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Adaptation in the Auditory Space Map of the Barn Owl

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Gutfreund, Yoram and Eric I. Knudsen. Adaptation in the auditory space map of the barn owl. *J Neurophysiol* 96: 813–825, 2006. First published May 17, 2006; doi:10.1152/jn.01144.2005. Auditory neurons in the owl's external nucleus of the inferior colliculus (ICX) integrate information across frequency channels to create a map of auditory space. This study describes a powerful, sound-driven adaptation of unit responsiveness in the ICX and explores the implications of this adaptation for sensory processing. Adaptation in the ICX was analyzed by presenting lightly anesthetized owls with sequential pairs of dichotic noise bursts. Adaptation occurred in response even to weak, threshold-level sounds and remained strong for more than 100 ms after stimulus offset. Stimulation by one range of sound frequencies caused adaptation that generalized across the entire broad range of frequencies to which these units responded. Identical stimuli were used to test adaptation in the lateral shell of the central nucleus of the inferior colliculus (ICCLs), which provides input directly to the ICX. Compared with ICX adaptation, adaptation in the ICCLs was substantially weaker, shorter lasting, and far more frequency specific, suggesting that part of the adaptation observed in the ICX was attributable to processes resident to the ICX. The sharp tuning of ICX neurons to space, along with their broad tuning to frequency, allows ICX adaptation to preserve a representation of stimulus location, regardless of the frequency content of the sound. The ICX is known to be a site of visually guided auditory map plasticity. ICX adaptation could play a role in this cross-modal plasticity by providing a short-term memory of the representation of auditory localization cues that could be compared with later-arriving, visual-spatial information from bimodal stimuli.

INTRODUCTION

The midbrain contains an auditory map of space that is based on the tuning of neurons for sound localization cues, such as interaural time difference (ITD) and interaural level difference (ILD) (Olsen et al. 1989; Wise and Irvine 1985). In the barn owl, this map forms in the external nucleus of the inferior colliculus (ICX), where frequency-specific information about sound localization cues, provided by the lateral shell of the central nucleus of the inferior colliculus (ICCLs), is integrated to create neurons that are broadly tuned for frequency but sharply for space (Gold and Knudsen 2001; Knudsen 1987; Wagner et al. 1987).

The majority of neurons in the ICX space map have been shown to adapt rapidly during auditory stimuli (Knudsen and Konishi 1978). In the present study we explored this conspicuous property of ICX neurons. *Adaptation*, defined as a stimulus-induced decline in neural responsiveness, has been shown to occur at many levels in the auditory system. For example, adaptation has been observed in the auditory nerve (Chimento and Schreiner 1991), the inferior colliculus (Litovsky and Yin

1998; Malone and Semple 2001), the medial geniculate body (Schreiner 1980), and the auditory cortex (Mickey and Middlebrooks 2001; Ulanovsky et al. 2003). Adaptation has been linked to several perceptual effects including forward masking (Smith 1977), the precedence effect (Litovsky and Yin 1998; Mickey and Middlebrooks 2005; Spitzer et al. 2004), novelty detection (Ulanovsky et al. 2003, 2004), and contrast enhancement (Furukawa et al. 2005).

A recent study has reported a type of adaptation in the ICX that operates across the auditory and visual modalities. The ICX is an auditory structure and visual stimuli do not normally drive these units. However, ICX units exhibit visual responses when inhibition is blocked at a higher level in the pathway, in the optic tectum (OT) (Gutfreund et al. 2002). The visual input, which appears in the ICX under these conditions, arrives well after the associated auditory input primarily as a result of the substantial transduction delays (about 50 ms) in the retina. When visual and auditory stimuli originate from the same location in space, ICX responses to the later-arriving visual inputs are suppressed. In contrast, when visual and auditory stimuli originate from different locations in space, responses to the later-arriving visual inputs remain strong. It was postulated that this space-specific, cross-modal effect may play a role in guiding auditory plasticity in the ICX (Brainard and Knudsen 1993; Gutfreund and Knudsen 2004; Hyde and Knudsen 2001).

In the present study we measured the responses of units in the ICCLs and ICX to pairs of auditory stimuli. Previous studies in barn owls have characterized responses to pairs of stimuli at short interstimulus intervals (ISIs) and/or overlapping times (Keller and Takahashi 1996; Spitzer et al. 2004). Here we focus, instead, on stimulus pairs with longer ISIs (50–300 ms), beyond the ISIs typically associated with reverberations (Litovsky and Shinn-Cunningham 2001). Such long ISIs mimic the visual-auditory delays that have been observed in the ICX (Gutfreund et al. 2002). We find that the responses of ICX neurons adapt strongly to sequential auditory stimulation, that a large portion of this adaptation develops specifically in the ICX, and that the kinetics of this adaptation are appropriate for it to influence responses to instructive visual signals.

METHODS

Animals and surgery

Six adult barn owls (*Tyto alba*) were used in this study. The owls were cared for in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and the guidelines of the Stanford University Animal Care and Use Committee. Each owl was prepared for electrophysiological experiments in a single surgical

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procedure. The owl was anesthetized with halothane (1.5%) in a mixture of nitrous oxide and oxygen (0.8:1). A small stainless steel plate was cemented to the base of the skull for securing the head in a stereotaxic apparatus, and craniotomies were made on both sides of the skull above the OT and inferior colliculus. The brain surface was covered with antibiotic ointment and the craniotomies were temporarily sealed with dental acrylic. The tissue surrounding the incision was treated with lidocaine and betadine and sutured together.

Electrophysiology

On the day of an experiment, the owl was anesthetized with halothane and nitrous oxide, wrapped in a soft leather jacket, and mounted in a stereotaxic apparatus with its head bolted in place. The recording apparatus was in the center of a sound-attenuating chamber (IAC 404A) with echo-suppressing foam covering its walls. Retinal landmarks were used to align the visual axes relative to a calibrated tangent screen. After the owl was positioned in the recording apparatus, one of the craniotomies was opened, the halothane was turned off, and the owl was maintained on a mixture of nitrous oxide and oxygen for the duration of the experiment.

Electrophysiological recordings were made extracellularly using tungsten microelectrodes (about 1 M Ω ; FHC). The electrodes were positioned stereotaxically and advanced with a remote-control stepping motor. A Tucker-Davis Technologies System3 was used to record and isolate action potentials from single neurons or small numbers of neurons. Spike waveforms and times were stored on a computer and analyzed using a custom Matlab program.

At the end of each recording session, the craniotomy was cleaned with antibiotic solution and resealed with dental acrylic. The owl was allowed to recover for 1–2 h under a heat lamp before being released back into the aviary.

Auditory stimulation

Computer-generated signals were transduced by a pair of matched miniature earphones (Knowles ED-1914). The earphones were placed in the center of the ear canal about 5 mm from the tympanic membrane. The amplitude and phase spectra of the earphones were equalized within ± 2 dB and ± 2 μ s between 2 and 12 kHz by computer adjustment of the stimulus waveform.

Acoustic stimuli consisted of bursts of either broadband (3–12 kHz) or narrowband (1-kHz bandwidth; finite impulse response filter order = 70) noise with rise/fall times of 3–5 ms, presented at an interstimulus interval of either 1 or 2 s. Sound levels were controlled by two independent attenuators and are reported as average binaural level (ABL) relative to a fixed arbitrary sound pressure level. Unit responses to an acoustic stimulus were quantified as the number of spikes in a given time window after stimulus onset minus the number of spikes during the same amount of time immediately before stimulus onset (baseline activity). Response threshold was defined as the lowest ABL that elicited a significant response (one-tailed *t*-test; $P < 0.01$; $n = 20$).

Tuning curves were generated by varying a single parameter (ITD, ILD, frequency, or ABL) while holding all other parameters constant. The value of the tested parameter was varied randomly in stimulus sets that were repeated 10–20 times. ITD tuning was measured by varying ITD in 10- μ s steps. The width of ITD tuning curves was defined as the range over which responses were $>50\%$ of the maximal response; best ITD was the midpoint of this range.

Frequency response curves were measured by varying the center frequency of narrowband noise bursts in 1-kHz steps. Sound stimuli were presented at the best ITD and best ILD and at a sound level 20 dB above the site's broadband threshold. The width of frequency tuning was defined as the range over which responses were $>50\%$ of the maximal response.

Response adaptation was measured using sequential pairs of noise bursts. The second stimulus, which tested the degree of adaptation, was held constant and consisted of a narrowband noise burst, 30 ms in duration, at the site's best ITD and best ILD, with a passband centered on the best frequency for the site. The ABL of the second stimulus was always set at 10 dB above threshold, as measured with this stimulus presented alone. Adaptation was quantified as the number of spikes in response to the second stimulus presented alone (40- or 50-ms time window starting at the onset of the stimulus) minus the number of spikes to the second stimulus (during the equivalent time window) when preceded by the first stimulus (the properties of which varied, depending on the experiment), divided by the number of spikes to the second stimulus presented alone. In most cases, the response to the first stimulus ended before the time window for counting responses to the second stimulus. In the few cases in which responses to the first stimulus might have overlapped with responses to the second stimulus, we measured responses to the first stimulus presented alone (during the time window used for measuring responses to the second stimulus) and subtracted these responses from the responses to the second stimulus.

Visual stimulation

The methods for stimulating and recording visual responses in the ICX (results shown in Fig. 9) are described in detail elsewhere (Gutfreund et al. 2002). Briefly, with a tungsten microelectrode positioned in the ICX, a glass multibarrel electrode was positioned in the OT at a site where the best ITD and best ILD matched those of the ICX site (best ITD: ± 5 μ s, best ILD: ± 2 dB). The central barrel, filled with a carbon fiber (diameter of 7 μ m), was used to record multiunit activity in the OT. The remaining four barrels had tip diameters of 3–6 μ m and were used to iontophorese bicuculline methiodide (10 mM in 0.9% saline, adjusted to pH 3.0 with HCl; Sigma). Bicuculline was initially applied in the OT with a low current level (typically 30–50 nA). We then searched for visual responses in the ICX by projecting a light bar onto a calibrated screen in front of the owl. If visual responses were not detected, we increased the iontophoretic current and searched again for visual responses. If visual responses were not observed at any current level ≤ 120 nA, the electrode in the ICX was advanced 100 μ m to a new site and the process was repeated. Once a visual response was detected, the same iontophoretic current level was maintained throughout the experiment. Visual receptive fields were mapped with bars and spots of light projected onto a screen located 1 m in front of the owl.

Targeting of nuclei

The OT was targeted stereotaxically and recognized by its characteristic bursting activity. Recording location in the OT was inferred from the location of visual receptive fields. The ICCLs was targeted stereotaxically by positioning the electrode 2 mm caudal and 3 mm medial from the tectal representation of 0° azimuth and +10° elevation (relative to the visual axes). The electrode was then moved laterally and rostrally in steps of about 300 μ m to sample neurons from the ICCLs and the ICX.

We recorded multiunit responses to pairs of sequential sounds from 72 sites in the inferior colliculus of six anesthetized barn owls: 24 sites in the ICCLs and 48 sites in the ICX. The following criteria were used to distinguish between ICX and ICCLs sites. Neurons in the ICCLs are sharply tuned for frequency and best frequency increases systematically from low to high with dorsoventral depth. In contrast, ICX units respond to broad ranges of frequencies with little change in best frequency with depth (Knudsen and Konishi 1978). In the ICCLs, tuning to ILD is broad and there is no systematic progression of best ILD with electrode depth. In the ICX, tuning to ILD changes systematically from right ear greater (dorsal) to left ear greater (ventral). In previous studies, anatomical reconstructions of recording sites in each

nucleus have confirmed the correspondence of these properties with the respective nuclei (Brainard and Knudsen 1993; Gold and Knudsen 2000).

RESULTS

Adaptation to sound level and frequency in the ICX

To explore the effects of sound level and frequency on adaptation in the ICX, we systematically changed the level or frequency of a first auditory stimulus, while testing the adaptation state of the site with a constant, second auditory stimulus (30-ms narrowband noise centered at the site's best frequency; 10 dB above threshold). Representative results are shown in

Fig. 1. The threshold sound level for the unit was -75 dB. Even when the level of the first stimulus was below threshold (-85 and -80 dB), responses to the second stimulus were suppressed compared with control responses (Fig. 1*B*, dark curve; $P < 0.05$, t -test). Thus adaptation occurred even when the neuron did not generate action potentials. Response adaptation increased with the strength of the first stimulus up to a sound level of -70 dB, above which responses to the second stimulus were no longer evoked (Fig. 1*A*).

In the first test, the frequency ranges of the first and second stimuli were matched (same frequency adaptation). In the second test (Fig. 1*C*), the center of the passband of the first stimulus was shifted to 8 kHz (still within the frequency-tuning

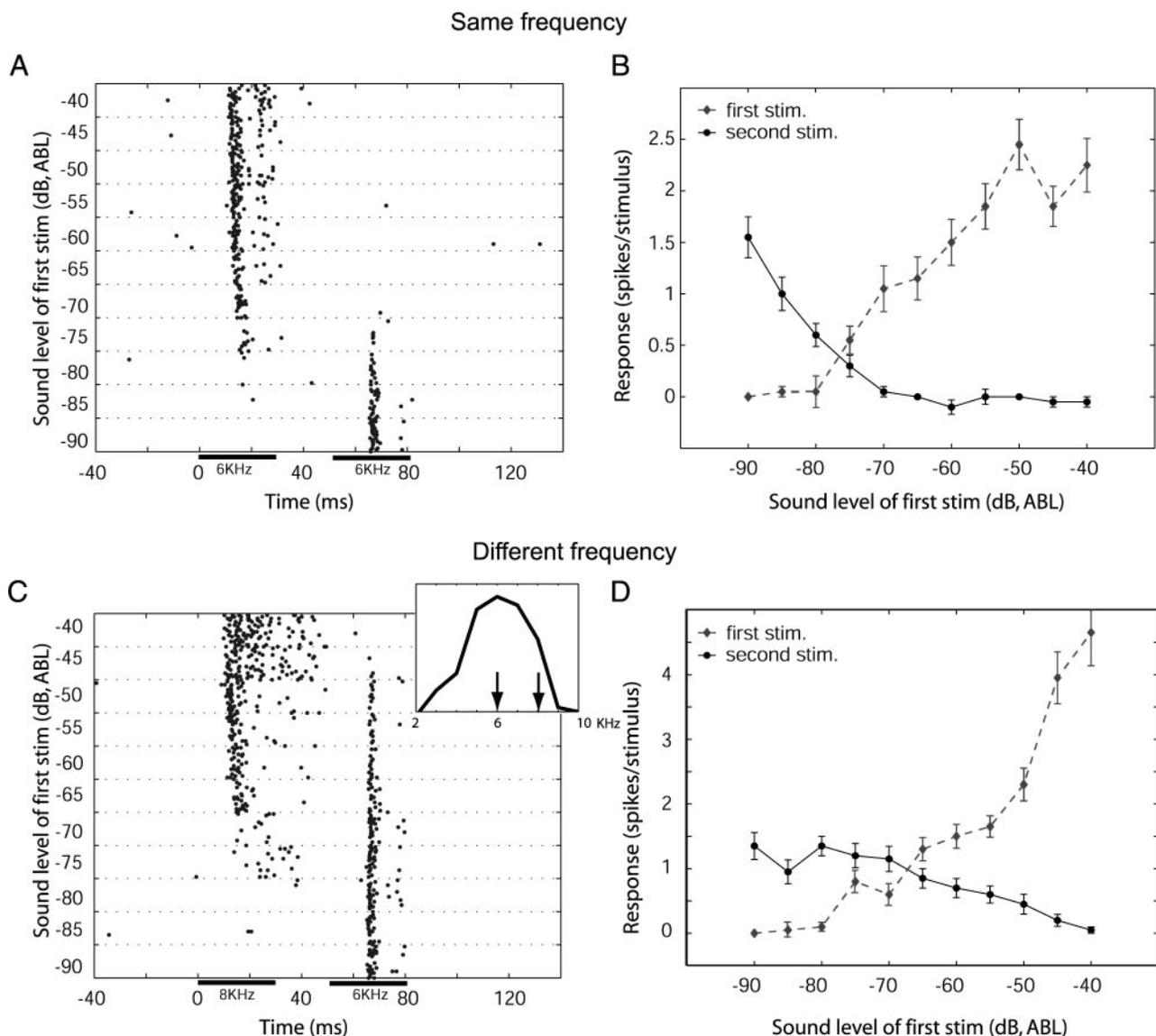


FIG. 1. Responses of an external nucleus of the inferior colliculus (ICX) site to a sequence of 2 auditory stimuli. *A–B*: responses of an ICX site to 2 narrowband noise bursts centered on the same frequency (30-ms duration; 5-ms rise/fall times; 20-ms gap between stimuli; narrowband noise centered on 6 kHz, the site's best frequency). *A*: y-axis represents the level of the 1st stimulus. Level of the 2nd stimulus was held constant at a level 10 dB above response threshold. Stimulus timing is represented by the bars at the bottom. *B*: average response to the 1st stimulus (during a time window of 0–50 ms relative to the onset of the 1st auditory stimulus) is shown in gray and the average response to the 2nd stimulus (during a time window of 50–100 ms relative to the onset of the 1st auditory stimulus) is shown in black. Neural responses are plotted as a function of the level of the 1st sound. *C*: responses from the same ICX site as in *A* and *B* to a sequence of 2 narrowband noise bursts centered on different frequencies (arrows in the inset of *C* show the center frequencies). Responses are shown vs. the level of the 1st sound. Inset: frequency-tuning curve measured for this site. *D*: response to the 2nd sound (black) and the response to the 1st sound (gray) vs. the level of the 1st sound. Error bars represent SE.

curve of the site; Fig. 1C, *inset*), whereas that of the second stimulus remained centered on 6 kHz (different frequency adaptation). A significant decrease in the response to the second stimulus was apparent when the first stimulus was 15 dB above threshold (-60 dB; $P < 0.01$, *t*-test) and responses to the second stimulus were eliminated when the first stimulus was 30 dB above threshold. Thus adaptation occurred even though the passbands of the first and second stimuli did not overlap. Adaptation across frequency channels was weaker, however, than same-frequency adaptation (compare Fig. 1, C and D with Fig. 1, A and B).

A summary of the results from all sites measured in the ICX is shown in Fig. 2. The average normalized response to the second stimulus is plotted as a function of the sound level of the first stimulus when the passbands of the first and second stimuli matched (solid curve) and when they differed by 2 kHz (dashed curve). When the stimulus passbands matched, a reduction in the population response to the second stimulus occurred ($P < 0.05$, *t*-test) after a -85 -dB first stimulus, which was below the average response threshold of units in the ICX (-77 ± 5 dB; $n = 30$), and the population response to the second stimulus was completely suppressed by a -40 -dB first stimulus. Cross-frequency adaptation was weaker, first appearing in the population response after a -80 -dB stimulus and reaching 75% after a -40 -dB stimulus.

Adaptation to sound level and frequency in the ICCLs

We compared adaptation in the ICX with adaptation in the ICCLs, the primary source of auditory input to the ICX (Albeck and Konishi 1995; Gold and Knudsen 2001; Rodriguez-Contreras et al. 2005). Figure 3 shows responses of an ICCLs site to two sequential narrowband stimuli. The stimulus paradigm was the same as that used to test ICX sites. Figure 3A shows the result of presenting sequential sounds with matching narrowband stimuli centered on the best frequency (4 kHz) for the

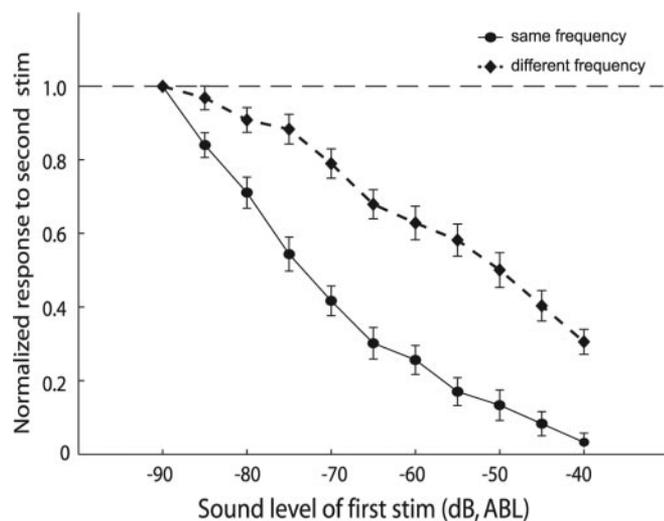


FIG. 2. Adaptation in the ICX. Mean response to the 2nd sound, averaged across all recording sites in the ICX, is shown as a function of the average binaural level (ABL) of the 1st sound. For each site, responses to the 2nd stimulus were normalized to the response to the same stimulus measured without adaptation (without a preceding stimulus). Solid curve represents results from experiments in which the 1-kHz passbands of the 2 stimuli were matched. Dashed curve represents results from experiments in which the centers of the 1-kHz passbands of the 2 stimuli differed by 2 kHz.

site. Adaptation occurred ($P < 0.05$) only after the level of the first stimulus exceeded that of the second stimulus (> -70 dB) and responses to the second stimulus were not eliminated over the range of sound levels tested.

Results from a cross-frequency adaptation experiment, performed at the same ICCLs site, are shown in Fig. 3C. In this experiment, the passband of the first stimulus was centered on 6 kHz and that of the second stimulus on 4 kHz. Because of the site's sharper frequency tuning, which is characteristic of ICCLs sites (Albeck and Konishi 1995; Brainard and Knudsen 1993; Knudsen and Konishi 1978), the frequency-tuning curve did not include 6 kHz (see *inset* in Fig. 3C) and adaptation in response to a 6-kHz first stimulus was not observed throughout the range of levels tested (Fig. 3D, solid curve).

A summary of the results obtained from all ICCLs sites is shown in Fig. 4, A and B (dark curves). Adaptation was evident for narrowband stimuli that shared the same narrow passband (Fig. 4A), but adaptation did not generalize to frequencies 2 kHz away (Fig. 4B). Same-frequency adaptation was weaker in the ICCLs than in the ICX (compare black curve with gray curve in Fig. 4A). Cross-frequency adaptation was not observed in the ICCLs at sound levels that induced clear adaptation in the ICX (compare black curve with gray curve in Fig. 4B).

To quantify the adaptation in ICX and ICCLs, we measured two properties: 1) *adaptation threshold*, the stimulus level that was necessary to reduce the response to the second stimulus by 30%; and 2) *adaptation strength*, the maximum reduction in response relative to the response to the stimulus alone for stimuli up to -40 dB. The average results, based on measurements at all sites in the ICX ($n = 30$) and in the ICCLs ($n = 24$), are shown in Fig. 4, C and D. Both measurements of adaptation showed significantly stronger adaptation in the ICX compared with the ICCLs (two-sample *t*-test, $P < 0.001$) for both same- and different-frequency stimuli.

Time window of adaptation

We characterized the effect of varying the time interval between the onset of the two auditory stimuli (ISI). In these experiments, both stimuli were narrowband noises with a 1-kHz passband centered on the best frequency for the recording site. The first stimulus was held constant at a level 20 dB above threshold for the site, whereas the second stimulus was held constant at 10 dB above threshold. The examples in Fig. 5 show responses from two sites: one in the ICX (Fig. 5, A and B) and the other in the ICCLs (Fig. 5, C and D). For the ICX site, a reduction in the response to the second stimulus was apparent throughout the range of ISIs tested, and the longest interval (320 ms) still yielded a response reduction of $>60\%$ relative to control responses. In contrast, for the ICCLs site, a reduction in responses to the second stimulus was observed for only the shortest ISI (40 ms), and for longer ISIs, responses to the second stimulus were not different from control responses ($P > 0.4$, *t*-test).

Summaries of the results from these experiments are shown in Fig. 5, E and F. The average normalized response as a function of ISI for all ICX sites tested in this manner ($n = 23$) is shown in Fig. 5E and for all ICCLs sites ($n = 21$) in Fig. 5F. At all ISIs, ICX sites showed stronger average adaptation than did ICCLs sites. The average adaptation was stronger in the

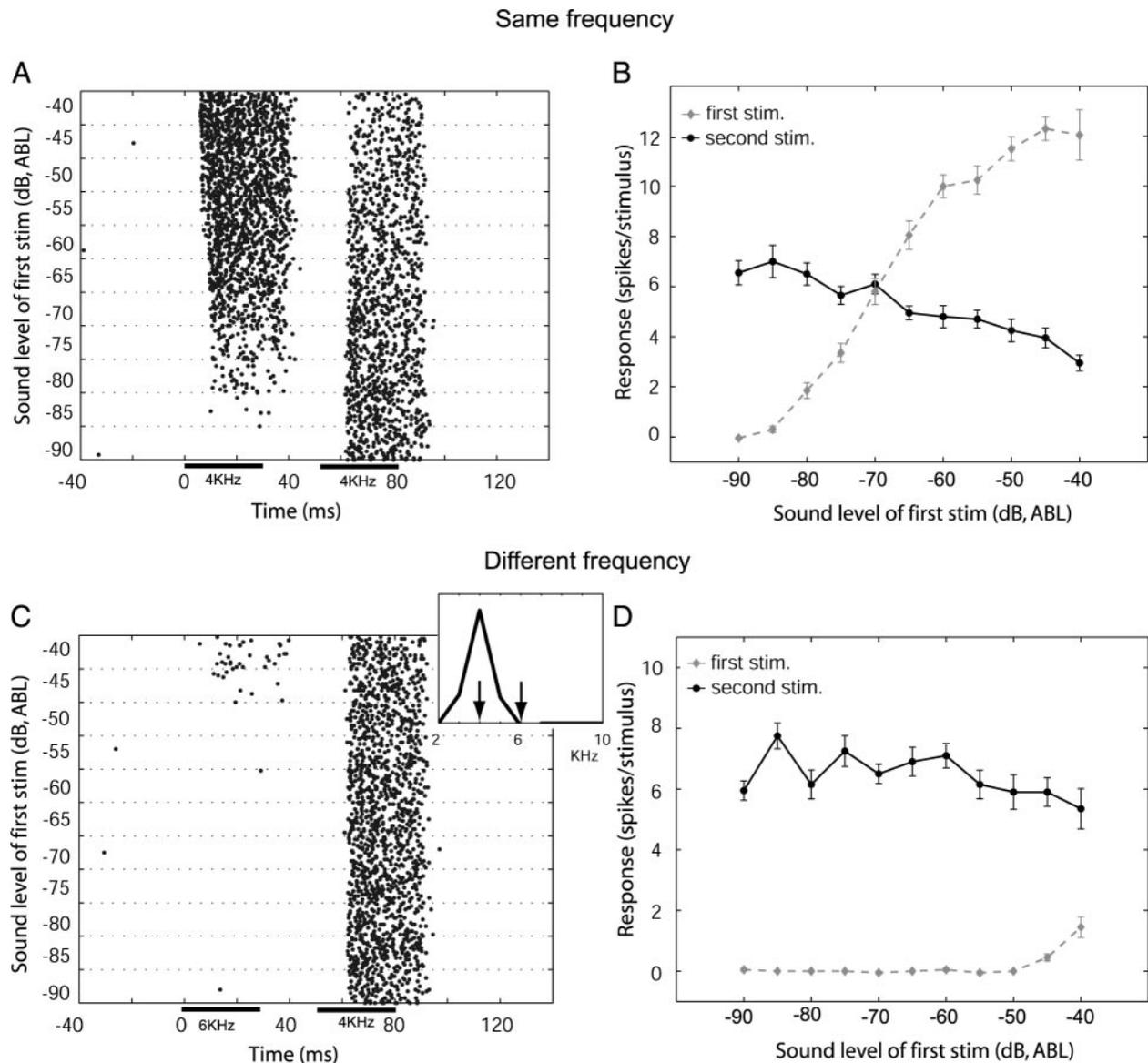


FIG. 3. Responses of a lateral shell of the central nucleus of the inferior colliculus (ICCLs) site to a sequence of 2 auditory stimuli. *A*: raster plot showing the responses of an ICCLs site to 2 dichotically presented noise bursts (30-ms duration; 5-ms rise/fall times; 20-ms gap between stimuli; narrowband noise centered on the site's best frequency). Level of the 2nd stimulus was held constant at a level 10 dB above response threshold. Stimulus timing is represented by the bars at the bottom. *B*: average response to the 1st stimulus (during a time window of 0–50 ms relative to the onset of the 1st auditory stimulus) is shown in gray. Average response to the 2nd stimulus (during a time window of 50–100 ms relative to the onset of the 1st auditory stimulus) is shown in black. Neural responses are plotted as a function of the level of the 1st sound. *C*: responses of the same ICCLs site as in *A* and *B* to a sequence of 2 narrowband noise bursts centered on different frequencies (arrows in the inset of *C* show the center frequencies). Responses are shown vs. the level of the 1st sound. Inset: frequency-tuning curve measured for this site. *D*: response to the 2nd sound (black) and the response to the 1st sound (gray) vs. the level of the 1st sound. Error bars represent SE.

ICX not only because of stronger response suppression but also because adaptation was elicited at more sites in the ICX than in the ICCLs (Table 1). For example, at ISIs of 120 ms about 80% of sites in ICX, compared with only about 15% of sites in ICCLs, showed significant adaptation (one-tailed *t*-test; $P < 0.01$). The difference between the proportions of significantly suppressed sites was more prominent at larger ISIs (Table 1), suggesting that ICX sites exhibited longer-lasting adaptation. We did not systematically explore ISIs >320 ms. However, at a few ICX sites that were tested with longer intervals (data not shown), significant response adaptation was observed 500 ms after the first stimulus.

We next tested the combined effects of stimulus duration and silent interval on response adaptation in the ICX and

ICCLs. The duration of the first stimulus was varied across values of 10, 30, and 50 ms, whereas that of the second stimulus was held constant at 30 ms (durations include 3-ms rise/fall times). The time to the second stimulus relative to the onset of the first stimulus was held constant at 60 ms. As a result, the effect of stimulus duration was combined with different durations of silent gaps between the stimuli. Therefore this test compared conditions favorable for adaptation (long duration of first stimulus with a short silent gap) with conditions unfavorable for adaptation (short duration with longer silent gap).

Figure 6 compares the results from the ICX and the ICCLs. A typical result from an ICX site is shown in Fig. 6, *A* and *B*. Even the shortest stimulus of 10-ms duration followed by a

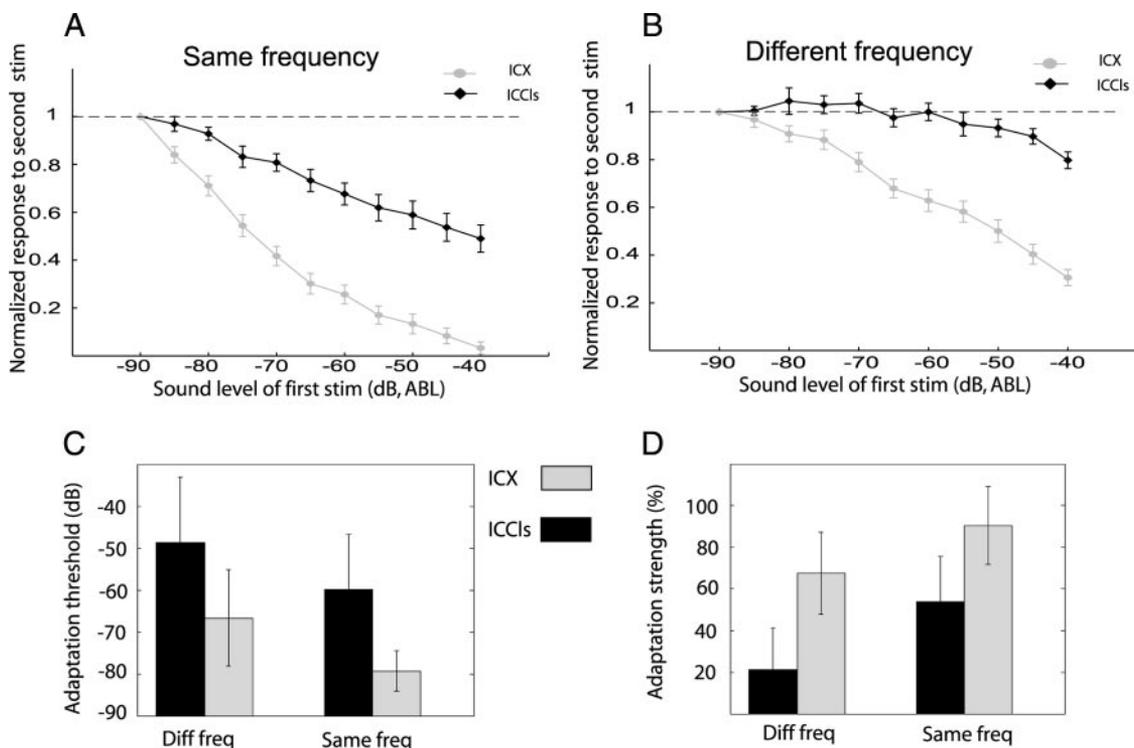


FIG. 4. Summary of adaptation effects. *A–B*: averaged response to the 2nd sound is shown as a function of the ABL of the 1st sound. Responses were normalized to the response without adaptation. *A*: results from experiments in which the 1-kHz passbands of the 2 stimuli were matched (same frequency). Gray curve represents the average for all sites in the ICX; black curve represents the average for all sites in ICCLs. *B*: results from experiments in which the centers of the 1-kHz passbands of the 2 stimuli differed by 2 kHz (different frequency), for ICX sites (gray curve) and for ICCLs sites (black curve). Error bars represent SEs. *C*: average adaptation threshold of all sites in the ICX (gray; $n = 30$) and of all sites in the ICCLs (black; $n = 24$). Adaptation threshold was defined as the stimulus level necessary to reduce the response to the 2nd stimulus by 30%. Results are shown from different frequency experiments (*left*) and same frequency experiments (*right*). Error bars show the SDs. *D*: average adaptation strength of all sites in the ICX (gray; $n = 30$) and in the ICCLs (black; $n = 24$). Adaptation strength was defined as the maximum reduction in response to the 2nd stimulus for 1st stimulus levels ranging from -90 to -40 dB. Error bars show the SDs.

50-ms gap was sufficient to eliminate responses to the second stimulus. In contrast, at the ICCLs site (Fig. 6, *C* and *D*), responses to the second stimulus remained strong after all three stimulus durations. Only the 50-ms stimulus followed by a 10-ms gap caused responses to the second stimulus to be reduced substantially relative to control responses (*t*-test; $P < 0.01$).

A summary of results from all sites tested in this manner ($n = 20$ in the ICX; $n = 19$ in the ICCLs) is shown in Fig. 6, *E* and *F*, which plots the average normalized response to the second stimulus as a function of the duration of the first stimulus. The average adaptation was substantially stronger in the ICX (Fig. 6*E*) than in the ICCLs (Fig. 6*F*) for all stimulus and gap durations. The adaptation produced in the ICX by a 10-ms stimulus followed by a 50-ms gap was greater than that produced in the ICCLs by a 50-ms stimulus followed by a 10-ms gap.

Effect of stimulus ITD

We next tested the effect of ITD on response adaptation in the ICX. An example is shown in Fig. 7. In this case, two auditory stimuli were presented with an ISI of 70 ms. The ITD of the first stimulus was varied randomly across a range of ITDs, whereas the ITD of the second stimulus was held constant at the best ITD for the site (corresponding to the center of its spatial receptive field). Figure 7 shows the response to the first stimulus alone (Fig. 7*A*) and to the two stimuli presented sequentially (Fig. 7*B*). Figure 7*C* shows the result of subtracting the data in Fig. 7*A* from those in Fig. 7*B*.

This subtraction isolated the influence of the ITD of the first stimulus on the response to the second stimulus. The response to the second stimulus was strongly modulated, depending on the ITD value of the first stimulus. A suppression of the second response was evident when the ITD of the first stimulus was near the best ITD of the site. This same effect was observed at all sites tested in the ICX ($n = 11$).

This result did not resolve whether the suppression effect was ITD specific (caused by the leading and lagging stimuli sharing the same ITD value) or simply activity dependent (caused by the strong neural responses to the best ITD).

To differentiate between these two possibilities, we tested the effect of a constant ITD first sound on the ITD tuning curve measured with the second stimulus. In this experiment, the ITD of the first stimulus was held constant at a suboptimal value for activating the unit and the ITD of the second stimulus was varied over a range that spanned the unit's excitatory range. The ITD of the first stimulus was chosen to elicit nearly 50% of the maximal response. An example is shown in Fig. 8*A*. The best ITD for this site was 10 μ s left ear leading and the ITD value of the first sound was 0 μ s. If adaptation were ITD specific, the effect on the ITD curve would have been asymmetric with stronger suppression in the flank corresponding with the ITD of the first stimulus (adapted flank), which in the example in Fig. 8*B* was the right flank. However, a leading noise burst with an ITD = 0 μ s caused a symmetrical attenuation of the response curve about the best ITD (Fig. 8*B*). This

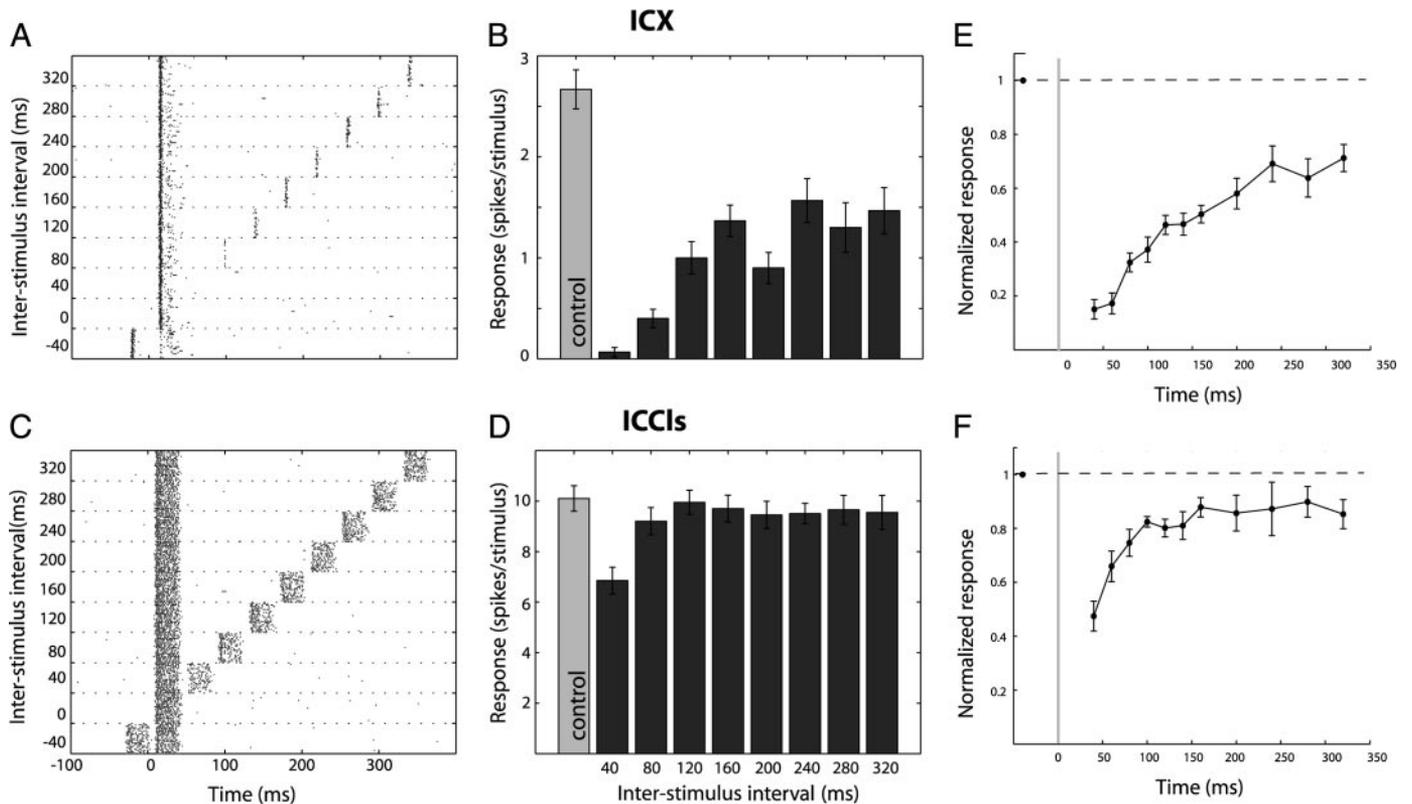


FIG. 5. Time window of adaptation in the ICX and the ICCIs. *A*: responses of an ICX site to 2 sequential auditory stimuli. Onset of the 1st stimulus (30-ms duration; 5-ms rise/fall times; 20 dB above threshold; narrowband centered at the site's best frequency) was fixed at *time 0*. Onset of the 2nd stimulus (30-ms duration; 5-ms rise/fall times; 10 dB above threshold; narrowband centered at the site's best frequency) was varied between 40 ms leading to 320 ms lagging. Each interstimulus interval (ISI) was repeated 20 times. *B*: response to the 2nd stimulus (average spikes per trial) vs. the ISI. Responses were measured during a 40-ms time window starting at the onset of the 2nd stimulus. Control response is the response to the same stimulus when it was leading (ISI = -40 ms). *C*: responses of an ICCIs site to the same stimuli as in *A*. *D*: responses of the site shown in *C* to the 2nd stimulus (average spikes per trial) vs. the ISI. *E*: average normalized response to the 2nd stimulus for all sites in ICX as a function of the ISI. *F*: average normalized response to the 2nd stimulus for all sites in the ICCIs as a function of the ISI. Responses in *E* and *F* are normalized to the response to the same stimulus when it was leading.

test was repeated at 11 ICX sites. For each site, the experiment was repeated twice: once the ITD of the first stimulus was shifted from the best ITD toward a more right ear leading ITD and once toward a more left ear leading ITD. The results are summarized in Fig. 8, *C* and *D*. The average adaptation effect was a uniform response decrease, independent of the ITD of the leading sound. This result indicated that adaptation was not ITD specific, but rather depended on the strength of the response to the preceding stimulus.

Cross-modal adaptation in the ICX

As previously reported (Gutfreund et al. 2002), iontophoretic injection of bicuculline into the OT caused visual responses to appear at the corresponding location in the ICX

auditory space map. An example of this effect is shown in Fig. 9, *A–D*. The response to a broadband noise burst as a function of ITD is shown in Fig. 9*A*; the response of the same site to a light flash is shown in Fig. 9*B*; and the response to simultaneous visual and auditory stimuli (bimodal stimuli) is shown in Fig. 9*C*. Bimodal stimuli resulted in sequential auditory and visual responses that were separated by about 60 ms, arising from the longer response latency to visual versus auditory stimuli (compare Fig. 9, *A* vs. *B*). The effect of ITD on visual responses was isolated by subtracting responses to the auditory stimulus alone (Fig. 9*A*) from responses to the bimodal stimulus (Fig. 9*C*). The result is shown in Fig. 9*D*. In this example, the ITD value that excited the site most powerfully (best ITD) was $-37 \mu\text{s}$ (left ear leading). Visual responses were sup-

TABLE 1. Response properties and prevalence of adaptation in the ICX and ICCIs

Response Threshold, dB	Frequency Tuning Width, kHz	Significant Adaptation (Number Significant/Total)				
		ISI = 60 ms		ISI = 120 ms		
		$\alpha = 0.01$	$\alpha = 0.05$	$\alpha = 0.01$	$\alpha = 0.05$	
ICX	-77.3 ± 5.2 ($n = 30$)	3.7 ± 1.0 ($n = 30$)	22/23	23/23	18/23	22/23
ICCIs	-79.6 ± 5.5 ($n = 24$)	2.2 ± 0.5 ($n = 24$)	14/21	17/21	3/21	6/21

On the left are the average response threshold (mean \pm SD) and average frequency tuning width (mean \pm SD). On the right are proportions of sites at which responses to the second stimulus were significantly lower than responses to the stimulus alone (one-tailed *t*-test) when tested with sequential frequency-matched stimuli.

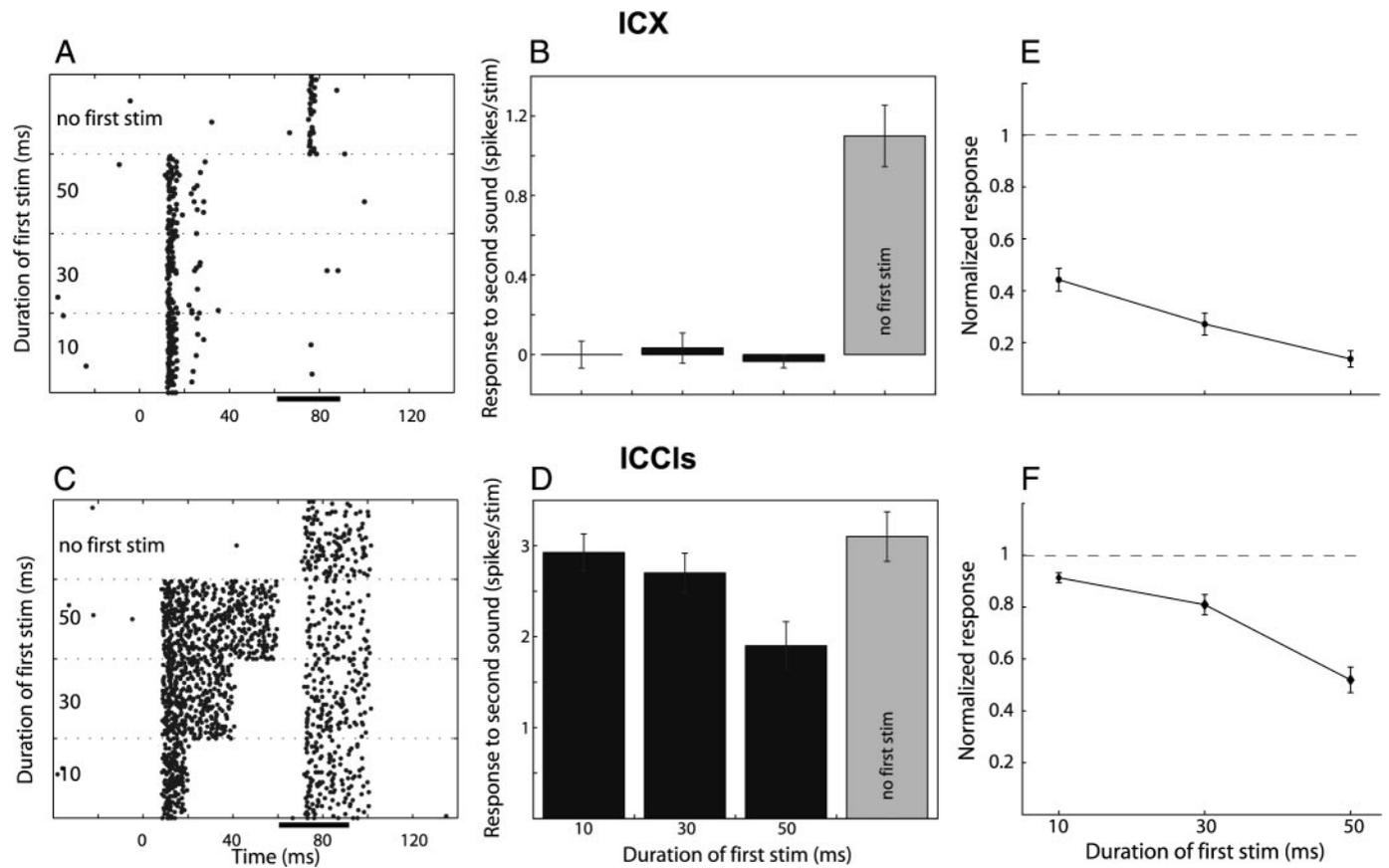


FIG. 6. Effect of stimulus duration and silent interval on adaptation in the ICX and ICCIs. *A*: responses from an ICX site. Duration of the 1st stimulus (30-ms duration; 5-ms rise/fall times; 20 dB above threshold; narrowband centered on the site's best frequency) was varied among no sound, 10, 30, and 50 ms. Onset of the 2nd stimulus (30-ms duration; 5-ms rise/fall times; 10 dB above threshold; narrowband centered on the site's best frequency) was held constant at 60 ms after the onset of the 1st stimulus. Therefore the silent interval varied among 50, 30, and 10 ms. Each block shows unit responses to 20 repetitions of a single combination of duration and silent interval. *B*: average response per trial for the data shown in *A* vs. the duration of the 1st stimulus. Control is the response to the same stimulus presented alone (*top raster* in *A*). *C*: data from an ICCIs site. Responses to the same stimuli as in *A* are shown. *D*: average response per trial for the data shown in *C* vs. the duration of the 1st stimulus. Control is the response to the same stimulus presented alone (*top raster* in *C*). *E*: average response to the 2nd stimulus for all sites in the ICX as a function of the duration of the 1st stimulus. Responses are normalized relative to the response to the 2nd stimulus presented alone. *F*: average response to the 2nd stimulus for all sites in the ICCIs as a function of the duration of the 1st stimulus. Data are normalized relative to the response to the 2nd stimulus presented alone. Error bars represent SEs.

pressed maximally when the ITD of the auditory stimulus was near $-37 \mu\text{s}$ (arrow in Fig. 1*D*). Note the similarity of this cross-modal effect to the isomodal, auditory–auditory effect (Fig. 7). In both cases, strong activation by a best ITD stimulus caused a dramatic suppression of subsequent responses.

A summary of this kind of analysis, averaged across 18 ICX sites, is shown in Fig. 1*E*. ITD axes were aligned on the best ITD for each site ($0 \mu\text{s}$ in Fig. 1*E*). Visual responses, which appeared 80–150 ms after stimulus onset and well after auditory responses ceased, were substantially reduced when the ITD of the auditory stimulus matched the best ITD for each site. Moreover, the magnitude of the visual response increased systematically as the stimulus ITD deviated from the best ITD for each site. The strength of the visual response encoded the magnitude of the difference between the ITD of the stimulus and the ITD expected by the site's best ITD. In other words, the visual response encoded the mismatch between the representations of the auditory and visual stimuli in the ICX space map.

DISCUSSION

The present work demonstrates that the responses to an auditory stimulus in the ICX are strongly suppressed by a

preceding auditory stimulus with matching values of binaural cues (that is, one that originates from the same location in space). In the following sections, we discuss the evidence for adaptation that is specific to the ICX and how this adaptation might influence auditory spatial processing and auditory–visual integration.

Adaptation in the auditory system

Previous work in the barn owl has characterized a form of adaptation that correlates with the perceptual phenomenon of echo suppression, also known as the precedence effect (Keller and Takahashi 1996; Spitzer et al. 2003, 2004). This form of adaptation is maximized when a lagging sound originates from a location in space that differs from that of the leading sound. This is in contrast to the adaptation we report here that is maximized when the leading and lagging sounds share the same binaural cue values (Fig. 7), that is, when they originate from the same location in space. However, in the previous studies, the focus was on the effects of short ISIs (<10 ms; Keller and Takahashi 1996) or partially overlapping stimuli (Spitzer et al. 2004). Lateral inhibition in the ICX may account for these cross-ITD suppression effects. The shortest ISI stud-

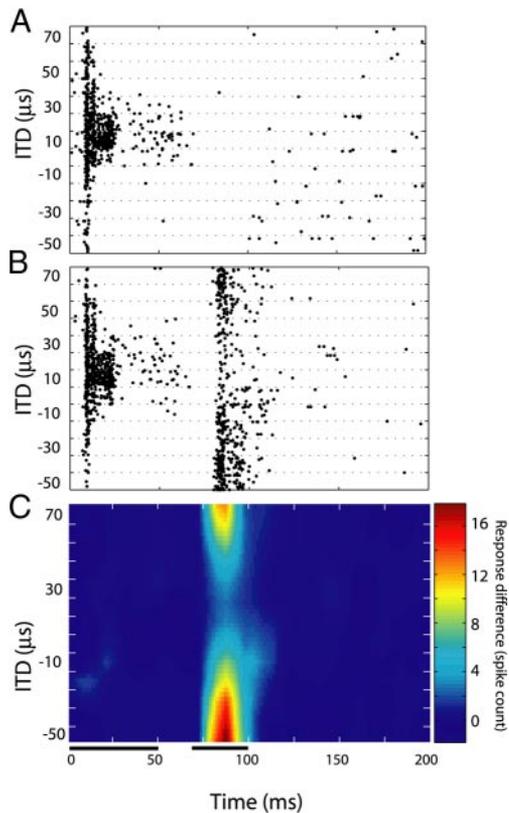


FIG. 7. Effect of interaural time difference (ITD) value of the preceding sound on auditory responses in the ICX. *A*: raster plot of responses from an ICX site to 50-ms noise bursts, presented at different ITDs. *B*: responses of an ICX site to 2 sequential auditory stimuli; the 1st stimulus was a 50-ms noise burst presented with an ITD value varying from 50 μ s left ear leading to 70 μ s right ear leading; the 2nd stimulus was a 30-ms noise burst presented at a constant best ITD value (15 μ s right ear leading). Trials shown in *B* were randomly interleaved with the trials shown in *A*. *C*: color-coded graph showing the result of subtracting the average response to the 1st stimulus alone (*A*) from the average response to a sequence of 2 stimuli (*B*). Subtraction was performed for each ITD tested, in 10-ms time bins. Result was smoothed with a 3×3 point running average.

ied in the present work was 50 ms and the shortest silent gap between successive stimuli was 10 ms. Using such conditions, we observed relatively modest response suppression when the ITD of the first stimulus was markedly different from the ITD of the second stimulus (data not shown), suggesting that if lateral inhibition underlies this effect, it does not persist beyond 10 ms after the offset of a stimulus.

In contrast, far more powerful adaptation resulted when the first and second stimuli shared the same ITD (Fig. 7). This form of adaptation is more similar to the forward inhibition or forward masking reported in the primary auditory cortex of cats and rats (Brosch and Schreiner 1997; Calford and Semple 1995; Wehr and Zador 2005). In the cortex, adaptation (forward masking), evoked by a 30- to 50-ms stimulus, lasts for ≤ 500 ms (Brosch and Schreiner 1997), comparable to the time course of adaptation we report here. Moreover, in the cortex, the most effective frequency range for inducing adaptation corresponds with the frequency-tuning curve of the unit. This is analogous to the results reported here for the ICX, where the most effective ITD range for inducing adaptation corresponds with the ITD tuning curve of the units (Fig. 7). Another striking similarity is the abrupt appearance of strong adaptation in the

auditory pathway. Neurons in the medial geniculate nucleus, which provides input to the cortex, exhibit relatively weak adaptation (Creutzfeldt et al. 1980; Wehr and Zador 2005), similar to that reported here for ICCls neurons. In contrast, the responses of most cortical neurons can be completely suppressed by preceding stimulus, similar to ICX neurons. It is possible that similar mechanisms underlie adaptation in the auditory cortex and in the ICX.

Site of adaptation

The strong adaptation observed in the ICX reflects the accumulating effect of adaptation at each level of the ascending pathway, including the ICX. However, our finding that the average adaptation measured in the ICX is stronger than the average adaptation measured in the nucleus one synapse before the ICX, the ICCls (Fig. 4, 5, and 6), suggests that a substantial fraction of this adaptation is a result of processes operating within the ICX itself. In barn owls the sensitivity to space depends on the combined sensitivity of neurons to ITD and ILD across broad ranges of frequency (Euston and Takahashi 2002; Moisef and Konishi 1981, 1983). Tuning to both ITD and ILD first occurs within frequency channels in the ICCls (Mazer 1998). The translation of this frequency-specific cue information into a representation of space depends on the convergence of information across frequency channels (Fujita and Konishi 1991; Takahashi and Konishi 1986). Consequently, neurons in the ICCls tend to have sharp frequency tuning, whereas neurons located laterally within the ICX tend to have broader frequency tuning (Brainard and Knudsen 1993; Gold and Knudsen 2000). Therefore our observation that adaptation tended to increase in ICX (Fig. 4) suggests that part of the adaptation develops in parallel with the development of spatial selectivity arising from mechanisms within the ICCls and ICX.

The results do not completely rule out alternative possibilities, however. One possibility is that adaptation is occurring somewhere else in the brain and is transmitted to the ICX through an input other than the ICCls. This possibility is unlikely because results from inactivation experiments indicate that auditory responses in ICX are determined by inputs from the ICCls (Gold and Knudsen 2001). In the barn owl only two other sources of input to the ICX are known: from the OT (Hyde and Knudsen 2000; Luksch et al. 2000) and from the arcopallium (Knudsen et al. 1993). Both of these inputs are sparse and their effect on auditory responses has not been demonstrated.

Another possibility is that a small subpopulation of ICCls neurons that is specifically vulnerable to adaptation contributes to responses in ICX. However, anatomical studies indicate a substantial number of ICX-projecting neurons in ICCls (Feldman and Knudsen 1997), seemingly more than project up to the auditory thalamus (Arthur 2005). A third alternative is that a slightly suppressed response entering the ICX may appear further suppressed in the ICX because of a nonlinear relationship between response strength in ICCls and response strength in the ICX. Such a nonlinear relationship, however, cannot explain the results shown in Table 1 for ISIs > 120 ms: about 80% of the sites in the ICX showed substantial adaptation compared with only 15% of the sites in the ICCls. Neverthe-

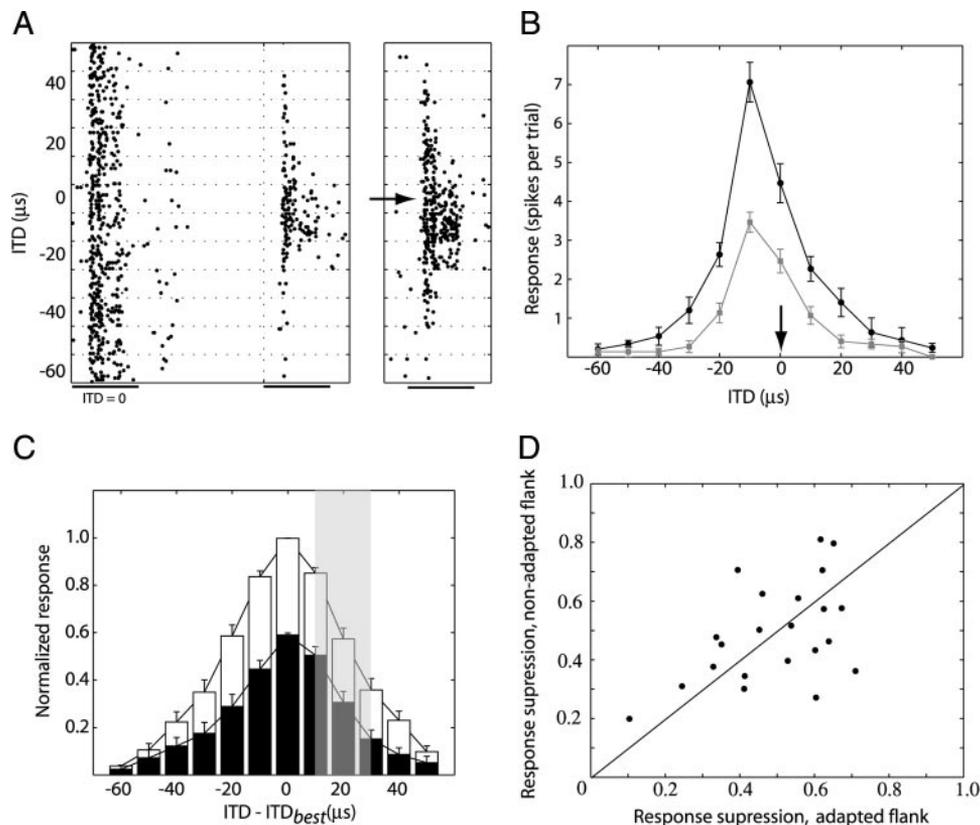


FIG. 8. Effect of a preceding sound on the ITD tuning curve. *A*: *left raster* shows the response of an ICX site to a sequence of 2 stimuli with an ISI of 90 ms. ITD value of the 1st stimulus (30-ms duration, 20 dB above threshold, broadband) was held constant at zero. ITD value of the 2nd stimulus (30-ms duration, 20 dB above threshold, broadband) was varied between 60 μ s left ear leading to 50 μ s right ear leading. Bars at the *bottom* represent stimulus duration. *Right raster* shows the response to the same stimulus and ITD range without the preceding stimulus. Arrow points to the ITD value of the 1st sound. Responses in the *right* and *left rasters* were evoked from randomly interleaved trials. *B*: average response to the 2nd stimulus in *A* as a function of the ITD (gray curve) compared with the control curve (average response to the same stimulus without a preceding sound, black curve). Arrow indicates the ITD value of the 1st sound. *C*: average adapted ITD tuning curve from all tests ($n = 22$, black histogram) compared with the average control ITD curve (white histogram). Curves from all sites were aligned according to the best ITD of the control response and averaged. Adapted flank is on the *right*. Gray bar indicates the range of ITD values used to induce adaptation. *D*: response suppression, measured as the adapted response (2nd stimulus) at an ITD value that elicited about 50% of maximal response divided by the control response at the same ITD value, was measured for both flanks. Suppression in the adapted flank is plotted against the suppression in the nonadapted flank. Line shows equal suppression.

less, further experiments are required to conclusively identify ICX as a site of adaptation.

Mechanisms of adaptation

The results obtained in this work are consistent with a model of adaptation that depends on the firing history of the neuron more than on the specific features of the stimulus. A stimulus that causes a unit to respond strongly gives rise to an adapted state, whereas a stimulus that causes little or no response fails to provoke such a state. This model explains the observation that the adaptation is not sensitive to the specific ITD of the stimulus (Fig. 8). This model also explains the observation that, at the level of the ICX (but not in the ICCIs), adaptation generalizes across frequency channels. In the ICCIs, units are sharply tuned for frequency (Knudsen and Konishi 1978) and they adapt only to frequencies within their tuning curves (Fig. 3). In the ICX, units are broadly tuned for frequency and adaptation caused by activation of one frequency channel produces adaptation to all frequency channels that are integrated by the unit. Wagner et al. (2002) reported inhibition in the core of the ICC (ICCore; a nucleus one synapse before the ICCIs) that occurs after response termination. Neurons in the

ICCore are narrowly tuned for frequency and thus this inhibition may contribute to the same-frequency adaptation we observed in the ICCIs. However, adaptation of narrowly tuned neurons (<2 kHz) cannot account for cross-frequency adaptation, as observed in the ICX (Fig. 2). Cross-frequency adaptation could be a result of either lateral suppression across narrowly tuned neurons or general adaptation of broadly tuned neurons. Because we did not observe cross-frequency suppression in the ICCIs (Fig. 3, *C* and *D*), we suggest that cross-frequency adaptation arises from general adaptation of broadly tuned neurons. The observation that cross-frequency adaptation is weaker than same-frequency adaptation (Figs. 1 and 4, *A* and *B*) is expected for two reasons. 1) Same-frequency adaptation also reflects adaptations occurring at frequency-specific levels in the ascending pathway. Cross-frequency adaptation, on the other hand, is first expressed in the ICX and is thus less likely to include additional effects from preceding levels. 2) The frequency of the first stimulus, in the cross-frequency experiments, was different by 2 kHz from the preferred frequency and therefore generated more moderate responses, resulting in a less-adapted state.

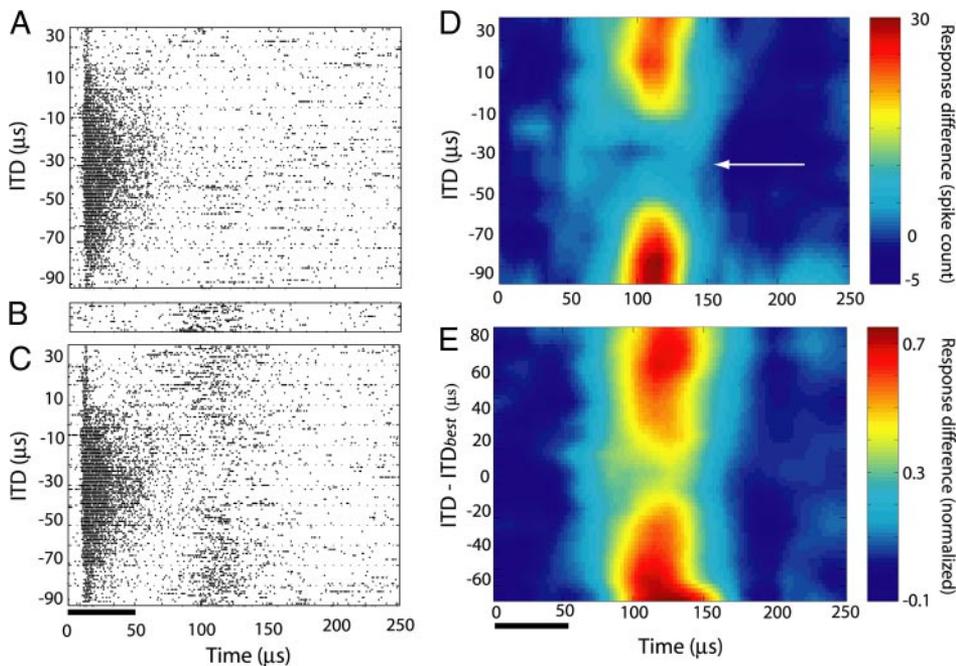


FIG. 9. Effect of ITD on visual-auditory interactions in the ICX. *A*: raster plot showing responses of an ICX site to 50-ms noise bursts, presented at different ITDs. *B*: responses of the same site as in *A* to a flash of light (50-ms duration) presented from an LED positioned at the center of the visual RF. *C*: responses of the same site to the same auditory stimuli as in *A*, but with a simultaneously presented flash of light, the same as in *B*. Trials shown in *C* were randomly interleaved with the trials shown in *A* and *B*. Bar at the bottom indicates the timing of the auditory and visual stimuli. *D*: color-coded graph showing the result of subtracting the average response to the sound (data in *A*) from the average response to the combined visual and auditory stimulus (data in *C*). Subtraction was performed for each ITD tested, in 10-ms time bins. Result was smoothed with a 3×3 point running average. *E*: average normalized difference between the responses to the combined auditory-visual stimulus and the responses to the auditory stimulus alone, averaged across all ICX sites ($n = 18$). Data are plotted vs. the ITD of the sound relative to the best ITD of the site.

Several types of mechanisms for adaptation have been described including synaptic depression (Wehr and Zador 2005), delayed synaptic inhibition (Schmidt and Perkel 1998; Tan et al. 2004; Wehr and Zador 2005), and intrinsic cellular properties such as voltage- or calcium-dependent potassium currents (Gollisch and Herz 2004). Synaptic depression is specific to the presynaptic pathway that is active, and thus inputs to the neuron from other sources should not be affected. On the other hand, intrinsic cellular properties or delayed postsynaptic inhibition can result in a general decrease in the responsiveness of a neuron to all of its inputs.

The distinction between a specific presynaptic effect and a general postsynaptic effect is not trivial because the responses to both auditory stimuli (first and second) are mediated by overlapping sets of synapses. However, responses to visual and auditory stimuli in the ICX are mediated, most likely, by nonoverlapping sets of synapses (Hyde and Knudsen 2000). Therefore if adaptation is a general postsynaptic effect, suppression of responses to visual inputs arriving shortly after strong auditory activation (as shown in Fig. 9) could be achieved by the same mechanism that suppresses responses to late-arriving auditory inputs (Fig. 7).

In our experiments, visual-auditory interactions were measured during bicuculline infusion into the OT, a condition not applied elsewhere in this study. This technical difference should not have altered how visually driven activity was modulated by prior auditory activity in the ICX because the bicuculline was injected into the OT and not into the ICX. Although we cannot rule out the possibility that an additional adaptation mechanism is active to specifically suppress the visual responses, our results provide no reason to introduce such an additional mechanism. Our results are consistent with a single, postsynaptic adaptation mechanism that is powerful and long-lasting and that affects the excitability of the entire ICX neuron based on its previous history of activation.

Implications of adaptation to sensory processing

The high sensitivity of ICX neurons to binaural cue values, along with their relative insensitivity to frequency content, allows ICX adaptation to provide a memory trace for spatial location, regardless of the frequency content of the stimulus. As discussed previously, our results suggest that auditory activation in the ICX space map leads to a persistent “negative image” of the computed location of the auditory stimulus. This long-lasting negative image will interact with subsequent inputs, suppressing signals in the ICX if they originate from the same location as that of the preceding stimulus, but not if they originate from a new location. Thus adaptation state can serve in the comparison of the locations of successive stimuli, by effectively enhancing responses to stimuli from different locations.

The decrease in unit responsiveness that follows the activation of a site in the space map is reminiscent of a behavioral phenomenon called *inhibition of return* (Posner and Cohen 1984). A sensory event (cue) at a specific location increases the reaction time to a second stimulus (target) positioned at the same location, when ISIs exceed about 200 ms. This phenomenon is strongly dependent on the relative locations of the stimuli, but not on their nature. Inhibition of return, thought to contribute to efficient exploration of space (Klein 2000), might be explained by space-specific adaptation (Itti and Koch 2001), similar to the adaptation we describe here.

In the ICX, visual inputs are integrated with auditory inputs under certain conditions (Gutfreund and Knudsen 2002). When they are integrated, visual and auditory inputs do not arrive synchronously in the ICX, at least not initially. Neural responses evoked by the auditory component of a bimodal stimulus usually reach the ICX much sooner than those evoked by the visual component, primarily as a result of longer sensory transduction delays in the retina than in the cochlea. However, because of the relatively slow speed of sound propagation through air (334 m/s), the difference in the relative timing of auditory and visual inputs to the ICX will decrease with the

distance of a bimodal stimulus from the animal (by about 3 ms for every meter of distance away from the owl). Nevertheless, by the time a visual input associated with a bimodal stimulus reaches the ICX, the ICX may have already finished processing the auditory component of the stimulus. This is noteworthy because visually based inputs are known to guide adaptive auditory plasticity in the ICX (Brainard and Knudsen 1993). For auditory–visual interactions to take place under these conditions, some trace of the auditory activation must persist in the network until the visual inputs arrive. As suggested in the present study, one such trace could be the degree of adaptation in the ICX.

If adaptation is to provide a spatial memory for visually guided auditory plasticity in the ICX it needs to meet several criteria. First, the adaptation must be generated by mechanisms in the ICX. As discussed previously, a substantial component of the adaptation measured in the ICX is most likely attributed to mechanisms within the ICX. Second, the adaptation must persist long enough to interact with visual responses that may be delayed by ≤ 80 ms. Adaptation in the ICX, even that triggered by short (10-ms) stimuli, is substantial over this period (Figs. 5 and 6). Third, it must be specific for the location of the stimulus. As can be seen in Figs. 7 and 9, adaptation is limited to the narrow ITD range to which the ICX site responds. Fourth, the frequency content of the auditory stimulus should not be critical. As shown in Fig. 2, adaptation in the ICX generalizes across frequency channels.

The ICX plays an important role in the spatial processing of auditory signals. The ICX integrates information about sound localization cues across frequency channels and creates a topographic representation of the locations of auditory stimuli. In addition, the ICX is a site of visually instructed plasticity. A problem arises from such dual functionality: visual instructive signals may interfere with auditory information processing (Gutfreund and Knudsen 2004; Troyer and Doupe 2000). Ideally, instructive signals should act only when a mismatch or a prediction error occurs, and be absent otherwise (Kim et al. 1998; Schultz and Dickinson 2000). An adaptation mechanism can achieve this goal (Schmidt and Perkel 1998; Troyer and Doupe 2000). Our results suggest that, as a result of response adaptation that is space specific, auditory activation in the ICX suppresses visual signals if they agree with the computed location of the auditory stimulus but not if they do not agree, generating a sensitivity to the mismatch between the spatial representation of the visual and auditory modalities.

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REFERENCES

Albeck Y and Konishi M. Responses of neurons in the auditory pathway of the barn owl to partially correlated binaural signals. *J Neurophysiol* 74: 1689–1700, 1995.

Arthur BJ. Distribution within the barn owl's inferior colliculus of neurons projecting to the optic tectum and thalamus. *J Comp Neurol* 492: 110–121, 2005.

Brainard MS and Knudsen EI. Experience-dependent plasticity in the inferior colliculus: a site for visual calibration of the neural representation of auditory space in the barn owl. *J Neurosci* 13: 4589–4608, 1993.

Brosch M and Schreiner CE. Time course of forward masking tuning curves in cat primary auditory cortex. *J Neurophysiol* 77: 923–943, 1997.

Calford MB and Semple MN. Monaural inhibition in cat auditory cortex. *J Neurophysiol* 73: 1876–1891, 1995.

Chimento TC and Schreiner CE. Adaptation and recovery from adaptation in single fiber responses of the cat auditory nerve. *J Acoust Soc Am* 90: 263–273, 1991.

Creutzfeldt O, Hellweg FC, and Schreiner C. Thalamocortical transformation of responses to complex auditory stimuli. *Exp Brain Res* 39: 87–104, 1980.

Euston DR and Takahashi TT. From spectrum to space: the contribution of level difference cues to spatial receptive fields in the barn owl inferior colliculus. *J Neurosci* 22: 284–293, 2002.

Feldman DE and Knudsen EI. An anatomical basis for visual calibration of the auditory space map in the barn owl's midbrain. *J Neurosci* 17: 6820–6837, 1997.

Fujita I and Konishi M. The role of GABAergic inhibition in processing of interaural time difference in the owl's auditory system. *J Neurosci* 11: 722–739, 1991.

Furukawa S, Maki K, Kashino M, and Riquimaroux H. Dependency of the interaural phase difference sensitivities of inferior collicular neurons on a preceding tone and its implications in neural population coding. *J Neurophysiol* 93: 3313–3326, 2005.

Gold JI and Knudsen EI. A site of auditory experience-dependent plasticity in the neural representation of auditory space in the barn owl's inferior colliculus. *J Neurosci* 20: 3469–3486, 2000.

Gold JI and Knudsen EI. Adaptive adjustment of connectivity in the inferior colliculus revealed by focal pharmacological inactivation. *J Neurophysiol* 85: 1575–1584, 2001.

Gollisch T and Herz AV. Input-driven components of spike-frequency adaptation can be unmasked in vivo. *J Neurosci* 24: 7435–7444, 2004.

Gutfreund Y and Knudsen EI. Visual instruction of the auditory space map in the midbrain. In: *The Handbook of Multisensory Processes*, edited by Calvert G, Spence C, and Stein BE. Cambridge, MA: The MIT Press, 2004, p. 613–624.

Gutfreund Y, Zheng W, and Knudsen EI. Gated visual input to the central auditory system. *Science* 297: 1556–1559, 2002.

Hyde PS and Knudsen EI. Topographic projection from the optic tectum to the auditory space map in the inferior colliculus of the barn owl. *J Comp Neurol* 421: 146–160, 2000.

Hyde PS and Knudsen EI. A topographic instructive signal guides the adjustment of the auditory space map in the optic tectum. *J Neurosci* 21: 8586–8593, 2001.

Itti L and Koch C. Computational modelling of visual attention. *Nat Rev Neurosci* 2: 194–203, 2001.

Keller CH and Takahashi TT. Responses to simulated echoes by neurons in the barn owl's auditory space map. *J Comp Physiol A Sens Neural Behav Physiol* 178: 499–512, 1996.

Kim JJ, Krupa DJ, and Thompson RF. Inhibitory cerebello-olivary projections and blocking effect in classical conditioning. *Science* 279: 570–573, 1998.

Klein RM. Inhibition of return. *Trends Cogn Sci* 4: 138–147, 2000.

Knudsen EI. Neural derivation of sound source location in the barn owl. An example of a computational map. *Ann NY Acad Sci* 510: 33–38, 1987.

Knudsen EI, Knudsen PF, and Masino T. Parallel pathways mediating both sound localization and gaze control in the forebrain and midbrain of the barn owl. *J Neurosci* 13: 2837–2852, 1993.

Knudsen EI and Konishi M. Space and frequency are represented separately in auditory midbrain of the owl. *J Neurophysiol* 41: 870–884, 1978.

Litovsky RY and Shinn-Cunningham BG. Investigation of the relationship among three common measures of precedence: fusion, localization dominance, and discrimination suppression. *J Acoust Soc Am* 109: 346–358, 2001.

Litovsky RY and Yin TC. Physiological studies of the precedence effect in the inferior colliculus of the cat. II. Neural mechanisms. *J Neurophysiol* 80: 1302–1316, 1998.

Luksch H, Gauger B, and Wagner H. A candidate pathway for a visual instructional signal to the barn owl's auditory system. *J Neurosci* 20: RC70:1–RC70:4, 2000.

- Malone BJ and Semple MN.** Effects of auditory stimulus context on the representation of frequency in the gerbil inferior colliculus. *J Neurophysiol* 86: 1113–1130, 2001.
- Mazer JA.** How the owl resolves auditory coding ambiguity. *Proc Natl Acad Sci USA* 95: 10932–10937, 1998.
- Mickey BJ and Middlebrooks JC.** Responses of auditory cortical neurons to pairs of sounds: correlates of fusion and localization. *J Neurophysiol* 86: 1333–1350, 2001.
- Mickey BJ and Middlebrooks JC.** Sensitivity of auditory cortical neurons to the locations of leading and lagging sounds. *J Neurophysiol* 94: 979–989, 2005.
- Moiseff A and Konishi M.** Neuronal and behavioral sensitivity to binaural time differences in the owl. *J Neurosci* 1: 40–48, 1981.
- Moiseff A and Konishi M.** Binaural characteristics of units in the owl's brainstem auditory pathway: precursors of restricted spatial receptive fields. *J Neurosci* 3: 2553–2562, 1983.
- Olsen JF, Knudsen EI, and Esterly SD.** Neural maps of interaural time and intensity differences in the optic tectum of the barn owl. *J Neurosci* 9: 2591–2605, 1989.
- Posner MI and Cohen Y.** Components of visual orienting. In: *Attention and Performance Vol. X*, edited by Bouma H and Bouwhuis D. Hillsdale, NJ: Erlbaum, 1984.
- Rodriguez-Contreras A, Liu XB, and DeBello WM.** Axodendritic contacts onto calcium/calmodulin-dependent protein kinase type II-expressing neurons in the barn owl auditory space map. *J Neurosci* 25: 5611–5622, 2005.
- Schmidt MF and Perkel DJ.** Slow synaptic inhibition in nucleus HVc of the adult zebra finch. *J Neurosci* 18: 895–904, 1998.
- Schreiner C.** Encoding of alternating acoustical signals in the medial geniculate body of guinea pigs. *Hear Res* 3: 265–278, 1980.
- Schultz W and Dickinson A.** Neuronal coding of prediction errors. *Annu Rev Neurosci* 23: 473–500, 2000.
- Smith RL.** Short-term adaptation in single auditory nerve fibers: some post-stimulatory effects. *J Neurophysiol* 40: 1098–1111, 1977.
- Spitzer MW, Bala AD, and Takahashi TT.** Auditory spatial discrimination by barn owls in simulated echoic conditions. *J Acoust Soc Am* 113: 1631–1645, 2003.
- Spitzer MW, Bala AD, and Takahashi TT.** A neuronal correlate of the precedence effect is associated with spatial selectivity in the barn owl's auditory midbrain. *J Neurophysiol* 92: 2051–2070, 2004.
- Takahashi T and Konishi M.** Selectivity for interaural time difference in the owl's midbrain. *J Neurosci* 6: 3413–3422, 1986.
- Tan AY, Zhang LI, Merzenich MM, and Schreiner CE.** Tone-evoked excitatory and inhibitory synaptic conductances of primary auditory cortex neurons. *J Neurophysiol* 92: 630–643, 2004.
- Troyer TW and Doupe AJ.** An associational model of birdsong sensorimotor learning. I. Efference copy and the learning of song syllables. *J Neurophysiol* 84: 1204–1223, 2000.
- Ulanovsky N, Las L, Farkas D, and Nelken I.** Multiple time scales of adaptation in auditory cortex neurons. *J Neurosci* 24: 10440–10453, 2004.
- Ulanovsky N, Las L, and Nelken I.** Processing of low-probability sounds by cortical neurons. *Nat Neurosci* 6: 391–398, 2003.
- Wagner H, Mazer JA, and von Campenhausen M.** Response properties of neurons in the core of the central nucleus of the inferior colliculus of the barn owl. *Eur J Neurosci* 15: 1343–1352, 2002.
- Wagner H, Takahashi T, and Konishi M.** Representation of interaural time difference in the central nucleus of the barn owl's inferior colliculus. *J Neurosci* 7: 3105–3116, 1987.
- Wehr M and Zador AM.** Synaptic mechanisms of forward suppression in rat auditory cortex. *Neuron* 47: 437–445, 2005.
- Wise LZ and Irvine DR.** Topographic organization of interaural intensity difference sensitivity in deep layers of cat superior colliculus: implications for auditory spatial representation. *J Neurophysiol* 54: 185–211, 1985.