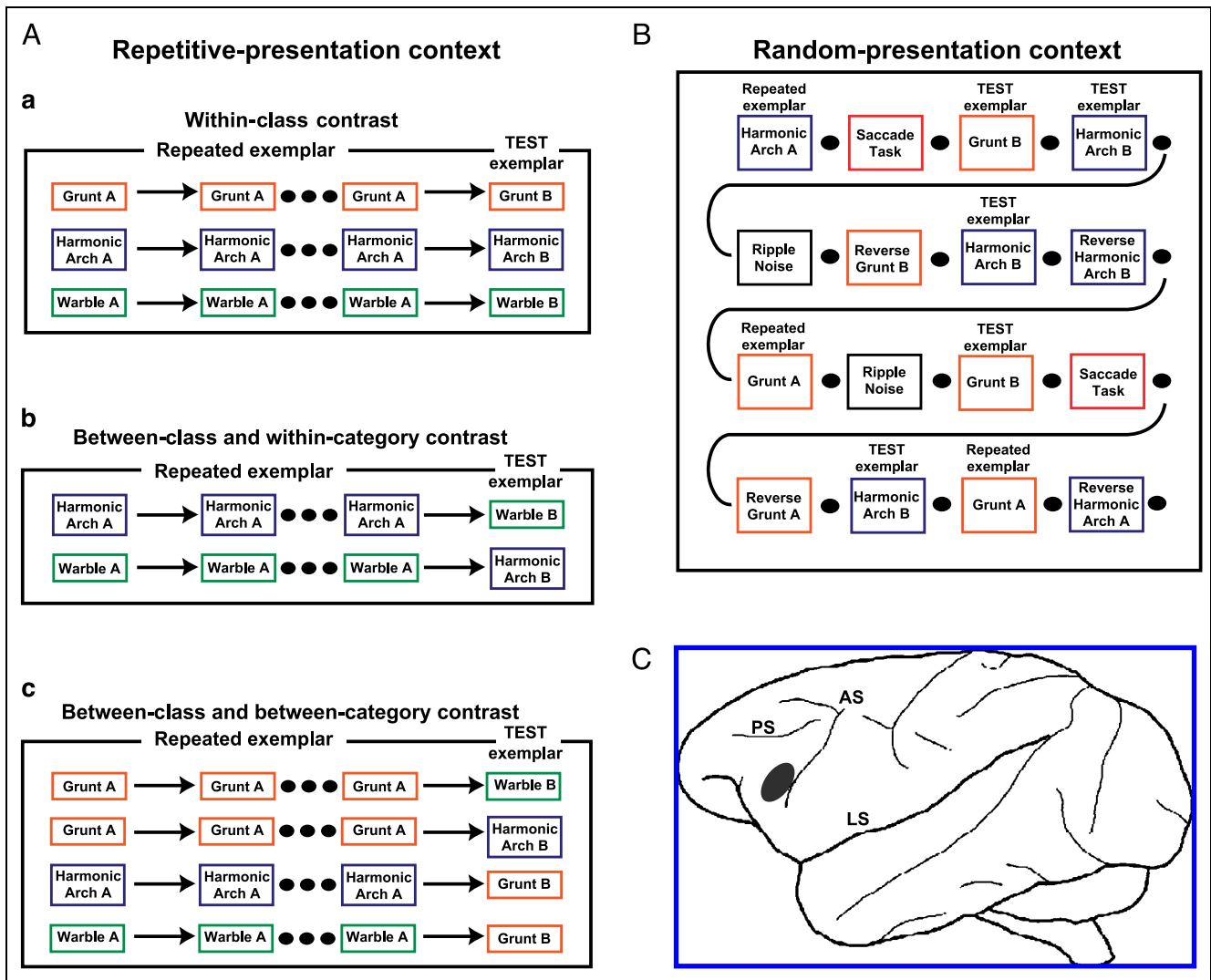


Figure 6. Stimulus-presentation contexts and rhesus brain schematic. (A) Schematic of the repetitive-presentation context. The schematics in each of the three panels illustrate examples of the presentation sequence that test transitions between the repeated and test SSVs when they (a) belong to the same acoustic classes, (b) belong to different acoustic classes and transmit the same food-quality information (same category), and (c) belong to different acoustic classes and transmit different types of food-quality information (different categories). (B) Schematic of the random-presentation context. The schematic illustrates a portion of the potential presentation order when the repeated and test exemplars are harmonic arches and the repeated and test exemplars are grunts. The repeated exemplars are denoted by an A and the test exemplars are denoted by a B. (C) A schematic of the rhesus brain illustrating the region (black ellipse) in which recorded auditory activity from two rhesus monkeys. AS = arcuate sulcus; LS = lateral sulcus; PS = principal sulcus.

SSVs originated from three different classes: harmonic arch, warble, and grunt. Exemplars of these three classes are shown in Figure 1A, B, and C. Harmonic arches and warbles have different acoustic structures but transmit the same information (discovery of rare, high-quality foods). Grunts have a different structure than harmonic arches and warbles and transmit a different type of information (discovery of common, low-quality foods) (Hauser, 1998; Hauser & Marler, 1993a). The SSVs were recorded and digitized as part of an earlier series of studies carried out with semi-free ranging rhesus monkeys (Hauser, 1998).

We used two classes of band-pass noise: “high pass” and “low pass” (Figure 1D and E). High-pass noise had a

pass-band between 9.75 and 15.75 kHz and low-pass noise had a pass-band between 0.55 and 2.8 kHz. The durations of the noise exemplars matched the distribution of the SSV durations.

Ripple noise is an artificial stimulus whose acoustic structure mimics the temporal and amplitude modulations of natural stimuli. Ripple noise was generated in the Matlab (The Mathworks, Natick, MA) programming environment using a previously described algorithm (DePireux, Simon, Klein, & Shamma, 2001).

The auditory stimuli were recorded to disk and presented through a D/A converter (DA1, Tucker Davis Technologies, Alchua, FL), amplifiers (SA1, Tucker Davis Technologies, and MPA-250, Radio Shack, Fort Worth,

TX), and transduced by a speaker. Each exemplar was presented at a sound level of 60 dB SPL.

Behavioral Tasks

Monkeys participated in the repetitive-presentation context, the random-presentation context, and the saccade task. The repetitive-presentation context (Figure 6A) tested the sensitivity of vPFC neurons to transitions from repeated presentations of one auditory stimulus to the single presentation of a different “test” auditory stimulus; this stimulus-presentation order is modeled on the order of stimulus presentation in our behavioral studies (Gifford, et al., 2003; Hauser, 1998). The random-presentation context (Figure 6B) tested the sensitivity of vPFC neurons to the identical test stimulus but without the temporal contingences established in the repetitive-presentation context. The monkeys participated in trials of the saccade task following a trial of the repetitive-presentation context and during the random-presentation context. The purpose of the saccade task was to (1) minimize temporal contingencies established during both contexts and (2) keep the monkeys in a consistent state during recording sessions.

When auditory stimuli were presented in the two contexts, the monkeys did not have any behavioral requirements nor did they receive juice rewards following stimulus offset. We chose this protocol to test the role of the vPFC in “spontaneous” discrimination of SSVs and not discriminations formed through laboratory-based operant training. The monkeys, though, were rewarded during the saccade task.

Repetitive-Presentation Context

Different instantiations of the repetitive-presentation context can be seen in Figure 6A. In general, a single trial of this context consisted of seven to nine presentations of a repeated auditory stimulus (with a 2–3 sec interstimulus interval) that was followed by a single presentation of a second (test) exemplar.

Similar to our behavioral study (Gifford et al., 2003), the repetitive-presentation context was conducted using either (1) a pair of SSVs as the repeated and test exemplars or (2) a pair of band-pass noise bursts as the repeated and test exemplars. When the repeated and test exemplars were both SSVs, we systematically varied the relationship between the repeated and test exemplars so that we could test whether vPFC neurons preferentially coded transitions between (1) SSVs that belonged to the same acoustic class (same category) (Figure 6Aa), (2) SSVs that belonged to different acoustic classes but transmitted the same food-quality information (same category) (Figure 6Ab), or (3) SSVs that belonged to different acoustic classes and transmitted different types of food-quality information (different categories) (Figure 6Ac).

Random-Presentation Context

In this context (Figure 6B), the test and repeated exemplars were also presented. However, the presentation order of these exemplars was randomized and interleaved between random presentations of ripple noise, time-reversed versions of the repeated and test exemplars, and individual trials of the saccade task. Time-reversed versions have the same complexity as the original stimuli but may be discriminated differently by rhesus (Ghazanfar, Smith-Rohrberg, & Hauser, 2001).

Saccade Task

After fixating a central LED, a peripheral LED was illuminated. After a random delay, the central LED was extinguished, signaling the monkeys to saccade to the peripheral LED. Their gaze remained at the peripheral LED for an additional 400–500 msec to be rewarded.

Recording Procedures

Single-unit extracellular recordings were obtained with tungsten microelectrodes (Frederick Haer & Co., Bوندoinham, ME) seated inside a stainless-steel guide tube. The electrode and guide tube were advanced into the brain with a hydraulic microdrive (MO-95, Narishige, East Meadow, NY). The electrode signal was amplified (MDA-4I, Bak Electronics, Mt. Airy, MD) and band-pass filtered (model 3700, Krohn-Hite) between 0.6 and 6.0 kHz. Single-unit activity was isolated using a two-window, time-voltage discriminator (Model DDIS-1, Bak Electronics). Neural events that passed through both windows were classified as originating from a single neuron. The time of occurrence of each action potential, with an accuracy of 0.01 msec, was stored for off-line analyses.

The vPFC was identified by its anatomical location (Figure 6C) and its neurophysiological properties. The vPFC is located anterior to the arcuate sulcus and area 8a and lies below the principal sulcus (Cohen, Russ, Gifford, Kiringoda, & MacLean, 2004; Romanski & Goldman-Rakic, 2002). vPFC neurons were further characterized by their strong responses to auditory stimuli (Cohen et al., 2004; Romanski & Goldman-Rakic, 2002; Newman & Lindsley, 1976).

Recording Strategy

An electrode was lowered into the vPFC. To minimize recording bias, any neuron that was isolated was examined.

Once a neuron was isolated, two exemplars from one acoustic class (e.g., harmonic arch) and two exemplars from a second, different acoustic class (e.g., warble) were randomly chosen. One exemplar from the first class and one exemplar from the second class were randomly designated as test exemplars. The other two

exemplars were designated as repeated exemplars. These four exemplars formed the basis for four different trials of the repetitive-presentation context: two trials tested within-class transitions (Figure 6Aa; e.g., both the repeated and test exemplars were warbles or both were harmonic arches) and two trials tested between-class transitions (Figures 6Ab, Ac; e.g., the repeated exemplar was a warble and the test exemplar was a harmonic arch or the repeated exemplar was a harmonic arch and the test exemplar was a warble).

After designating the exemplars, the monkeys participated in a trial of the repetitive-presentation context (Figure 6A). This was followed by a 10- to 15-min block of the saccade task. This process was repeated until the monkeys participated in all four trials of the repetitive-presentation context.

A unique and important feature of this study was that we tested vPFC activity in SSV discrimination from single-trial presentations of the SSV. We used this task design to mimic the single-trial discrimination procedures that we have used in our behavioral studies (Gifford et al., 2003; Hauser, 1998). A further concern was that neural responses to a particular test stimulus during the repetitive-presentation context may not be stationary. Indeed, although human event-related potential studies (Näätänen, 1992) and a related single-unit study (Ulanovsky et al., 2003) in an anesthetized cat suggest that this is an unlikely possibility, we chose the single-presentation strategy because we did not know whether repeated presentations of behaviorally relevant vocalizations would attenuate single-unit responses in an awake nonhuman primate.

Finally, after another block of the saccade task, the monkeys participated in the random-presentation context (Figure 6B). The stimuli in this context were the two test and repeated exemplars, their time-reversed versions, and ripple noise. In the random-presentation context, we regularly recorded activity in response to 10–20 presentations of each test exemplar.

Neural Analysis

Because a test exemplar was presented once in a trial of the repetitive-presentation context, commonly used analysis techniques that require multiple presentations of the same stimulus, such as peristimulus time histograms, were not appropriate. Instead, we used an algorithm designed to estimate each neuron's firing-rate function from a single trial (Pauluis & Baker, 2000). In brief, this algorithm detects significant ($p < .05$) changes in the time of occurrence of action potentials to create a continuous estimate of a neuron's single-trial, time-varying firing rate. This algorithm is akin to that used in previous studies to determine changes in a neuron's firing rate from single trials (Bisley, Krishna, & Goldberg, 2004; Hanes, Thompson, & Schall, 1995; Maunsell & Gibson, 1992; Legendy & Salzman, 1985).

Using this algorithm, on a neuron-by-neuron basis, we calculated the time-varying firing rate for each neuron's response to auditory stimuli during the repetitive- and random-presentation contexts.

Next, we used these firing-rate functions to generate a time-varying "population response." To account for differences in the magnitude or variance of these functions, the firing rates for each neuron were first normalized. In this normalization, on a neuron-by-neuron basis, we first determined the mean firing rate value for all auditory-stimulus presentations, independent of presentation context, and then scaled each firing rate function relative to this mean value. The population response was formed by averaging together these normalized firing rate functions as a function of the auditory stimulus and the presentation context. In addition, we calculated the "population firing rate." The population firing rate was formed first by dividing the normalized firing rate functions by a time period of interest (e.g., repeated-exemplar duration), on a neuron-by-neuron basis, and then averaging these values together as a function of the auditory stimulus and the presentation context.

Acknowledgments

We thank H. Hersh, N. Ulanovsky, and A. Ghazanfar for helpful discussions and comments on previous versions of the manuscript; T. Laroche for assistance with MRI; and A. Underhill for her exceptional technical support. YEC was supported by grants from the Whitehall Foundation, NIH, and a Burke Award. MDH was supported by grants from the NSF, the Leakey Foundation, McDonnell Foundation and Harvard's Mind, Brain & Behavior Program, the NIH (NCR grant CM-5-P40RR003640-13 award to the Caribbean Primate Research Center), and the University of Puerto Rico-Medical Sciences Campus for financial support for this study.

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REFERENCES

- Amunts, K., Weiss, P. H., Mohlberg, H., Pieperhoff, P., Eickhoff, S., Gurd, J. M., Marshall, J. C., Shah, N. J., Fink, G. R., & Zilles, K. (2004). Analysis of neural mechanisms underlying verbal fluency in cytoarchitectonically defined stereotaxic space—The roles of Brodmann areas 44 and 45. *Neuroimage*, *22*, 42–56.
- Bisley, J. W., Krishna, B. S., & Goldberg, M. E. (2004). A rapid and precise on-response in posterior parietal cortex. *Journal of Neuroscience*, *24*, 1833–1838.
- Bunge, S. A., Kahn, I., Wallis, J. D., Miller, E. K., & Wagner, A. D. (2003). Neural circuits subserving the retrieval and maintenance of abstract rules. *Journal of Neurophysiology*, *90*, 3419–3428.
- Cohen, Y. E., Russ, B. E., Gifford, G. W., 3rd, Kiringoda, R., & MacLean, K. A. (2004). Selectivity for the spatial and nonspatial attributes of auditory stimuli in the ventrolateral prefrontal cortex. *Journal of Neuroscience*, *24*, 11307–11316.
- Deacon, T. W. (1992). Cortical connections of the inferior arcuate sulcus cortex in the macaque brain. *Brain Research*, *573*, 8–26.

- Demb, J. B., Desmond, J. E., Wagner, A. D., Vaidya, C. J., Glover, G. H., & Gabrieli, J. D. (1995). Semantic encoding and retrieval in the left inferior prefrontal cortex: A functional MRI study of task difficulty and process specificity. *Journal of Neuroscience*, *15*, 5870–5878.
- DePireux, D. A., Simon, J. Z., Klein, D. J., & Shamma, S. A. (2001). Spectro-temporal response field characterization with dynamic ripples in ferret primary auditory cortex. *Journal of Neurophysiology*, *85*, 1220–1234.
- Fiebach, C. J., Schlesewsky, M., Lohmann, G., Von Cramon, D. Y., & Friederici, A. D. (2004). Revisiting the role of Broca's area in sentence processing: Syntactic integration versus syntactic working memory. *Human Brain Mapping*, *24*, 79–91.
- Freedman, D. J., Riesenhuber, M., Poggio, T., & Miller, E. K. (2001). Categorical representation of visual stimuli in the primate prefrontal cortex. *Science*, *291*, 312–316.
- Ghazanfar, A. A. (2003). *Primate audition: Ethology and neurobiology*. New York: CRC Press.
- Ghazanfar, A. A., Smith-Rohrberg, D., & Hauser, M. D. (2001). The role of temporal cues in rhesus monkey vocal recognition: Orienting asymmetries to reversed calls. *Brain, Behavior and Evolution*, *58*, 163–172.
- Gifford, G. W., III, Hauser, M. D., & Cohen, Y. E. (2003). Discrimination of functionally referential calls by laboratory-housed rhesus macaques: Implications for neuroethological studies. *Brain, Behavior and Evolution*, *61*, 213–224.
- Gil-da-Costa, R., Braun, A., Lopes, M., Hauser, M. D., Carson, R. E., Herscovitch, P., & Martin, A. (2004). Toward an evolutionary perspective on conceptual representation: Species-specific calls activate visual and affective processing systems in the macaque. *Proceedings of the National Academy of Sciences, U.S.A.*, *101*, 17516–17521.
- Hackett, T. A., Stepniewska, I., & Kaas, J. H. (1999). Prefrontal connections of the parabelt auditory cortex in macaque monkeys. *Brain Research*, *817*, 45–58.
- Hanes, D. P., Thompson, K. G., & Schall, J. D. (1995). Relationship of presaccadic activity in frontal eye field and supplementary eye field to saccade initiation in macaque: Poisson spike train analysis. *Experimental Brain Research*, *103*, 85–96.
- Hauser, M. D. (1998). Functional referents and acoustic similarity: Field playback experiments with rhesus monkeys. *Animal Behaviour*, *55*, 1647–1658.
- Hauser, M. D. (2000). Primate vocalizations as reflections of emotion and thought. In N. Wallin, B. Merker, & S. Brown (Eds.), *The origins of music* (pp. 77–102). Cambridge: MIT Press.
- Hauser, M. D., & Marler, P. (1993a). Food-associated calls in rhesus macaques (*Macaca mulatta*): 1. Socioecological factors influencing call production. *Behavioral Ecology*, *4*, 194–205.
- Hauser, M. D., & Marler, P. (1993b). Food-associated calls in rhesus macaques (*Macaca mulatta*): II. Costs and benefits of call production and suppression. *Behavioral Ecology*, *4*, 206–212.
- Judge, S. J., Richmond, B. J., & Chu, F. C. (1980). Implantation of magnetic search coils for measurement of eye position: An improved method. *Vision Research*, *20*, 535–538.
- Jürgens, U. (2002). Neural pathways underlying vocal control. *Neuroscience and Biobehavioral Reviews*, *26*, 235–258.
- Legendy, C. R., & Salzman, M. (1985). Bursts and recurrences of bursts in the spike trains of spontaneously active striate cortex neurons. *Journal of Neurophysiology*, *53*, 926–939.
- Marler, P., Evans, C. S., & Hauser, M. D. (1992). Animal signals? Reference, motivation, or both? In H. Papoušek, U. J. Jürgens, & M. Papoušek (Eds.), *Nonverbal vocal communication: Comparative and developmental approaches* (pp. 66–86). Cambridge, UK: Cambridge University Press.
- Maunsell, J. H., & Gibson, J. R. (1992). Visual response latencies in striate cortex of the macaque monkey. *Journal of Neurophysiology*, *68*, 1332–1344.
- Miller, E., & Cohen, J. D. (2001). An integrative theory of prefrontal cortex function. *Annual Review of Neuroscience*, *24*, 167–202.
- Miller, E. K., Freedman, D. J., & Wallis, J. D. (2002). The prefrontal cortex: Categories, concepts, and cognition. *Philosophical Transactions of the Royal Society of London, Series B, Biological Science*, *29*, 1123–1136.
- Muller, R. A., & Basho, S. (2004). Are nonlinguistic functions in “Broca's area” prerequisites for language acquisition? FMRI findings from an ontogenetic viewpoint. *Brain and Language*, *89*, 329–336.
- Näätänen, R. (1992). *Attention and brain function*. Hillsdale, NJ: Erlbaum.
- Newman, J. D., & Lindsley, D. F. (1976). Single unit analysis of auditory processing in squirrel monkey frontal cortex. *Experimental Brain Research*, *25*, 169–181.
- Nieder, A., Freedman, D. J., & Miller, E. K. (2002). Representation of the quantity of visual items in the primate prefrontal cortex. *Science*, *297*, 1708–1711.
- Pauluis, Q., & Baker, S. N. (2000). An accurate measure of the instantaneous discharge probability, with applications to unitary joint-event analysis. *Neural Computation*, *12*, 647–699.
- Price, C. J. (1998). The functional anatomy of word comprehension and production. *Trends in Cognitive Sciences*, *2*, 281–288.
- Puce, A., & Perrett, D. (2003). Electrophysiology and brain imaging of biological motion. *Philosophical Transactions of the Royal Society of London, Series B, Biological Science*, *358*, 435–445.
- Reber, P. J., Gitelman, D. R., Parrish, T. B., & Mesulam, M. M. (2003). Dissociating explicit and implicit category knowledge with fMRI. *Journal of Cognitive Neuroscience*, *15*, 574–583.
- Rolls, E. T. (2004). Invariant object and face recognition. In L. M. Chalupa & J. S. Werner (Eds.), *The visual neurosciences* (pp. 1165–1178). Boston: MIT Press.
- Romanski, L. M., Bates, J. F., & Goldman-Rakic, P. S. (1999). Auditory belt and parabelt projections to the prefrontal cortex in the rhesus monkey. *Journal of Comparative Neurology*, *403*, 141–157.
- Romanski, L. M., & Goldman-Rakic, P. S. (2002). An auditory domain in primate prefrontal cortex. *Nature Neuroscience*, *5*, 15–16.
- Romanski, L. M., Tian, B., Fritz, J., Mishkin, M., Goldman-Rakic, P. S., & Rauschecker, J. P. (1999). Dual streams of auditory afferents target multiple domains in the primate prefrontal cortex. *Nature Neuroscience*, *2*, 1131–1136.
- Sawamura, H., Shima, K., & Tanji, J. (2002). Numerical representation for action in the parietal cortex of the monkey. *Nature*, *415*, 918–922.
- Strange, B. A., Henson, R. N., Friston, K. J., & Dolan, R. J. (2000). Brain mechanisms for detecting perceptual, semantic, and emotional deviance. *Neuroimage*, *12*, 425–433.
- Tian, B., Reser, D., Durham, A., Kustov, A., & Rauschecker, J. P. (2001). Functional specialization in rhesus monkey auditory cortex. *Science*, *292*, 290–293.
- Ulanovsky, N., Las, L., & Nelken, I. (2003). Processing of low-probability sounds by cortical neurons. *Nature Neuroscience*, *6*, 391–398.

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