

Uri Werner-Reiss · Kristin Kelly Porter  
Abigail M. Underhill · Jennifer M. Groh

## Long lasting attenuation by prior sounds in auditory cortex of awake primates

Received: 16 February 2005 / Accepted: 5 October 2005 / Published online: 23 November 2005  
© Springer-Verlag 2005

**Abstract** How the brain responds to sequences of sounds is a question of great relevance to a variety of auditory perceptual phenomena. We investigated how long the responses of neurons in the primary auditory cortex of awake monkeys are influenced by the previous sound. We found that responses to the second sound of a two-sound sequence were generally attenuated compared to the response that sound evoked when it was presented first. The attenuation remained evident at the population level even out to inter-stimulus intervals (ISIs) of 5 s, although it was of modest size for ISIs > 2 s. Behavioral context (performance versus non-performance of a visual fixation task during sound presentation) did not influence the results. The long time course of the first sound's influence suggests that, under natural conditions, neural responses in auditory cortex are rarely governed solely by the current sound.

**Keywords** Inter-stimulus interval · Memory · Stimulus history · Habituation · Adaptation

### Introduction

A variety of previous studies have shown that the brain's responses to sounds are not stationary: a given sound does not always evoke the same response (for example, humans: Naatanen et al. 1986; Mantysalo and Naatanen 1987; Sams et al. 1993; Robson et al. 1998); (monkeys: Gottlieb et al. 1989; Javitt et al. 1992; Brosch et al. 1999; Bartlett and Wang 2005); (cats: Hocherman and Gilat

1981; Calford and Semple 1995; Brosch and Schreiner 1997, 2000; Lu and Wang 2000; Reale and Brugge 2000; Mickey and Middlebrooks 2001; Ulanovsky et al. 2003); (rabbits: Fitzpatrick et al. 1999); (bats: Suga 1965). Rather, neural responses vary as function of the nature of the previous sound(s) and how much time has elapsed in the interim. This dependence on sound history is likely to be important for a variety of auditory perceptual phenomena on timescales ranging from milliseconds (e.g. the precedence effect, forward masking) to seconds (e.g. speech comprehension) to minutes (e.g. loudness adaptation). Previous single and multi-unit recording studies (anesthetized bat: Suga 1965); (anesthetized cat: Hocherman and Gilat 1981; Calford and Semple 1995; Brosch and Schreiner 1997, 2000; Lu and Wang 2000; Reale and Brugge 2000; Mickey and Middlebrooks 2001; Ulanovsky et al. 2003); (awake baboon: Gottlieb et al. 1989); (anesthetized monkey: Brosch et al. 1999); (awake rabbit: Fitzpatrick et al. 1999) have primarily concentrated on shorter time scales (usually < 1 s) than those used in the human evoked potential studies, where the effect has been shown to persist for seconds (for review, see Naatanen and Picton 1987); (see also Mantysalo and Naatanen 1987; Sams et al. 1993; Robson et al. 1998). How long the effect of stimulus history endures is important not only for establishing a link between neural recording and ERP/MEG/fMRI studies, but also for practical reasons: how far apart must stimuli be separated in time in order for the responses to each sound to be independent of the preceding one? Furthermore, the duration of the effect will constrain hypotheses concerning the mechanism underlying this form of auditory memory. Finally, as many of the previous animal studies have been conducted under anesthesia, we were curious to know if behavioral context of sound presentation would affect the pattern of sensitivity to stimulus history in awake animals.

Accordingly, we evaluated the neural responses to sound sequences as a function of the ISI and behavioral context in primary auditory cortex of awake monkeys. We found that responses were attenuated by previous

Uri Werner-Reiss, Kristin Kelly Porter contributed equally to this work

U. Werner-Reiss · K. K. Porter · A. M. Underhill  
J. M. Groh (✉)  
Department of Psychological and Brain Sciences,  
Center for Cognitive Neuroscience, Dartmouth College,  
Hanover, NH, 03755 USA  
E-mail: jennifer.m.groh@dartmouth.edu  
Tel.: +1-603-6460241  
Fax: +1-603-6461419

sounds out to the longest ISI tested (5 s) and that behavioral context did not affect the results.

Preliminary reports of these findings have appeared previously (Kelly et al. 2002; Werner-Reiss et al. 2003a).

---

## Methods

### General procedures

All procedures were conducted in accordance with the principles of laboratory animal care of the National Institutes of Health (publication No. 86-23, revised 1985) and were approved by the Institutional Animal Care and Use Committee at Dartmouth College. The details have been reported elsewhere (Groh et al. 2003; Werner-Reiss et al. 2003a). Two adult female rhesus monkeys underwent surgeries under isoflurane anesthesia to implant a head post for restraining the head, a cylinder to allow access to the auditory cortex, and a scleral eye coil for monitoring eye position at a 500 Hz sample rate (Robinson 1972; Judge et al. 1980). In the performing condition, the animals were trained to maintain fixation on a visual stimulus while two broadband noise sounds (500–18 kHz, 51 dB SPL, duration 200 ms, ISIs: 200, 500, 800, 1000, 2000, 3000, 4000, and 5000 ms) were presented successively from a loudspeaker located directly in front of them ( $n=61$  neurons). The animals received liquid reinforcement for maintaining fixation throughout the two-sound sequence. The liquid was delivered via a solenoid valve that made a minimally audible clicking sound. The non-performing condition was the same except that the animals sat passively during sound presentation and were not rewarded ( $n=35$  neurons, of which  $n=15$  were also tested in the performing condition).

The minimum interval between the end of one trial and the first sound presentation of the next inter-trial interval (ITI) was 6 s. When the monkeys were performing a behavioral task, there was variability in the actual interval between the end of one correctly performed trial and the start of the next, as the monkeys occasionally skipped trials or delayed the start of trials by up to a few seconds by failing to look immediately to the fixation light. The overall median interval between the last sound presentation of one trial and the first sound presentation of the next correctly performed trial was 7.9 s and the mean was 10.5 s (standard deviation 2.9 s).

The length of the ITI constrains testing of ISIs. We tested ISIs of up to 5 s, shorter than the shortest ITI, because when the  $ISI = ITI$ , the effect of the second sound from the previous trial on the response to the first sound should be equal to the effect of first sound in the current trial on the response to the second sound.

The experiments were conducted in a single-walled sound attenuation chamber (IAC) lined with sound absorbent foam (3" Sonex One) to reduce echoes. Experiments were conducted in darkness (except for the fixation point, where applicable). Standard recording

techniques were used: electrical potentials were amplified and action potentials were detected using a dual window discriminator (Bak Electronics). The time of occurrence of action potentials was stored for off-line analysis. The locations of our recording penetrations were confirmed using MRI and the response latencies of our neurons were similar to those of previous reports in auditory cortex (for details see supplemental material).

Neurons were considered auditory and included in the sample if their discharge rate in response to the first 100 ms of the first sound differed significantly from their responses during the preceding 100 ms of spontaneous activity (two-tailed paired  $t$ -test,  $p < 0.05$ ).

### Location of recordings

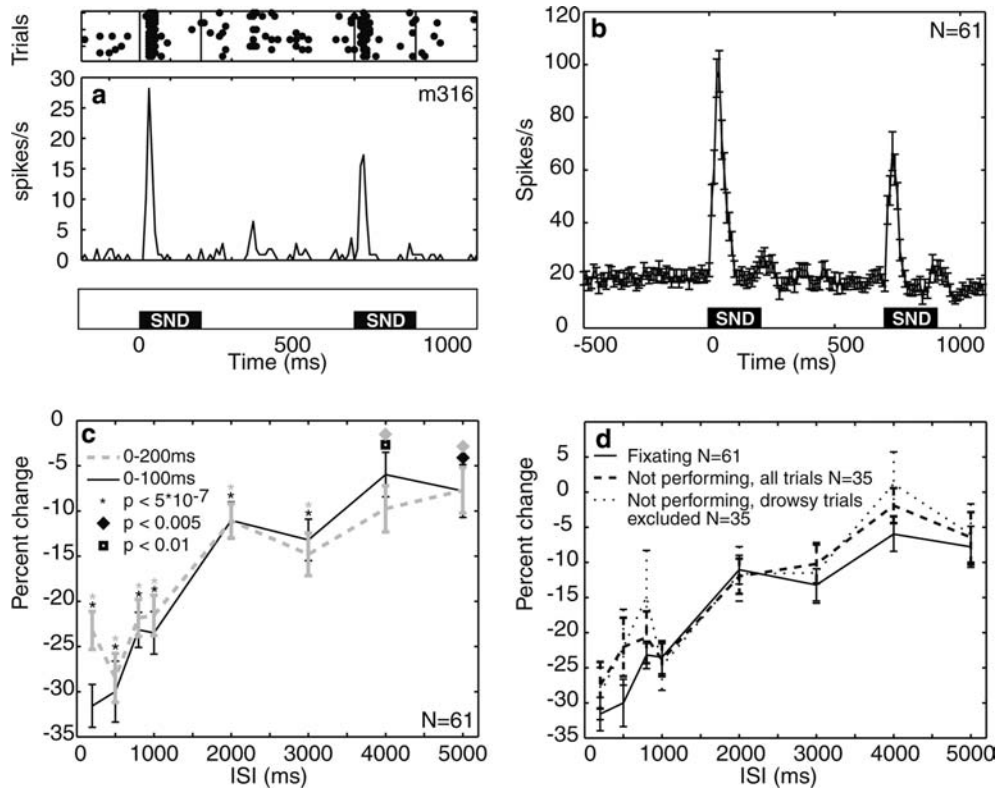
The locations of our recording penetrations were identified using MRI at the Dartmouth College Brain Imaging Center (GE 1.5T scanner, 3D T1 weighted gradient echo pulse sequence, 5" receive-only surface coil). One or more tungsten electrodes were inserted just above the dura for the scan; these electrodes were readily visible in the images and served as reference points for the reconstruction of the recording locations. In accordance with the boundaries of the core auditory cortex identified in the literature (for details see Werner-Reiss et al. 2003b), we limited our recording locations to those greater than or equal to 5 mm rostral from the caudal end of the supratemporal plane, greater than or equal to 2 mm from the medial end of the supratemporal plane in the region caudal to the insula/circular sulcus, and greater than or equal to 2 mm from the lateral edge of the supratemporal plane. In the region adjacent to the insula/circular sulcus, recording locations were restricted to those within the supratemporal plane rather than dipping down onto the lower/outer bank of the circular sulcus. All recording sites were well caudal of the RT region of core, and consisted of sites mainly in putative A1 but potentially in R as well. The mean response latency of the neurons in our sample was 26.3 ms, which is similar to a previous report in auditory cortex of awake monkeys (Recanzone et al. 2000) and slightly longer than the latencies reported in anesthetized primates (Recanzone et al. 1993; Recanzone et al. 1999; Kajikawa et al. 2005) and in awake primates using current source density analysis (Fu et al. 2004). Latency was calculated from the peristimulus time histograms (PSTH's) with 3 ms bins. The onset of the response was judged to occur at the center of the first bin whose height exceeded the mean baseline activity level by 3 standard deviations of the mean baseline bin height.

---

## Results

### General findings

The response to the second sound presentation was often weaker than the response to the first sound presentation. Figure 1a shows the response of an example neuron to



**Fig. 1** Response attenuation in auditory cortex. **a** Rasters and peristimulus time histogram (PSTH, 10 ms bin, no smoothing) illustrating the response profiles of an example neuron to sequences of two identical broadband noises (200 ms duration, 50 dB SPL) separated by a 500 ms ISI. **b** Average population response of 61 individual neurons to sequences of two identical broadband noise stimuli separated by 500 ms (*bars* indicate (+/- standard error of the mean)). **c** Mean percent change in response to the second of a sequence of two identical broadband noise sounds in the population of neurons with respect to the response elicited by the first sound. Results from both the full 0–200 ms response period (*dashed gray line*) and our standard 0–100 ms spike counting window (*solid black line*) are shown. We assessed the statistical significance of the effect at each ISI using a one-tailed *t*-test to determine whether the distribution of values of percent change in mean response of the population of neurons differed from zero (i.e.,

each neuron contributed one percent change value, and the statistical test was conducted on the list of values from the population of neurons). The symbols indicate that for all ISIs tested, the change in response was significantly less than 0 (all *p*'s < 0.01; *gray symbols* correspond to 0–200 ms response period, *black symbols* correspond to 0–100 ms response period). **d** Percent change in responses of neurons recorded when the animals fixated an LED (*N* = 61, *solid line*, same data as shown in panel C), compared to percent change in responses of neurons recorded when the animals performed no task at all (*N* = 35, *dashed line*, 0–100 ms spike counting window). We also repeated the analysis with trials in which the animal may not have been alert excluded. This was achieved by eliminating trials from the non-performing dataset if eye position changed by more than 2° during the presentation of sound 1. The results after these trials were excluded were very similar (*dotted line*)

two identical broadband noises separated by 500 ms: the response to the second sound was diminished compared to the first. Figure 1b shows a peristimulus time histogram (PSTH) illustrating this phenomenon for a population of neurons (*N* = 61): the second peak in the PSTH is considerably smaller than the first peak in the PSTH. We quantified the effects of the first sound on the response to the second sound by calculating the percent change in response to a given sound when it was presented second versus when it was presented first:

$$\text{Percent Change} = 100 \times \frac{\overline{\text{Resp2}} - \overline{\text{Resp1}}_{\text{ref}}}{\overline{\text{Resp1}}_{\text{ref}}} \quad (1)$$

$\overline{\text{Resp2}}$  was the mean of the neural responses to a given second sound and for a given ISI.  $\overline{\text{Resp1}}_{\text{ref}}$  was the mean of all responses to that same sound when it was presented first.

Figure 1c shows the mean percent change in response in our population of recorded neurons as a function of ISI for pairs of broadband noise stimuli. Relatively short ISIs (200 and 500 ms) resulted in the most attenuation, approximately 30%. Recovery was slow, reaching a plateau at 5–10% attenuation during the interval from 2 to 5 s. We did not observe a complete recovery from attenuation even at ISIs of 5 s: for all ISIs tested the percent change was significantly different from zero, as indicated by the symbols (*t*-test). This suggests that the effect of a previous sound lasts at least 5 s.

The effects of prior sounds are independent of task performance

The effects of sound sequences reported thus far were observed while animals performed a fixation task with

multiple sound presentations followed by a fluid reward that was itself associated with a faint click. Although the sounds delivered during the trial did not have any deliberate relevance to the animal, they did serve as markers of the passage of time through each trial (it is challenging to maintain fixation for 5-ish seconds), and thus were predictive of the ensuing reward. In addition, it is conceivable that fixation of the visual target per se could influence the findings, perhaps by focusing attention away from the sounds. To determine whether any of these factors affected the results, we repeated the experiment when the animals were not required to perform any task at all. Under these conditions, a “trial” is a completely artificial construct with no meaning to the animal, and there is nothing to distinguish the ISI from the ITI except that the shortest ITI was longer than the longest ISI.

When the responses to both trial types, fixating ( $N=61$ , solid line) versus not performing ( $N=35$ , dashed line), were compared, the result was the same pattern of attenuation (Figure 1d). The responses to sound sequences in both trial types were influenced by the ISI; however, the pattern of attenuation was similar between the two groups of neurons. In the subpopulation of neurons tested in both paradigms ( $N=15$ ), no statistically significant difference as a function of task was observed ( $t$ -test,  $p=0.2977$ ). We also considered the possibility that the level of alertness of the animal might affect the results. Drowsiness is readily apparent from the pattern of spontaneous eye movements, which contain a greater proportion of slow, drift movements when the animal is sleepy. We therefore repeated the analysis with such trials excluded. The pattern of results was very similar (Figure 1d, blue dotted line).

---

## Discussion

We found that the first sound in a two-sound sequence attenuated the responses of auditory cortical neurons to the second sound for the entire range of ISIs tested, although the effect was modest in size at ISIs  $> 3$  s. The results were very similar regardless of whether the monkeys were performing a task or not.

By definition, the attenuation metric has to return to zero when the ISI and ITI have the same duration. Thus, it is not possible with our experimental design and parameters to establish the true time interval at which the response fully recovers from the effects of the previous sound, it is only possible to estimate a lower bound on the time course of that recovery. Our results therefore can only provide a minimum estimate for how long a silent period is required for neural responses to recover from the influence of the previous sound. Further experiments with a longer ITI would permit exploration of longer ISIs.

The similarity between the results during the performing and non-performing conditions suggests that the response attenuation is at least partly composed of

an automatic process that is not dependent on behavioral context. It is possible that the results were so similar between the non-performing and performing conditions because neither condition required the animal to respond to the sounds. Indeed, perhaps performance of a sound discrimination task might tend to reduce the degree of response attenuation. Additional studies with a range of different task types would be needed to investigate this possibility.

Numerous single and multi-unit recording studies in primary auditory cortex of animals have reported attenuation in the responses to the second sound in a two-sound sequence for ISIs up to  $\sim 1$ – $2$  s (Hoehnerman and Gilat 1981; Calford and Semple 1995; Brosch and Schreiner 1997; Reale and Brugge 2000); Bartlett and Wang, 2005; Fitzpatrick et al. 1999; see also McKenna et al. 1989. Our results extend this time window out to 3–5 s, the longest we could test.

Many types of auditory perception are affected by stimulus history. Phenomena such as the precedence effect and forward masking generally occur on quite short time scales of a few ms to a few hundred ms. The effects of stimulus history in auditory cortex clearly persist much longer than this, and may therefore also relate to perceptual phenomena that occur on long time scales, such as speech perception and loudness adaptation. Under normal circumstances, sounds occur virtually continuously, and prolonged intervals of silence between stimuli are the exception rather than the rule. The implication is that auditory cortical activity is likely to be chronically influenced by the sounds that came before. The response attenuation we observed may reflect a generalized gain control mechanism that aids in maintaining sensitivity in a changing auditory environment.

**Acknowledgments** We would like to thank Yale Cohen, Howard C. Hughes, Ryan Metzger, and O’Dhanial Mullette-Gillman for providing useful comments on this study and Tammy Laroche of the Dartmouth College Brain Imaging Center for assistance with MRI. We are grateful for financial support to K.K. P. from the National Institutes of Health (NIH) NS 44666-02 and to J.M.G. from the following sources: Alfred P. Sloan Foundation McKnight Endowment Fund for Neuroscience, Whitehall Foundation, John Merck Scholars Program, ONR Young Investigator Program, EJLB Foundation, NIH NS 17778-19, and the Nelson A. Rockefeller Center at Dartmouth.

---

## References

- Bartlett EL, Wang X (2005) Long-lasting modulation by stimulus context in primate auditory cortex. *J Neurophysiol* 94(1): 83–104
- Brosch M, Schreiner CE (1997) Time course of forward masking tuning curves in cat primary auditory cortex. *J Neurophysiol* 77:923–943
- Brosch M, Schreiner CE (2000) Sequence sensitivity of neurons in cat primary auditory cortex. *Cereb Cortex* 10:1155–1167
- Brosch M, Schulz A, Scheich H (1999) Processing of sound sequences in macaque auditory cortex: response enhancement. *J Neurophysiol* 82:1542–1559
- Calford MB, Semple MN (1995) Monaural inhibition in cat auditory cortex. *J Neurophysiol* 73:1876–1891

- Fitzpatrick DC, Kuwada S, Kim DO, Parham K, Batra R (1999) Responses of neurons to click-pairs as simulated echoes: auditory nerve to auditory cortex. *J Acoust Soc Am* 106:3460–3472
- Fu KM, Shah AS, O'Connell MN, McGinnis T, Eckholdt H, Lakatos P, Smiley J, Schroeder CE (2004) Timing and laminar profile of eye-position effects on auditory responses in primate auditory cortex. *J Neurophysiol* 92:3522–3531
- Gottlieb Y, Vaadia E, Abeles M (1989) Single unit activity in the auditory cortex of a monkey performing a short term memory task. *Exp Brain Res* 74:139–148
- Groh JM, Kelly KA, Underhill AM (2003) A monotonic code for sound azimuth in primate inferior colliculus. *J Cogn Neurosci* 15:1217–1231
- Hocherman S, Gilat E (1981) Dependence of auditory cortex evoked unit activity on inter-stimulus interval in the cat. *J Neurophysiol* 45:987–997
- Javitt DC, Schroeder CE, Steinschneider M, Arezzo JC, Vaughan HG Jr (1992) Demonstration of mismatch negativity in the monkey. *Electroencephalogr Clin Neurophysiol* 83:87–90
- Judge SJ, Richmond BJ, Chu FC (1980) Implantation of magnetic search coils for measurement of eye position: an improved method. *Vision Res* 20:535–538
- Kajikawa Y, de La Mothe L, Blumell S, Hackett TA (2005) A comparison of neuron response properties in areas A1 and CM of the marmoset monkey auditory cortex: tones and broadband noise. *J Neurophysiol* 93:22–34
- Kelly KA, Werner-Reiss U, Underhill AM, Groh JM (2002) History of recent past affects neural responses in auditory cortex of awake primates. In: Association for Research in Otolaryngology, Mid Winter Meeting, Abstr. 448
- Lu T, Wang X (2000) Temporal discharge patterns evoked by rapid sequences of wide- and narrowband clicks in the primary auditory cortex of cat. *J Neurophysiol* 84:236–246
- Mantysalo S, Naatanen R (1987) The duration of a neuronal trace of an auditory stimulus as indicated by event-related potentials. *Biol Psychol* 24:183–195
- McKenna TM, Weinberger NM, Diamond DM (1989) Responses of single auditory cortical neurons to tone sequences. *Brain Res* 481:142–153
- Mickey BJ, Middlebrooks JC (2001) Responses of auditory cortical neurons to pairs of sounds: correlates of fusion and localization. *J Neurophysiol* 86:1333–1350
- Naatanen R, Paavilainen P, Alho K, Reinikainen K, Sams M (1986) Inter-stimulus interval and the mismatch negativity. In: International Evoked Potentials Symposium, Berlin, Germany, pp 392–397
- Naatanen R, Picton T (1987) The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. *Psychophysiology* 24:375–425
- Reale RA, Brugge JF (2000) Directional sensitivity of neurons in the primary auditory (AI) cortex of the cat to successive sounds ordered in time and space. *J Neurophysiol* 84:435–450
- Recanzone GH, Guard DC, Phan ML (2000) Frequency and intensity response properties of single neurons in the auditory cortex of the behaving macaque monkey. *J Neurophysiol* 83:2315–2331
- Recanzone GH, Schreiner CE, Merzenich MM (1993) Plasticity in the frequency representation of primary auditory cortex following discrimination training in adult owl monkeys. *J Neurosci* 13:87–103
- Recanzone GH, Schreiner CE, Sutter ML, Beitel RE, Merzenich MM (1999) Functional organization of spectral receptive fields in the primary auditory cortex of the owl monkey. *J Comp Neurol* 415:460–481
- Robinson DA (1972) Eye movements evoked by collicular stimulation in the alert monkey. *Vision Res* 12:1795–1808
- Robson MD, Dorosz JL, Gore JC (1998) Measurements of the temporal fMRI response of the human auditory cortex to trains of tones. *Neuroimage* 7:185–198
- Sams M, Hari R, Rif J, Knuutila JE (1993) The human auditory sensory memory trace persists about 10 s: neuromagnetic evidence. *J Cogn Neurosci* 5:363–370
- Suga N (1965) Functional properties of auditory neurons in the cortex of echo-locating bats. *J Physiol* 181:671–700
- Ulanovsky N, Las L, Nelken I (2003) Processing of low-probability sounds by cortical neurons. *Nat Neurosci* 6:391–398
- Werner-Reiss U, Kelly KA, Underhill AM, Groh JM (2003a) Long inter-stimulus intervals affect responses in primate auditory cortex. In: Society of Neuroscience, Abstr. CD-ROM, 181.12
- Werner-Reiss U, Kelly KA, Trause AS, Underhill AM, Groh JM (2003b) Eye position affects activity in primary auditory cortex of primates. *Curr Biol* 13:554–562