Neuron
Article

Sensitivity to Complex Statistical Regularities in Rat Auditory Cortex

Amit Yaron,[1,2,3] Itai Hershenhoren,[1,2,3] and Israel Nelken[1,2,3,4,*]
[1]Department of Neurobiology, Institute of Life Sciences, Jerusalem 91904, Israel
[2]The Interdisciplinary Center for Neural Computation, The Hebrew University of Jerusalem, Jerusalem 91904, Israel
[3]The Edmond and Lily Safra Center for Brain Sciences, Jerusalem 91904, Israel
[4]Present address: Department of Neurobiology, The Alexander Silberman Institute of Life Sciences, Edmond J. Safra campus, Hebrew University, Jerusalem 91904, Israel
*Correspondence: israel@cc.huji.ac.il
http://dx.doi.org/10.1016/j.neuron.2012.08.025

SUMMARY

Neurons in auditory cortex are sensitive to the probability of stimuli: responses to rare stimuli tend to be stronger than responses to common ones. Here, intra- and extracellular recordings from the auditory cortex of halothane-anesthetized rats revealed the existence of a finer sensitivity to the structure of sound sequences. Using oddball sequences in which the order of stimulus presentations is periodic, we found that tones in periodic sequences evoked smaller responses than the same tones in random sequences. Significant reduction in the responses to the common tones in periodic relative to random sequences occurred even when these tones consisted of 95% of the stimuli in the sequence. The reduction in responses paralleled the complexity of the sound sequences and could not be explained by short-term effects of clusters of deviants on succeeding standards. We conclude that neurons in auditory cortex are sensitive to the detailed structure of sound sequences over timescales of minutes.

INTRODUCTION

To survive in an ever-changing environment, creatures must be able to predict what is going to occur next in order to plan their reactions appropriately. The natural world is not random: natural stimuli are highly redundant due to the physical properties of the world. For example, Ruderman and Bialek (1994) showed that there are strong statistical dependencies between luminance values in different pixels of natural scenes, and Nelken et al. (1999) found strong statistical regularities in natural sounds. In the presence of such regularities, the past can help predict the future.

A way to do this is to use information from the past for building a statistical model of the environment (Winkler et al., 2009). The model is then used for predicting the future and interpreting it. Indeed, numerous studies have demonstrated sensitivity of neural activity to the overall probability of a stimulus, an important characteristic of the statistical structure of stimulation sequences. Since their introduction as a tool for studying single neurons in the auditory system by Ulanovsky et al. (2003), oddball sequences have been used to study probability sensitivity in a number of animal models and at different levels of auditory pathway, including the inferior colliculus of rats (Malmierca et al., 2009; Zhao et al., 2011), the auditory thalamus of mice (Anderson et al., 2009) and rats (Antunes et al., 2010), and auditory cortex of rats (Farley et al., 2010; Taaseh et al., 2011; von der Behrens et al., 2009). These studies demonstrated that the probability of appearance of a stimulus affects the responses of many neurons at least to the same degree as the physical characteristics of the stimulus such as its frequency. In fact, cortical responses to rare tones embedded in sequences of common tones are larger than expected from a model of adaptation in narrow frequency channels, suggesting the presence of true deviance sensitivity in auditory cortex (Taaseh et al., 2011).

Oddball sequences are most commonly constructed by selecting the sounds essentially randomly given their probabilities. However, the statistical structure of the auditory environment is richer than that of such random sequences. For example, language and music incorporate sequential dependencies, so that the probability of a sound depends much more subtly on the recent auditory past. The goal of the current study was to examine the sensitivity of neuronal responses to statistical contexts that include sequential dependence. We contrasted neuronal responses to sequences in which the overall probability of the rare tone was identical but the rare tone itself was either randomly presented or appeared periodically among the common tones. If the periodic order can be recognized, periodic sequences should evoke less surprise, and therefore smaller neuronal responses. Our data, from intracellular and extracellular recordings in the auditory cortex of anesthetized rats, suggest that neurons are sensitive to the periodic order of presentations, even for periods of length 20 (rare tone probability of 0.05).

RESULTS

We recorded responses in the left auditory cortex of halothane-anesthetized rats to sounds presented monaurally to their right ear. We used both intracellular recordings (n = 17 neurons in

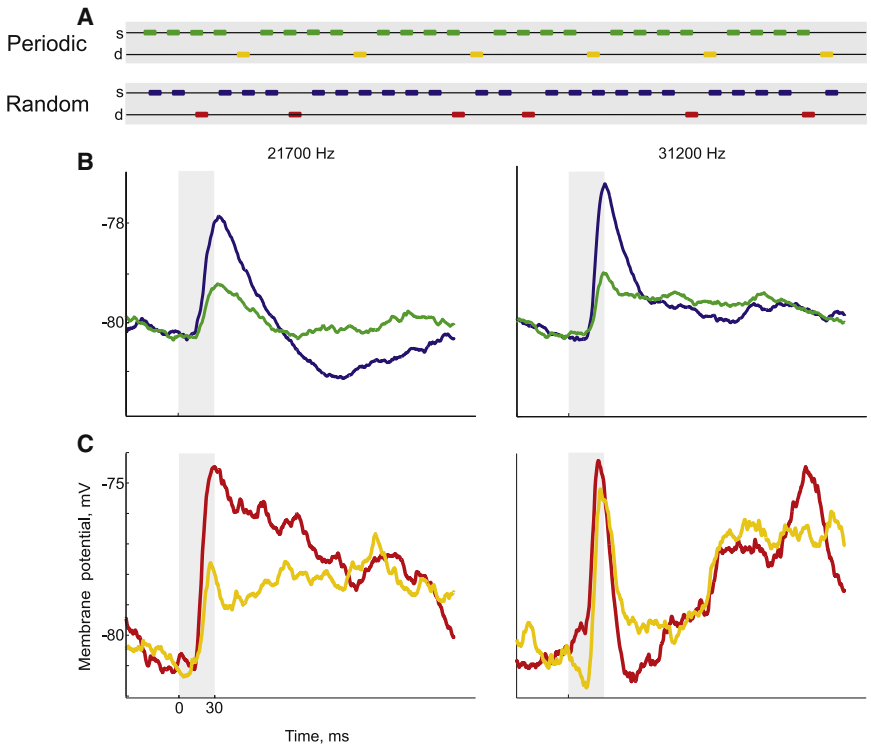

Figure 1. Periodic and Random Sequences

(A) Schematic representation of the two sequences used in this study. The sequences are shown for deviant probability of 20%; a high deviant probability is used for clarity of illustration, but note that in (B) and (C) deviant probability was 5%. In the Random condition, the sequence of tones consisted of a random permutation of f1 and f2 tones, with the overall number of each set according to its probability. For the periodic condition the deviant tone appears once after every 1/p-1 standards.

(B) The average membrane potential of an auditory cortex neuron in response to the two frequencies in the standard condition (f1 = 21.7 kHz [left] and f2 = 31.2 kHz [right], deviant probability = 5%). The color scheme corresponds to the one used in (A). The average response to both frequencies was significantly smaller in the Periodic than in the Random condition.

(C) The average membrane potential of the same neuron as in (B) in response to the two frequencies in the deviant condition. The color scheme corresponds to the one used in (A). The average response to f1 in the Periodic condition was smaller than in the Random condition. However, the responses to f2 were about the same in both conditions.

16 rats) and extracellular recordings (n = 180 recording locations in 12 rats) to collect membrane potentials, local field potentials (LFPs), and multiunit activity (MUA). We analyzed, for each recording location, the responses to the two frequencies composing the two tone sequences separately. Significant responses occurred for both tones in all neurons recorded intracellularly (34 combinations of tone frequencies and neurons). The extracellular recordings resulted in 360 combinations of tone frequency and recording locations. Out of these, 309 of the LFP recordings and 196 of the MUA recordings had a significant response in at least one of the conditions, and only these are further analyzed below.

Neurons in Auditory Cortex Respond Differentially to Random and Periodic Tone Sequences

We presented two types of oddball sequences composed of pure tones of two frequencies (f1 and f2; 500 stimulus presentations in total) with a frequency difference f2/f1 = 1.44. The two frequencies were selected based on a previous measurement of the frequency response area. They usually straddled best frequency, and were selected to evoke about the same response level. All intracellular recordings have been performed with the probability of the rare tone set to 5% (25 out of 500 stimulus presentations). In one of the sequences, the order of stimulus presentation was random and in the other one the order was periodic, with the deviant tone appearing at every 20th position. A schematic illustration of the two sequences appears in Figure 1A. Note that in Figure 1A, the deviant probability is 20% to make the graphical display clearer. Each tone frequency was tested in four different conditions (Periodic and Random; standard and deviant).

The responses of a neuron recorded intracellularly are displayed in Figures 1B and 1C. In all tests of this neuron, f1 was 21.7 kHz and f2 was 31.2 kHz. In the Random-f2 sequence, f1 was played 475 times (95%, the "standard") and f2 was played 25 times (5%, the "deviant"), but the order of the stimuli was random. In the Random-f1 sequence, the probabilities of the two tones were switched, so that f1 was played 25 times and f2 was played 475 times. These two sequences are similar to those used in other studies of stimulus-specific adaptation (e.g., Taaseh et al., 2011, who used exactly the same stimulation parameters in the same preparation with similar results). In the two Periodic sequences, the probabilities of the two tones were the same as in the Random sequences, but the order of the stimuli was periodic: for example, in the Periodic-f2 sequence, f1 was played 19 times, then f2 was played once, and this pattern was repeated 25 times.

Although the probabilities of the two tones were the same in the corresponding Random and Periodic sequences, the responses displayed in Figure 1B were not. The average response (here and elsewhere, corrected for baseline level) to both frequencies, when standard, was significantly smaller in the Periodic than in the Random condition [one-tailed t test on the average response, $t(f1) = 3.51$, $t(f2) = 4.93$, $df = 948$, $p(f1) = 2.30*10^{-4}$, $p(f2) = 4.81*10^{-7}$]. When deviant (Figure 1C), the average response to f1 in the Periodic condition was smaller than in the Random condition (one-tailed t test, $t = 2.96$, $df = 48$, $p = 0.002$). However, the responses to f2 were about the same in both conditions (one-tailed t test, $t = 0.33$, $df = 48$, $p = 0.373$).

A summary of the results from all neurons recorded intracellularly (n = 17 neurons, 34 individually tested tone frequencies) is

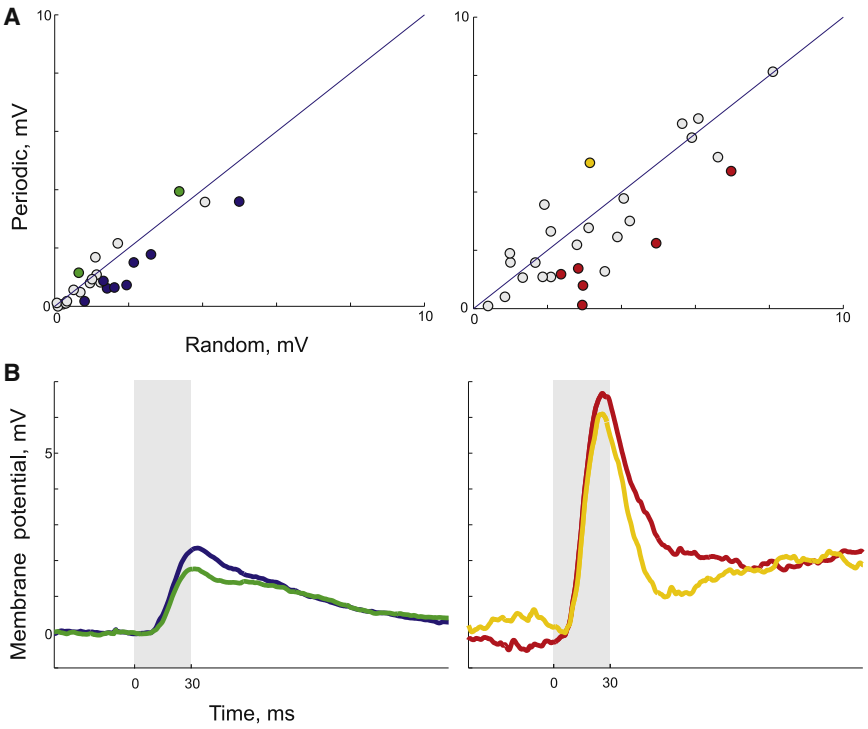

Figure 2. Population Summary of Intracellular Recordings in the Periodic and Random Conditions

(A) The average responses (above baseline) of single neurons in the Random condition (abscissa) versus the responses of the same neurons in the Periodic condition (ordinate). Each point represents one of the frequencies (either f1 or f2). Filled points correspond to cases in which the responses in the Periodic and Random conditions were significantly different from each other (two-tailed t test on response size, $p < 0.05$). Left: standards, right: deviants. The responses to standards and deviants in the Random condition were significantly larger than the responses in the Periodic condition in a substantial number of cases, while the reverse occurred less frequently. (B) The population averages of the responses to the standard (left) and deviant (right) tones for the Periodic and Random sequences. The average response to both standards and deviants in the Periodic condition is significantly smaller than in the Random condition.

shown in Figure 2. The left panel of Figure 2A compares the responses to standards in the Periodic and Random conditions, and the right panel compares the responses to the deviants in the two conditions. Each neuron is represented twice in each panel, once for each frequency. The responses in the Random condition are represented along the abscissa, while the responses in the Periodic condition are represented along the ordinate. Colored points correspond to cases in which the statistical test comparing the responses in the Periodic and Random sequences showed a significant difference ($p < 0.05$). The responses to standards and deviants in the Random condition were significantly larger than the responses in the Periodic condition in a substantial number of cases, while the reverse occurred less frequently. Overall, the number of cases in which the response was larger in the Random condition than in the Periodic condition was 26/34 (76%) for the standard condition and 74% (25/34) for the deviant condition. Figure 2B shows the population averages of the responses to the standard and deviant tones for the Periodic and Random sequences. The average response to both standards and deviants in the Periodic condition was significantly smaller than in the Random conditions (standards: $t = 3.02$, $df = 33$, $p = 0.0048$; deviants: $t = 3.34$, $df = 33$, $p = 0.0021$).

Differential Responses to Random and Periodic Sequences: Effect of Tone Probability

In order to study the reflection of sequence type in population responses as well as in single neurons, we collected LFP and MUA responses, which can be simultaneously recorded across the auditory cortex by using multiple electrodes. Examples of LFP and MUA responses in three recording sites are shown in Figure 3, for deviant probability of 0.05 (as in Figures 1 and 2). In all examples, the responses to standards in the Periodic condition tended to be smaller than in the Random condition. The differences between the responses to the same tones used as deviants were overall smaller and less consistent.

The use of extracellular recordings made it possible to record for longer times, and to test the influence of additional parameters on the responses. We therefore recorded the responses to the Random and Periodic sequences with deviant probability of 10% and 20% in addition to 5%. The overall results are summarized in Figure 4. Results are plotted on a log-log scale where each point represents the average response to one of the tones in one of the recording locations in the Random condition (abscissa) versus the average response to the same tone in the Periodic condition (ordinate). The colored points represent cases in which the response to one of the conditions was significantly different ($p < 0.05$) from the response to the other condition.

The responses to the sequences with deviant probability of 5% are presented in the left column of Figure 4. In the LFP recordings (Figure 4B, left), the responses to standard tones in the Random condition were mostly larger than in the Periodic condition (99/124 frequencies and recording locations, 80%). Furthermore, the average response to standards in the Random condition was larger than the response to standards in the Periodic condition (one-tailed paired t test, $t = 6.88$, $df = 123$, $p = 1.94*10^{-10}$). While only a minority of the individual cases showed significant difference between the responses to standards in the two conditions, in most (34/40) of these cases the response to the standard in the Random condition was larger than in the Periodic condition. Although the tests were not corrected for multiple comparisons, note that at a significance level

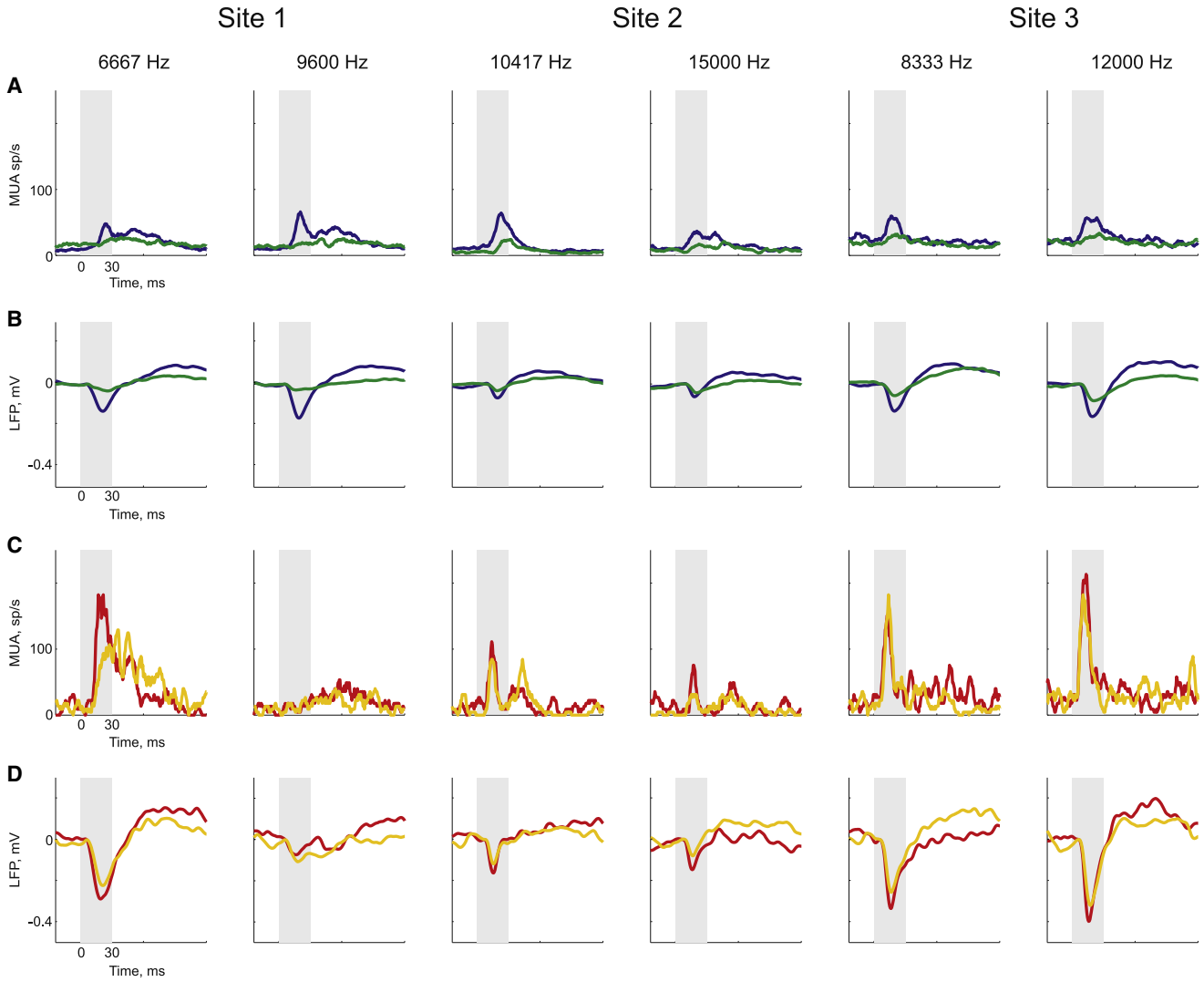

Figure 3. Responses of Multiunit Clusters and LFPs to Random and Periodic Sequences

(A) MUA responses at three different recording sites to the standards in the Periodic (green) and Random (blue) conditions.

(B) LFP responses of at the same recording sites to the standards in the Periodic (green) and Random (blue) conditions.

(C) MUA responses at three different recording sites to the deviants in the Periodic (yellow) and Random (red) conditions.

(D) LFP responses at the same recording sites to the standards in the Periodic (yellow) and Random (red) conditions.

In all examples, the responses to standards in the Periodic condition tended to be smaller than in the Random condition. The differences between the responses to the same tones used as deviants were overall smaller and less consistent.

of 5%, about 6/124 cases are expected to be detected by chance, much less than the 40 recording locations that were actually found.

Similar results were found for the MUA (Figure 4A, left): a majority of the cases (60/85, 71%) had larger responses in the Random than in the Periodic condition. The average response was significantly larger in the Random condition as well (one-tailed paired t test, $t = 5.33$, $df = 98$, $p = 6.18*10^{-7}$). Moreover, most of the individual (21/23) data points that had a significant difference ($p < 0.05$) between the responses in the two conditions showed larger responses in the Random condition. There were again a substantially larger number of recording locations with significant differences than expected by chance for a test with a significance level of 5% (about 4/85).

In contrast, the responses to the deviants did not show a consistent effect of sequence type (Figures 4C and 4D, left). About half of the recordings showed responses that were larger in the Random than in the Periodic condition (LFP: 66/138, MUA: 36/81). In addition, the average responses were not different from each other (LFP: paired t test, $t = 0.82$, $df = 153$, $p = 0.41$; MUA: paired t test, $t = -0.21$, $df = 94$, $p = 0.83$). Finally, individual points with significant differences between the Random and Periodic responses were about equally divided above and below

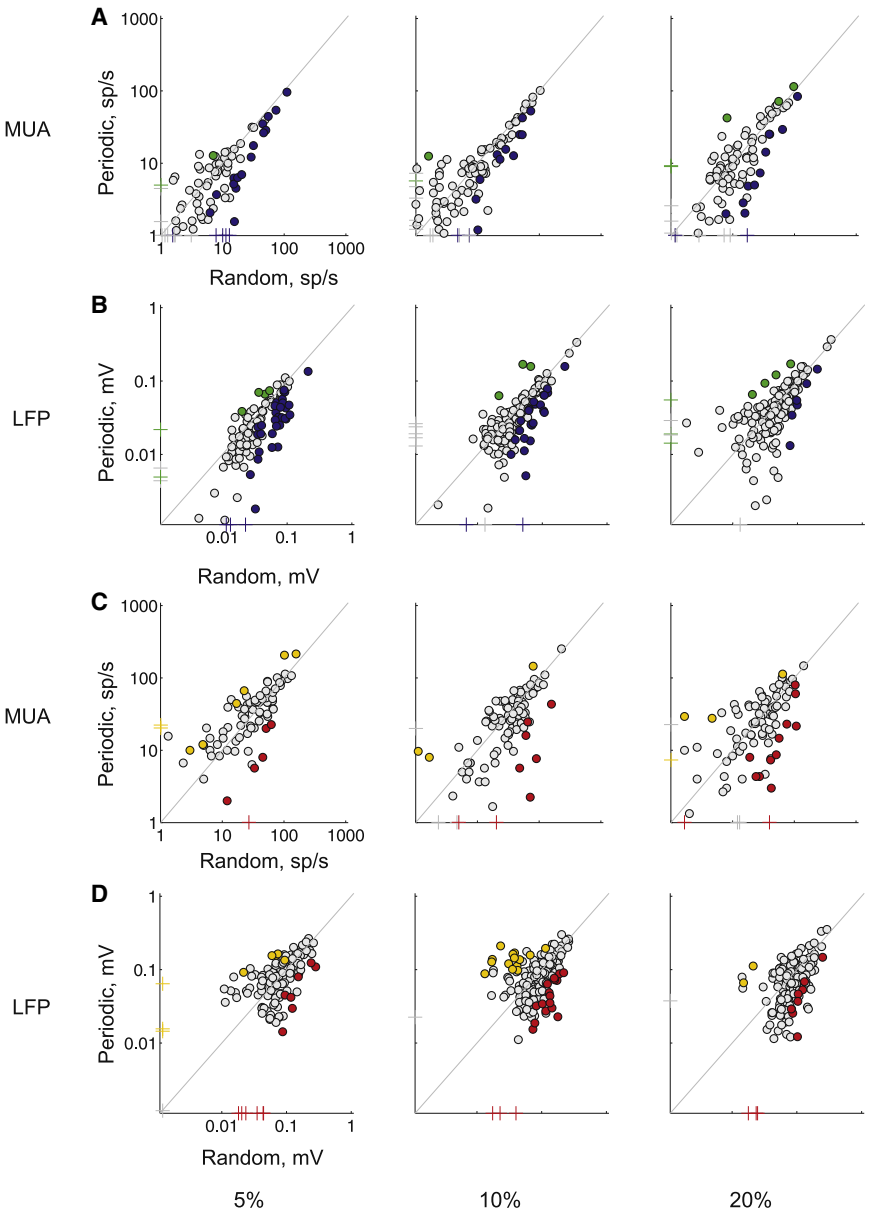

Figure 4. Effect of Deviant Probability

(A–D) MUA (A and C) and LFP (B and D) responses (above baseline) to standards (A and B) and deviants (C and D) in the Random condition (abscissa) versus the responses in the Periodic condition (ordinate). Each point represents one of the main frequencies (either f1 or f2) in a specific recording site. LFP responses occur as negative deflections; here they are inverted and plotted as positive values. Colored points correspond to cases in which the t test comparing the responses in the Periodic and Random conditions showed significant difference ($p < 0.05$). Each column corresponds to one deviant probability. For both MUA and LFP, with small deviant probability (5% and 10%) the responses to the standard tones were larger in the Random than in the Periodic condition, whereas responses to the deviant tones were affected to a lesser degree. At larger deviant probabilities (20%), the pattern was reversed, with the responses to the standard tones being about the same in both types of sequences, while the responses to the deviant tones were somewhat larger in the Random than in the Periodic sequences.

the diagonal (LFP: 13/21 Random > Periodic; MUA: 6/14 Random > Periodic).

In conclusion, MUA and LFP responses to the standard tones showed the same tendencies as the intracellular responses when the deviant probability was 5%: the responses to standards were larger in the Random than in the Periodic condition. On the other hand, the responses to the deviants, while being possibly affected to a small extent by the type of the sequence, did not show a consistent effect.

The tendencies we observed depended on the probability of the deviants. These effects can be seen in Figure 4 and are quantified in Tables 1 and 2. Generally, increasing deviant probability increased the difference between the responses to deviants in the Periodic and Random conditions so that the responses in the Random condition became somewhat larger than in the Periodic condition. While the 5% deviant responses were essentially as likely to be larger or smaller in the Random compared to the Periodic condition (66/138, 48%), the majority of the responses to 20% deviants were larger in the Random compared to the Periodic condition (103/156, 66%); furthermore, the average response to the 20% deviants was significantly larger in the Random than in the Periodic condition. The responses to standards followed the reverse tendencies: the differences between the responses in the Periodic and Random conditions became less prominent with increasing deviant probability (and decreasing standard probability). Thus, while the LFP responses to Periodic standards were overwhelmingly smaller than the responses to Random standards for 5% deviant probability (99/124, 80%), the imbalance in the standard response was substantially smaller when deviant probability was 20% (85/147, 58%).

Sequential Effects

It has been previously shown that SSA has several timescales, from hundreds of milliseconds to tens of seconds (Ulanovsky et al., 2004). In order to examine the time course of the effects shown above, we calculated the average responses to the standards with different time resolutions along the sequence.

Figure 5 shows the average LFP responses to standards (Figure 5A) and deviants (Figure 5B), as a function of the sequential position of the stimulus within the sequence for the 5% (left) and 20% (right) deviant probabilities. In Figure 5A, the blue and

Table 1. Relationships between Responses to Stimuli in Random and Periodic Sequences: Summary of all Recording Locations

	Standards			Deviants		
	95%	90%	80%	20%	10%	5%
LFPs						
Number of cases Random > Periodic	99/124	113/167	85/147	103/156	99/174	66/138
Fraction	80%	68%	58%	66%	57%	48%
t test	t = 6.88	t = 4.19	t = 0.55	t = 4.72	t = 1.59	t = 0.82
t test	df = 123	df = 166	df = 146	df = 155	df = 173	df = 137
t test	$p = 2.7*10^{-10}$	$p = 4.5*10^{-5}$	p = 0.58	$p = 5.2*10^{-6}$	p = 0.11	p = 0.41
MUA						
Number of cases Random > Periodic	60/85	61/103	54/97	52/92	67/101	36/81
Fraction	71%	60%	56%	57%	66%	44%
t test	t = 5.33	t = 3.38	t = 1.37	t = 1.3	t = 3.47	t = −0.21
t test	df = 84	df = 102	df = 96	df = 91	df = 100	df = 80
t test	$p = 8.1*10^{-7}$	p = 0.001	p = 0.17	p = 0.20	$p = 7.7*10^{-4}$	p = 0.83

green bars represent the average response to the standard stimuli at four ranges of trials along the sequence (1–19, 20–80, 81–278, 279–475 for the 5% conditions; 1–4, 5–19, 20–59, 60–100 for the 20% conditions) in the Random and Periodic conditions, respectively. In Figure 5B, the red and yellow bars represent the average response to the deviant stimuli in four ranges of trials (1:3, 4:6, 8:16, 17:25) in the Random and Periodic conditions, respectively. We analyzed the data with a three-way ANOVA on time bin and sequence type, with recording site as a random factor. The main effects of time bin were significant for all conditions [5%: standards $F(3,2032) = 46.01$, $p << 0.01$; deviants $F(3,2508) = 3.22$, $p = 0.022$; 20%: standards $F(3,3076) = 47.57$, $p << 0.01$; deviants $F(3,3172) = 4.85$ $p = 2.3*10^{-3}$]. The main effect of sequence type (Periodic versus Random) was significant for the standards in the 5% conditions [$F(1,2032) = 52.75$, $p << 0.01$] but not for the deviants [$F(1,2508) = 0.16$ $p = 0.69$]. In contrast, in the 20% conditions the main effect of sequence type was significant for the deviants [$F(1,3172) = 14.5$ $p = 1*10^{-4}$] but not for the standards [$F(1,3076) = 0.29$ $p = 0.59$]. When significant, the increased responses in the Random condition persisted throughout much of the duration of the sequence: for example, in the 5% condition, the average standard responses in the Random sequences were significantly larger than in the Periodic sequence in trial ranges 1–19, 20–80, and 81–278 (post hoc comparisons, $p < 0.05$) and larger, although not significantly so, in trial range 279–475. Thus, the difference between the Random and Periodic sequences developed already at the beginning of the sequence, presumably because in many random sequences there was a deviant already among the first 19 sound presentations of the sequence. Importantly, the average response to the Random standards remained larger than to the Periodic standards even later in the sequence. The sequences with deviant probability of 10% showed similar effects to those with deviant probability of 5%, although the effects were smaller. Furthermore, MUA responses showed similar effects to LFP responses (see Figure S1 and Table S1 available online).

One possible explanation for the larger responses to the standards in the Random condition is the presence of short-term effects of the deviant tones on the following standard responses. For example, in the Random condition, it is possible to find by chance a few deviants near in time to each other. During that period, the responses to the standards may be somewhat larger (see Ulanovsky et al., 2004 for examples of short-term effects in oddball sequences), biasing the overall average response to the standards. In order to study such short-term effects, we

Table 2. Relationships between Responses to Stimuli in Random and Periodic Sequences: Locations with Significant Differences between the Two Conditions

	Standards			Deviants		
	95%	90%	80%	20%	10%	5%
LFPs						
Significant points with Random > Periodic/all significant points	34/40	25/28	6/13	11/13	19/33	13/21
Fraction	85%	89%	46%	85%	58%	62%
Expected number of significant points for a significance level of 5%	5/6	6/8	4/7	5/8	5/9	3/7
MUA						
Significant points with Random > Periodic/all significant points	21/23	13/15	13/18	13/17	8/11	6/14
Fraction	91%	87%	72%	76%	73%	43%
Expected number of significant points for a significance level of 5%	3/4	3/5	3/5	3/5	3/5	2/4

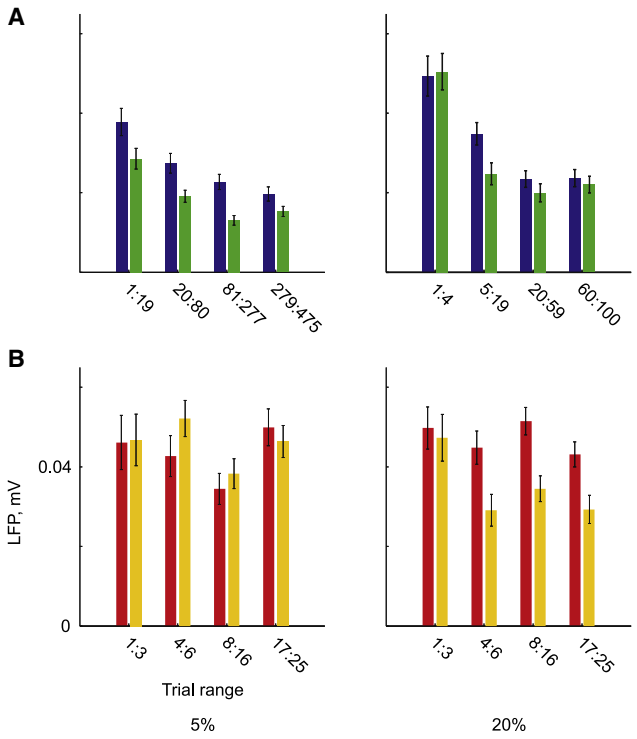

Figure 5. Sequential Effects: Trial Number

Average LFP responses to standards (A) and deviants (B) as a function of the sequential position of the stimulus within the sequence for the 5% (left) and 20% (right) deviant probabilities. (A) The blue and green bars represent the average response (above baseline) to the standard stimuli in four ranges of trials in the Random and Periodic conditions, respectively. The four ranges consisted of trials 1–19, 20–80, 81–278, 279–475 for the 5% conditions, and trials 1–4, 5–19, 20–59, 60–100 for the 20% conditions. In the 5% condition but not in the 20%, the responses in the Random condition are larger than in the Periodic condition throughout the sequence. (B) The red and yellow bars represent the average response (above baseline) to the deviant stimuli in different ranges of deviant trials in the Random and Periodic conditions, respectively. The four ranges consisted of trials 1–3, 4–6, 8–16, 17–25, both in the 5% and 20% conditions. In the 20% but not in the 5% condition, the responses for the Random condition were larger than the responses in the Periodic condition throughout the sequence.

All error bars represent one SE ± mean. See also Figure S1 and Table S1.

calculated the average responses to the standards as a function of their position following the last preceding deviant. Short-term interactions would appear as larger responses to standards during the first few tone presentations following the last preceding deviant. If all the differences between the Random and Periodic conditions were due to such local effects, the responses to standard tones that are distant enough from their last preceding deviant would be the same in the two conditions.

Figure 6 shows the average responses to standard and deviants, separately for LFP and MUA and separately for the different probability conditions. In these plots, the deviant is plotted at position 0, and the average response to the deviant stimuli in the Random and Periodic conditions are drawn in red and yellow bars, respectively. The blue and green bars represent the average response to the standard stimuli at the corresponding positions after the last preceding deviant in the Random and Periodic conditions, respectively. Location −1 corresponds to the standard that occurred just before a deviant.

In all the conditions, the average responses to the first standard following a deviant were larger than to the standard just preceding the deviant, and also to standards at later locations after the deviant. Thus, as expected, there were local effects of the deviants on the responses to the following standards (as already shown in Ulanovsky et al., 2004). However, these effects were about as large in the Periodic as in the Random condition. On the other hand, the larger responses to standards in the Random condition were present at almost all positions after a deviant, and did not taper off with increased sequential position following the last preceding deviant, with significant differences for standards up to 19 positions away from the last preceding deviant.

These results were borne out by the statistical analysis. We analyzed the data with a three-way ANOVA on sequential position of stimulus and sequence type, with recording site as a random factor. The main effect of sequential position of the standard was significant in all probability conditions for both LFP and MUA. The main effect of sequence type in the LFP responses was highly significant for the 5% sequences [$F(1,6499) = 83.62$, $p << 0.01$], and for the 10% sequences [$F(1,3455) = 17.55$, $p = 2.9*10^{-5}$], but not for the 20% sequences [$F(1,1281) = 0.07$, $p = 0.80$]. Similarly, for the MUA responses, the main effect of sequence type was significant for the 5% sequences [$F(1,3776) = 24.33$, $p = 8.5*10^{-7}$] and for the 10% sequences [$F(1,2006) = 12.64$, $p = 3.9*10^{-4}$], but not for the 20% sequences [$F(1,763) = 2.19$, $p = 0.14$]. The interaction between the sequential position and sequence type was significant for the 5% and 10% condition for LFP [$F(18,6499) = 2.37$, $p = 0.0009$ and $F(8,3455) = 3.13$, $p = 0.0016$ for the 5% and 10% standards, respectively]. However, post hoc comparisons of the interactions in the 5% and 10% conditions showed significant differences between standards in the Periodic and Random conditions at many sequential positions distant from the deviant, up to the 19th standard after the last preceding deviant. Thus, although present, this interaction does not indicate the tapering off of the differences between responses in the Random and Periodic conditions expected from local sequential effects.

Effect of the Diversity of Interdeviant Intervals

To study further the underlying reasons for the differences between the responses to Random and Periodic sequences, we recorded extracellular responses (MUA and LFP) to a large number of sequence types (including the Random and Periodic sequences) in seven additional rats. Because we wanted to test sequences with a large number of different structures, we used only deviant probability of 5%.

To select additional sequences for testing, we hypothesized that it is the diversity of the interdeviant intervals (IDIs) (defined as the number of standard tone presentations between successive deviant presentations) that governs the size of the responses. In the Periodic sequences, there is a single IDI (20 stimuli) that occurs 24 times in a sequence of 500 stimuli that includes 25 deviants. On the other hand, in a Random sequence,

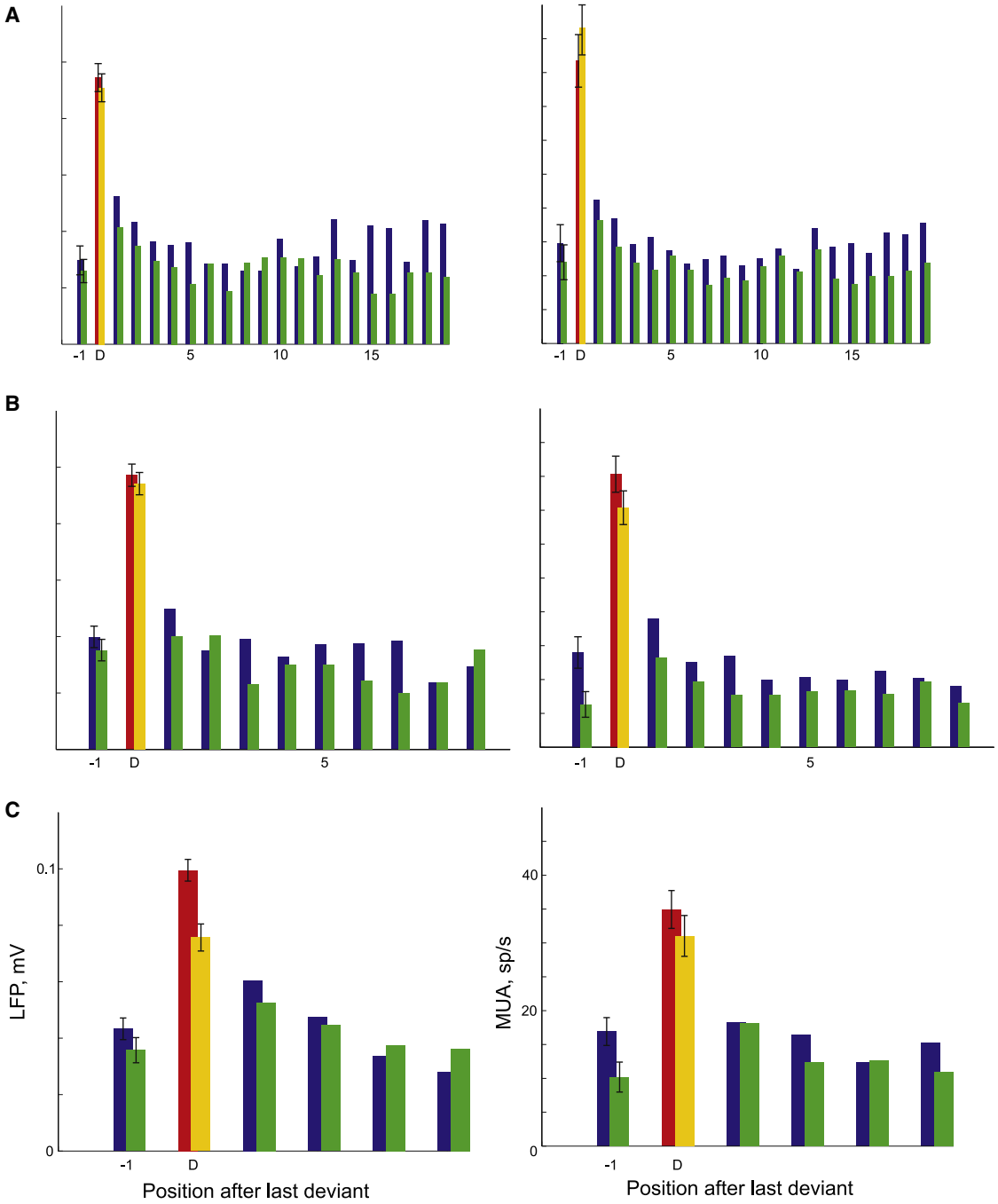

Figure 6. Sequential Effects: Position after Last Preceding Deviant

Average LFP and MUA responses to standards and deviants as a function of position following the last preceding deviant. The deviant is plotted at position 0, and the average responses (above baseline) to the deviant in the Random and Periodic conditions are plotted in red and yellow bars, respectively. The blue and green bars represent average responses (above baseline) to standards in the Random and Periodic conditions, respectively. The bars represent the average responses to standards presented at the corresponding position following the last preceding deviant (with no other intervening deviants). Location −1 corresponds to standards that occurred just before a deviant. Error bars (1 SE ± mean) are presented on only some of the bars, to avoid visual clutter. Each bar represents the average of thousands of single trials (e.g., in A, 12,475 single trials at position n = 1, 4,532 single trials at position n = 19). (A–C) Deviant probabilities of 5%, 10%, and 20%, respectively. Left: LFP responses. Right: MUA responses. The larger responses to standards in the Random condition were present at almost all positions after a deviant and did not taper off with increased sequential position after the last preceding deviant.

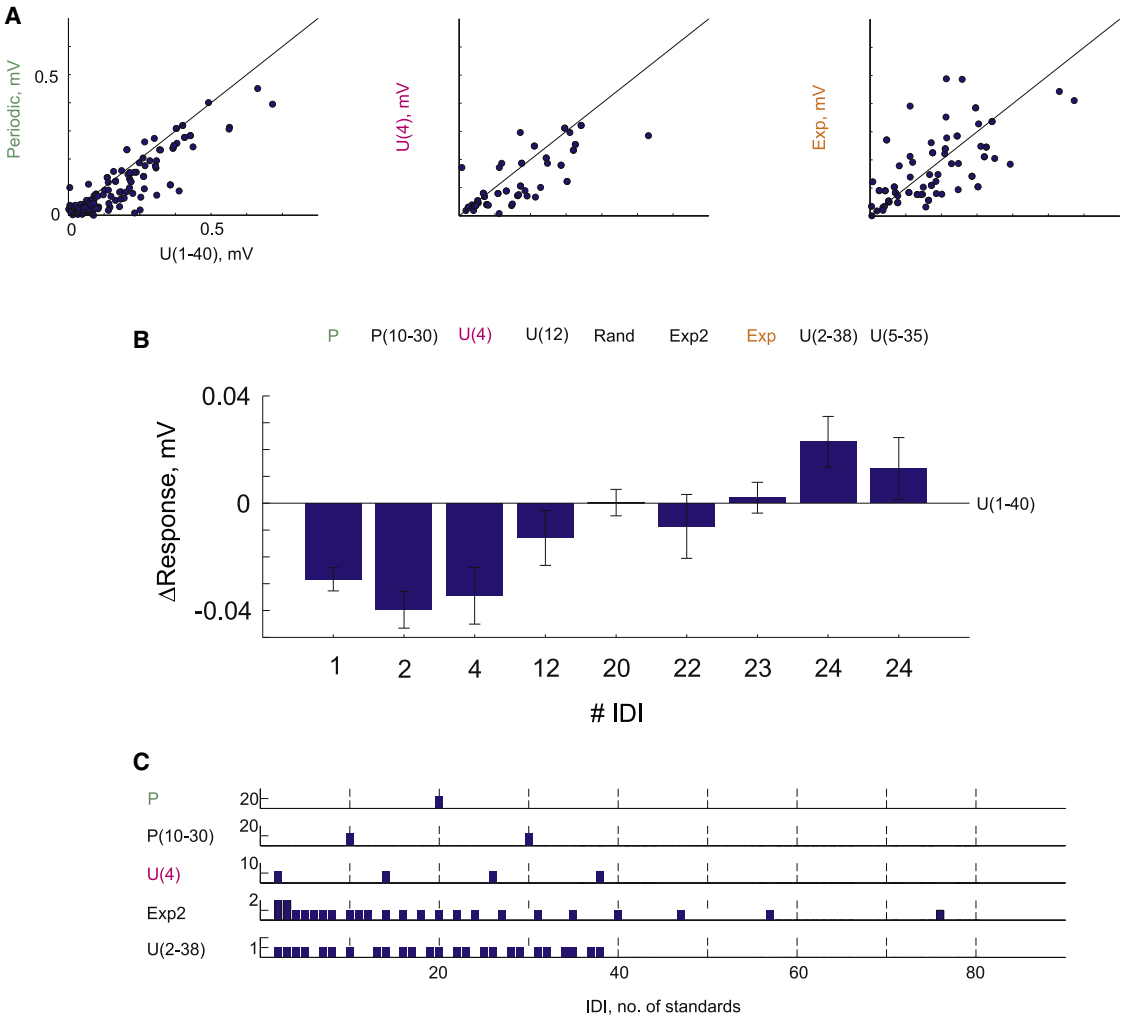

Figure 7. Effect of Number of Interdeviant Intervals

(A) Scatterplots of the LFP responses to standards in the periodic, U(4), and Exp sequences against the responses at the same recording location in the U(1–40) sequence. Standard responses in the periodic and U(4) responses are smaller than in the U(1–40) responses, while standard responses in the Exp sequence are roughly the same.

(B) Average difference between the responses to standards in each of the sequences and the responses to standards in the U (1–40) sequence. The abscissa displays the number of unique IDIs that occur in each type of sequence. Responses increased on average with the number of unique IDIs. Error bars represent 1 SE ± mean.

(C) Illustration of the IDI distributions of some of the sequences. The bars represent the number of repetitions of every unique interval in each paradigm. Note the difference in scale of the ordinates.

See also Figure S2.

there are about 20 different IDIs (some repeat more than once by chance). To test our hypothesis, we used sequences with 2, 4, 12, 22, 23, and 24 unique IDIs. The sequence with 2 IDIs alternated IDIs of 10 and 30 stimuli between successive deviants. The sequences with 4 and 12 IDIs had equally distributed IDIs between 1 and 40 each of which repeated an equal number of times, and are called U(4) and U(12) below. The sequences with 22 and 23 IDIs mimicked an exponential distribution of intervals. The Exp sequence contained 23 IDIs, with IDI = 1 (two successive deviants) repeating twice, and the IDIs increased exponentially in size. The sequence with 22 IDIs, called Exp2, had similar structure except that the two IDI = 1 intervals were removed, IDI = 2 and IDI = 3 were repeated twice and the other IDIs slightly corrected to reach an average of 20. The three sequences with 24 IDIs included a uniform distribution of IDIs between 1 and 40, called U(1–40), as well as similarly constructed U(2–38) and U(5–35) sequences. The IDI distributions of some of these sequences are illustrated in Figure 7C.

Figure 7A shows scatterplots of the responses to standards in the periodic, U(4) and Exp sequences against the responses to standards in the U(1–40) sequence at the same recording locations. Our hypothesis implies the prediction that standard

responses in the periodic and U(4) responses should be smaller than in the U(1–40) responses, while standard responses in the Exp sequence would be roughly the same. The results are fully compatible with this prediction. Figure 7B displays the average difference between the responses to standards in each of the newly tested sequences and the responses to standards in the U(1–40) sequence. Sequences with 1–4 IDIs evoked about the same size of responses, and all were significantly smaller than the responses to the U(1–40) sequence. The average responses to standards in the sequence with 12 IDIs were still smaller than the responses to standards in the U(1–40) sequence, but the differences were much smaller. The sequences with 22–24 IDIs evoked mostly comparable responses to those of the U(1–40) sequence, except that the U(2–38) seemed to evoke on average larger responses. These were due to a few outliers, so we did not pursue this issue further.

Statistical analysis fully supported these results. Two-way ANOVA on number of unique IDIs (#IDI) and recording site showed a highly significant main effect of #IDI [$F(8,808) = 6.75$, $p << 0.01$]. To emphasize the hypothesized monotonic relationship between #IDI and response, we tested a linear dependence of the responses on #IDI as well as on log(#IDI). The effect of the linear term was highly significant [#IDI: $F(1,815) = 42.22$, $p << 0.01$; log(#IDI): $F(1,815) = 35.73$, $p << 0.01$], but there was no clear advantage to either. The resulting slope was positive, consistent with our claim that response increases with the number of unique IDIs that appear in the sequence.

Figure S2 shows the same data for MUA recordings. These responses were more variable, and the pattern of the results is somewhat noisier. Nevertheless, the same general pattern was found, and the statistical tests support the same conclusions.

These results suggest that the responses to tones in oddball sequences are sensitive to the complexity of the distribution of IDIs. The main data of the paper, showing the differences in the responses to periodic and random sequences, become thus an important special case of a more general finding.

DISCUSSION

In this paper, we compared responses to oddball sequences in which the deviant tones occurred randomly to ones in which the deviant tones occurred periodically, as well as to sequences that are intermediate in their complexity. The main result of this paper is the demonstration that the neural responses were sensitive to this difference. In all cases, responses in the Random condition tended to be the same or larger than the responses in the Periodic condition, although the details varied as a function of deviant probability. The larger responses to Random sequences were found with a number of measures of neural activity, including membrane potential responses of single neurons, but also LFPs, which are usually attributed to summed synaptic activity, and in MUA that reflects the output of multiple neighboring neurons in the network.

Previous studies (Anderson et al., 2009; Malmierca et al., 2009; Taaseh et al., 2011; Ulanovsky et al., 2003) used oddball sequences similar to the ones we used here in the Random condition. These studies demonstrated, in a number of animal models and at different levels of the auditory pathway, that stimuli elicited a larger response when they were rare than when they were frequent. The responses to Random sequences described here reproduce such data, with the further information that a similar contrast between the responses to common and rare tones can be found also at the level of the membrane potential responses of neurons in auditory cortex.

To the best of our knowledge, the contrast between Periodic and Random sequences has not been studied before in animal models. The closest sequences to those we used here are the roving sequences in (Reches and Gutfreund, 2008), in which a stimulus changed exactly every ten presentations. These are therefore Periodic sequences, but the overall probability of each of the two stimuli in these sequences was 50%. Reches and Gutfreund observed differences between the responses to the first and to the last stimulus of each successive group of ten presentations and used them as a replacement for bona fide oddball sequences. However, roving sequences with equiprobable tones elicit different responses than oddball sequences, as recently shown in the auditory thalamus of the gerbil (Bäuerle et al., 2011). In these experiments, the contrast between first and last stimulus in a sequence of successive identical stimuli was substantially smaller than the difference between the responses to the same tone when common and when rare in an oddball sequence.

In contrast with these studies, we used Periodic sequences that had a probability imbalance between the two stimuli. Remarkably, we observed that Random sequences evoked as a rule stronger responses than Periodic sequences. The detailed pattern of these differences depended on deviant probability. With deviant probability of 5%, the standards evoked significantly stronger responses in the Random than in the Periodic condition. With deviant probability of 20%, it was the deviants that evoked stronger responses in the Random than in the Periodic condition. With deviant probability of 10% (incidentally, the one most often used in previous studies of stimulus-specific adaptation, Antunes et al., 2010; Malmierca et al., 2009; Ulanovsky et al., 2003), the differences between the Periodic and the Random sequences were smaller, but still standards evoked stronger responses in the Random than in the Periodic condition.

There are only few attempts to account for stimulus-specific adaptation in mechanistic terms. Taaseh et al. (2011) studied adaptation in narrow frequency channels, due, e.g., to synaptic depression of frequency-specific inputs, as a possible mechanism for stimulus-specific adaptation. We show in the Supplemental Information that this model is unable to account for the results shown here, predicting instead that the responses to both standards and deviants should be smaller in the Random than in the Periodic condition (see Figures S3, S4, S5, S6, S7, and S8). Mill et al. (2011) analyzed a similar model, and also a model with two layers of depressive synapses; although the model was not tested in the Periodic configuration, there is no reason to believe that it would reverse the advantage of the Periodic sequences in the single-layer configuration.

Ulanovsky et al. (2004) used two factors to model the average responses in two tone sequences—a local context, that measured the probability of the current tone within the last four to five stimuli, and a global context, which consisted of the probability of the tone within the sequence. Since Random

and Periodic sequences had the same global context, a model such as that of Ulanovsky et al. (2004) has to account for the differences between responses to Random and Periodic sequences using local context effects only. Thus, such a model requires the response to the current tone to depend on a short preceding subsequence of tones, independent of whether this subsequence is embedded within a Random or a Periodic sequence. The differences between the average responses in the two conditions are then due to the different probabilities with which such subsequences occur in the two types of sequences. We develop the required theory in the Supplemental Information. It makes three specific predictions, all of which are falsified by the data. First, the theory predicts that difference between the responses to standards in the two conditions should decrease with deviant probability, but our data show that this difference is larger for deviant probability of 5% than for deviant probabilities of 10% and 20%. Second, the effects of preceding short sequences, estimated from the data, were not independent of the condition. Figure S3 shows this for all sequences of up to five tones preceding standards, while Figure 6 illustrates the influence of the sequence type on the average responses to tones preceded by subsequences as long as 19 tones. Finally, the theory makes explicit the importance of the responses to standards that have two or more deviants in close proximity. Such clusters of deviants may occur in the Random sequences but not in the Periodic sequences. The increased responses to standards under these conditions should be large enough in order for the average response to standards in Random sequences to be larger than in Periodic sequences, and the theory offers an exact numerical criterion of that to happen. The measured responses to standards under these conditions failed this criterion (Figure S4).

The results illustrated in Figure 7 shed further light on this issue. The responses to sequences with a large number of IDIs were large almost independently of the exact values of these IDIs. Indeed, a U(1–40) sequence, which included a number of very close deviants, evoked standard responses that were essentially the same as those evoked by a U(5–35) sequence, which did not include any clusters of closely occurring deviants. Thus, the data strongly suggest that short-term interactions between standards and deviants do not underlie the effects shown here.

Since the difference in the responses between the two types of sequences with deviant probability of 5% is established within the first 20 stimuli of the sequence, one possible account for the difference between the Random and Periodic sequences would posit that the responses reflect some internal estimate of the probabilities of the standard and of the deviant, but that this estimate is biased by early events in the tone sequence. Thus, the appearance of a deviant before position 20 in the sequence would bias the network estimate of the standard probability to lower values, and that of deviant probability to larger values, biasing the responses accordingly. In this case, there is no true sensitivity to the order of the sequence, and a Random sequence with deviant probability of 5%, in which the first deviant appeared at position 20, should have the same average standard response as a Periodic sequence with the same deviant probability. We tested therefore the dependence of the responses to standards in Random sequences on the position of the first deviant in the sequence. This dependence was not significant—the responses to standards at all four ranges of positions used in Figure 5 were not significantly affected by the position of the first deviant. Thus, such account, which is not truly order sensitive, is not supported by the data.

A truly order-sensitive account of these results would require the network to store an estimate of the number of standards between successive deviants. Now, if the activity in the network habituates when this estimate remains fixed, the effects described here could occur. For example, the network might reduce its overall excitability if there are common occurrences of a sequence of 19 standards followed by a deviant. In Periodic sequences with deviant probability of 5%, the same sequences of 19 standards followed by a deviant would occur repeatedly, strengthening this habituation. Figures 7 and S2 strongly support this view, by showing that the responses to standards are larger on average in sequences with large variety of interdeviant intervals. Such a model requires the distribution of IDIs to be estimated and somehow stored. Thus, this account suggests that detailed information about tone order of a sequence of 500 tones is stored and updated over a few minutes. Whether and how such memory can be implemented remains an open question.

On the other hand, the dependence of responses on the variety of IDIs demonstrated in Figure 7 may account for the complex pattern of responses as a function of deviant probability shown in Figure 4. The waiting time between successive deviants in our Random sequences is approximately geometrical, so that its SD is equal to the mean. Thus, for a deviant probability of 5%, the SD is 20, while there are only 25 deviants in the sequence. In consequence, many different IDIs occur, presumably leading to the larger responses to standards in Random sequences than in Periodic sequences, which have a single value of IDI. On the other hand, when deviant probability is 20%, the average number of standards between successive deviants is 4, and the variability is much smaller. In consequence, the variety of IDIs is much more limited, and the contrast with the Periodic sequence, with a single IDI, is smaller, leading to smaller differences between the standard responses in the two cases.

The sensitivity to rather fine features of the order of tone presentations has possible implications to the processing of statistical regularities of the real world (see also Asari and Zador, 2009). Humans have language and music, both of which have complex structure that is crucial for accomplishing their effects. Animal calls may have "syntax" in that some sequences of calls are more probable than others (e.g., Holy and Guo, 2005). The sensitivity to order we describe here may be a mechanisms for reading out such syntactic regularities. In fact, human babies are sensitive to probabilistic rules that mimic some properties of languages (Marcus et al., 1999; Saffran et al., 1996); these results have been at least partially reproduced in rats (Toro and Trobalón, 2005). Our results suggest a neural correlate for such sensitivity. Furthermore, these results suggest that statistical information accumulated over very long durations influences neural activity as early as in primary auditory cortex. Thus, while the complexity of these sequences is

obviously far below that of speech or music, the ability of rats to differentially encode Random and Periodic sequences may suggest the presence of the capabilities required to process such natural stimuli.

EXPERIMENTAL PROCEDURES

Preparation

We used 35 adult female Sabra rats weighing 140–300 g for this study (Harlan Laboratories Ltd., Jerusalem, Israel). The joint ethics committee (IACUC) of the Hebrew University and Hadassah Medical Center approved the study protocol for animal welfare. The Hebrew University is an AAALAC International accredited institute.

Detailed methods are described in Taaseh et al. (2011). In short, the animals were initially anesthetized with an intramuscular injection of ketamine and medetomidine. Following tracheotomy, they were ventilated through a tracheal cannula by a mixture of O_2 and halothane (0.5%–1.5% as needed). Throughout the experiment, animals where monitored for temperature, respiratory CO_2, and respiration quality. The left temporal portion of the skull was cleaned from skin, muscles, and connective tissue.

Intracellular Recording

Intracellular recordings with sharp electrodes were performed in 16 rats (females, 200–250 g). Electrodes were prepared from a filamented borosilicate tube (1.5 mm outer diameter, 0.86 mm inner diameter, Sutter Instruments) by a single stage vertical puller (PE-2, Narishige, Japan) and were filled with 1 M potassium-acetate solution. The resistance of the electrodes was in the range of 45–95 MΩ. The bridge was balanced and capacitance compensation was used in all experiments.

A small craniotomy (0.5–1 mm) was performed over part of the estimated location of the auditory cortex (see below) followed by a smaller duratomy. The cisterna magna was perforated, and agarose gel (3%–4% Agarose type III-A, Sigma Chemical Co., MO, in saline) was used to decrease brain pulsation. The signal was amplified ×10 (NeuroData IR283, Cygnus Technologies, Inc., Delaware Water Gap, PA), sampled at 12.207 kHz (RP2.1, TDT, Tucker-Davis Technologies, Alachua, FL) for online display, and stored for offline analysis.

A blind search for neurons was conducted 400–1,000 μm below the surface in order to record neurons at the estimated depth of layer IV (500–750 μm).

Extracellular Recording

We recorded extracellularly using an array of four to eight glass-coated tungsten electrodes (Alpha-Omega Ltd., Nazareth-Illit, Israel). A craniotomy was performed over the whole estimated location of the left auditory cortex—2.5–6.5 mm posterior to and 2–6 mm ventral to bregma. The electrodes were assembled together with separations of ~600 μm. The electrodes were lowered into the cortex using a microdrive (MP-225, Sutter Instrument Company, Novato, CA). The electrical signals were preamplified (×10), filtered between 3 Hz and 8 kHz to obtain both local LFPs and action potentials, and then amplified again, for a total gain of ×5,000 (MCP, Alpha-Omega, Nazareth Illit, Israel), to yield the raw signals. The raw signals were sampled at 25 kHz and stored for offline analysis. The analog signals were also sampled at 977 Hz after antialiasing filtering (RP2.1, TDT, Tucker-Davis Technologies, Alachua, FL), stored for LFP analysis, and used for online display.

Auditory Stimulation

All experiments were conducted in a sound-proof chamber (IAC, Winchester, UK). Sounds were synthesized online using Matlab (The Mathworks, Inc., Natick, MA), transduced to voltage signals by a sound card (HDSP9632, RME, Germany), attenuated (PA5, TDT), and played through a sealed speaker (EC1, TDT) into the right ear canal of the rat.

Sound calibration was performed in the ear of some of animals using a custom-made adaptor for a miniature microphone (model EK-3133-000, Knowles, England) precalibrated against a B&K 1/4 in microphone. The calibration was found to be stable across animals. For pure tones, attenuation level of 0 dB corresponded to about 100 dB SPL. Noise stimuli were synthesized at a spectrum level of −50 dB/sqrt (Hz) relative to pure tones at the same attenuation level.

For extracellular experiments, recording sites were selected by their response to a broad-band noise (BBN). The electrodes were positioned at the location and depth that showed the largest evoked LFPs. Once selected, we validated and recorded the BBN responses of the recording site using a sequence of 280 BBN bursts with duration of 200 ms, 10 ms linear onset and offset ramps, ISI of 500 ms, and seven different attenuation levels, between 0 and 60 dB with 10 dB steps, that were presented pseudorandomly so that each level was presented 40 times. The main data were collected if the noise threshold level was lower than 30 dB attenuation and noise evoked potentials changed regularly with level; otherwise, the electrodes were moved to a different location. For intracellular recordings, we used similar stimuli to verify that the neuron responded to auditory stimuli. If no responses could be evoked to noise stimuli, we did not collect the main data.

We used several quasi-random frequency sequences of 370 tone bursts (50 ms duration, 5 ms onset/offset linear ramps, 500 ms ISI) at 37 frequencies (1–64 kHz, six tones/octave) at several attenuation levels, from threshold and up to an attenuation of 10 dB, to map the frequency response area of the neuronal responses.

Two frequencies evoking large responses were selected for further study. The lower frequency was denoted f1, the higher was denoted f2, and they were selected such that the difference between them, defined as: $\Delta f = f2/f1 - 1$, was 44%. This interval corresponds to 0.526 octaves.

Several types of tone sequences were used. All sequences consisted of pure tones whose duration was 30 ms (5 ms rise/fall time), presented at an ISI of 300 ms. The deviant frequency (either f1 or f2) had a probability of 5%, 10%, or 20%. Each sequence contained 25 deviants and the appropriate number of standards (475, 225, and 100 for 5%, 10%, and 20% deviant probability). The tones in the sequence could be presented in random order, as commonly used in similar experiments (e.g., Ulanovsky et al., 2003; Antunes et al., 2010), or using a fixed order in which one deviant occurred after exactly $1/p - 1$ standards (with p being the probability of the deviant). The order of presentation of Random and Periodic sequences was counterbalanced across sites.

Data Analysis

The data were analyzed with Matlab (The Mathworks, Inc., Natick, MA).

Intracellular Recordings

In cells that had spiking activity, the signal was first high-pass filtered with a corner frequency of 30 Hz. Spikes were detected using a dynamic threshold that was 60 times the median of the absolute deviations from the median (MAD) of the signal. The quality of spike detection was verified by visual inspection of the plots. The beginning of the spike was determined by the time point of maximum acceleration in the rising phase, and its end was determined by the time point when the derivative was closest to zero within a period of 1.5 times the spike width after the peak of the spike. The spikes were clipped from the unfiltered signal, and were replaced by a straight line from start to end of the spike. The clipped signal thus obtained was considered in this study as the membrane potential signal.

Extracellular Recordings

To detect MUA, the raw signals were filtered between 200 and 8,000 Hz, and large, fast events were marked as spikes. The threshold for spike detection was set to seven times the MAD of the filtered voltage traces (corresponding to more than four SDs for Gaussian signals). The resulting spike trains were aligned on stimulus onset and averaged.

The strength of responses in MUA, LFP and membrane potentials was determined as the average response in the interval 0–40 ms after stimulus onset, corrected for the baseline activity estimated by the average response in the 30 ms preceding stimulus onset.

The inclusion criterion for data (LFP, spikes, and membrane potential) was the presence of significant responses to at least one of the deviants (Random and Periodic sequences). Significance test was performed by a t test between the set of single-trial responses and the corresponding prestimulus activity levels.

Throughout the paper, tests are considered as significant if $p < 0.05$.

SUPPLEMENTAL INFORMATION

Supplemental Information includes eight figures, one table, and supplemental text and can be found with this article online at http://dx.doi.org/10.1016/j.neuron.2012.08.025.

ACKNOWLEDGMENTS

Support for this research was provided by grants to I.N. from GIF, the German-Israeli Foundation for Scientific Research and Development; the Israel Science Foundation (ISF); the Israeli Ministry of Health under the framework of ERA-Net NEURON; by a generous donation of the Bnei Brith Leo Baeck (London) Lodge; and by the Gatsby Charitable Foundation.

Accepted: August 15, 2012
Published: November 7, 2012

REFERENCES

Anderson, L.A., Christianson, G.B., and Linden, J.F. (2009). Stimulus-specific adaptation occurs in the auditory thalamus. J. Neurosci. *29*, 7359–7363.

Antunes, F.M., Nelken, I., Covey, E., and Malmierca, M.S. (2010). Stimulus-specific adaptation in the auditory thalamus of the anesthetized rat. PLoS ONE *5*, e14071.

Asari, H., and Zador, A.M. (2009). Long-lasting context dependence constrains neural encoding models in rodent auditory cortex. J. Neurophysiol. *102*, 2638–2656.

Bäuerle, P., von der Behrens, W., Kössl, M., and Gaese, B.H. (2011). Stimulus-specific adaptation in the gerbil primary auditory thalamus is the result of a fast frequency-specific habituation and is regulated by the corticofugal system. J. Neurosci. *31*, 9708–9722.

Farley, B.J., Quirk, M.C., Doherty, J.J., and Christian, E.P. (2010). Stimulus-specific adaptation in auditory cortex is an NMDA-independent process distinct from the sensory novelty encoded by the mismatch negativity. J. Neurosci. *30*, 16475–16484.

Holy, T.E., and Guo, Z. (2005). Ultrasonic songs of male mice. PLoS Biol. *3*, e386.

Malmierca, M.S., Cristaudo, S., Pérez-González, D., and Covey, E. (2009). Stimulus-specific adaptation in the inferior colliculus of the anesthetized rat. J. Neurosci. *29*, 5483–5493.

Marcus, G.F., Vijayan, S., Bandi Rao, S., and Vishton, P.M. (1999). Rule learning by seven-month-old infants. Science *283*, 77–80.

Mill, R., Coath, M., Wennekers, T., and Denham, S.L. (2011). A neurocomputational model of stimulus-specific adaptation to oddball and Markov sequences. PLoS Comput. Biol. *7*, e1002117.

Nelken, I., Rotman, Y., and Bar Yosef, O. (1999). Responses of auditory-cortex neurons to structural features of natural sounds. Nature *397*, 154–157.

Reches, A., and Gutfreund, Y. (2008). Stimulus-specific adaptations in the gaze control system of the barn owl. J. Neurosci. *28*, 1523–1533.

Ruderman, D.L., and Bialek, W. (1994). Statistics of natural images: Scaling in the woods. Phys. Rev. Lett. *73*, 814–817.

Saffran, J.R., Aslin, R.N., and Newport, E.L. (1996). Statistical learning by 8-month-old infants. Science *274*, 1926–1928.

Taaseh, N., Yaron, A., and Nelken, I. (2011). Stimulus-specific adaptation and deviance detection in the rat auditory cortex. PLoS ONE *6*, e23369.

Toro, J.M., and Trobalón, J.B. (2005). Statistical computations over a speech stream in a rodent. Percept. Psychophys. *67*, 867–875.

Ulanovsky, N., Las, L., and Nelken, I. (2003). Processing of low-probability sounds by cortical neurons. Nat. Neurosci. *6*, 391–398.

Ulanovsky, N., Las, L., Farkas, D., and Nelken, I. (2004). Multiple time scales of adaptation in auditory cortex neurons. J. Neurosci. *24*, 10440–10453.

von der Behrens, W., Bäuerle, P., Kössl, M., and Gaese, B.H. (2009). Correlating stimulus-specific adaptation of cortical neurons and local field potentials in the awake rat. J. Neurosci. *29*, 13837–13849.

Winkler, I., Denham, S.L., and Nelken, I. (2009). Modeling the auditory scene: predictive regularity representations and perceptual objects. Trends Cogn. Sci. *13*, 532–540.

Zhao, L., Liu, Y., Shen, L., Feng, L., and Hong, B. (2011). Stimulus-specific adaptation and its dynamics in the inferior colliculus of rat. Neuroscience *181*, 163–174.