Physiological studies of the precedence effect in the inferior colliculus of the kitten[a),b)]

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The precedence effect (PE) is a perceptual phenomenon that reflects listeners' ability to suppress echoes in reverberant environments. The PE is not present at birth and appears only several months postnatal. Recent physiological studies have demonstrated correlates of the PE in the central nucleus of the inferior colliculus (ICC) of adult animals. The present study extended the same techniques to search for similar correlates in the ICC of kittens during the first postnatal month. Stimuli consisted of pairs of clicks or noise bursts presented from different locations in free field or with different inter-aural differences in time (ITD) under headphones, with an inter-stimulus-delay (ISD) between their onsets. Results suggest that a physiological correlate of the PE, i.e. suppression of responses to the second source, is present as early as 8 days postnatal, and occurs at similar ISDs to those recorded in adult cats. Suppression in kitten neurons varies with stimulus level, duration, and azimuthal position, in a similar manner to that in adult neurons. The age at which correlates of the PE in the kitten can be found precedes the age at which kittens can localize sound sources effectively, and presumably before the age at which they would demonstrate the PE behaviorally. Thus, the neural mechanisms that might be involved in the first stages of processing PE stimuli may be in place well before the behavioral correlate develops. © *1998 Acoustical Society of America.* [S0001-4966(98)04604-9]

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INTRODUCTION

When a sound is produced in a reverberant environment it propagates in many directions and is subsequently reflected from nearby surfaces, hence a listener receives both the direct sound and multiple reflections of that sound. One can think of this scenario as involving competition between the first sound and its reflections for perception and localization. Despite this clutter of information two-eared animals are remarkably accurate at identifying the location and content of sound sources. This reduction in interference from reflections is thought to be related to the precedence effect (PE). Perceptual studies on the PE generally involve a simplified version of the multiple-source scenario that occurs in real rooms. That is, one source (lead) and one echo (lag) are simulated, with a variable inter-stimulus-delay (ISD). Psychophysical studies have shown that when the ISD is short (<10 ms for clicks) listeners perceive one fused auditory event whose apparent location is dominated by the lead (Blauert, 1997; Litovsky *et al.*, 1997; Wallach *et al.*, 1949; Zurek, 1980, 1987).

Developmental studies suggest that the PE is not exhibited behaviorally by newborn human infants (Clifton *et al.*, 1981; Muir *et al.*, 1989; Burnham *et al.*, 1993) or dogs (Ash-

mead *et al.*, 1987). Although newborn infants and dogs are able to localize the hemifield containing a single-source sound (one sound emitted from a single location), under conditions of the PE the leading source does not seem to dominate perception and localization in the same way that it does for adults (for review see Litovsky and Ashmead, 1997). The PE is first manifested behaviorally in humans at around 4–5 months of age, however at this age it is still not fully mature (Clifton, 1985; Muir *et al.*, 1989). In fact, some aspects of the PE are not fully mature in children as old as 5 years (Litovsky, 1997; Litovsky and Ashmead, 1997).

Physiological substrates of the PE are not well understood. In recent years there has been increasing interest in measuring the responses of neurons in the brainstem to PE stimuli. Several studies have shown that the central nucleus of the inferior colliculus (ICC) may be involved in mediating some basic physiological aspects of the PE. The ICC is an obligatory synaptic stage in the lemniscal pathways which transmit information to the cortex. In the adult cat, ICC neurons are known to be sensitive to wide ranges of acoustic signals, and in particular, to interaural differences in time (ITD) and intensity (IID), which are the primary cues used in azimuthal sound localization (Hind *et al.*, 1963; Kuwada and Yin, 1983; Rose *et al.*, 1966; Semple and Aitkin, 1979; Yin and Kuwada, 1983). Studies on correlates of the PE in the ICC have been made in anaesthetized cats (Yin, 1994; Yin and Litovsky, 1995; Litovsky *et al.*, 1997; Litovsky and Yin, 1998a, b) as well as in the awake rabbit (Fitzpatrick *et al.*, 1995) and awake owl (Keller and Takahashi, 1996). In these studies the PE is simulated by presenting pairs of clicks or noise bursts with variable ISDs. In all three species it has been shown that most neurons exhibit a physiological corre-

late of the PE. That is, responses to the lagging stimulus are suppressed at short ISDs at a similar time course to those observed in the psychophysics. More important, ICC neurons exhibit several direct correlates of the PE, such as variation of suppression with stimulus level, duration and location or ITD of the lead. Finally, at ISDs ±2 ms neuronal responses are consistent with an aspect of the PE known as ''summing localization'' (Yin, 1994; Yin and Litovsky, 1995), whereby both humans (Blauert, 1997) and cats (Populin and Yin, 1998) perceive a phantom sound source and localize it between the lead and lag locations.

The present study describes similar physiological recordings made in the ICC of kittens during the first month of life. Kittens are known to orient towards a *single* sound source in a similar fashion to human infants and dogs, and they do so by the third postnatal week (Clements and Kelly, 1978; Norton, 1974; Olmstead and Villiblanca, 1980), suggesting that they may be utilizing binaural cues during those early postnatal days. In fact, kittens as young as 2 weeks old receive binaural excitatory and inhibitory input in about the same proportion as in the adult cat (Aitkin and Reynolds, 1975; Moore and Irvine, 1980, 1981). In addition, binaural sensitivity to IID has been reported at one month (Moore and Irvine, 1981), and as early as 8 days postnatal (Blatchley and Brugge, 1990); sensitivity to phase differences and ITDs has been reported as early as 12 days (Blatchley and Brugge, 1990). To the author's knowledge, kittens' behavioral responses to PE stimuli have not been measured. However, given the similarity in the onset of responses to single source stimuli by kittens, dogs and humans, it is reasonable to suspect that kittens probably do not show the PE during the first month or two of postnatal life. Behavioral studies must be conducted before a firm conclusion can be made.

The results presented here suggest that neural sensitivity to PE stimuli is remarkably similar in kittens to that observed in adult cats. Thus, the neural mechanisms that might be involved in the first stages of processing PE stimuli may be in place well before the behavioral correlate is expected to develop.

I. MATERIALS AND METHODS

Recordings were made from 57 neurons isolated in the ICC of 16 barbiturate/ketamine-anesthetized kittens 8–29 days old. Methods are similar to those described previously (Yin, 1994; Litovsky and Yin, 1993, 1994, 1998a, b) for measurements made in the ICC of adult cats.

A. Surgery

Preparation of the animal has been described in detail elsewhere (Brugge *et al.*, 1978; Kettner *et al.*, 1985). In short, after anesthesia was induced using ketamine (35 mg/kg), a venous cannula was inserted into the femoral vein to administer pentobarbital as needed throughout the experiment and a tracheal cannula was inserted. Body temperature was maintained at 37 °C. The dorsal surface of the inferior colliculus (IC) was exposed with a craniotomy on the right side. The overlying cortex was aspirated and in some animals the tentorium was partially removed to expose a more posterior area of the IC.

Extracellular recordings were made from the IC using commercial tungsten microelectrodes (Microprobe) with tip exposures of 8–12 μm. A motor-driven hydraulic microdrive was used to move the electrode remotely from outside the room. Single spikes were discriminated using either a level detector or a peak-detector circuit. During the experiment physiological criteria were used to locate cells within the ICC (Carney and Yin, 1989). At the end of the experiment the animals were overdosed with anesthetic and the brains immersed in 10% formalin in saline. After fixation the brainstem was removed and cut in the coronal plane with frozen sections at 50 μm thickness and stained with cresyl violet. Confirmation of the penetrations through the ICC was made from anatomical examination of these sections.

B. Stimuli

Stimuli were either 100 μsec clicks or noise stimuli usually delivered every 300 ms and repeated 20 or 50 times. Noise stimuli were either broadband or narrow bandpass noise bursts, usually 0.2 kHz wide, digitally filtered with sharp slopes (100 dB/octave) and centered at the characteristic frequency (CF) of the cell. CFs were determined by tonal tuning curves in response to contralateral or binaural stimulation.

C. Free field setup and stimuli

Experiments were conducted in a sound-insulated room (IAC) (2.25×2.15 and 2 m) (Fig. 1A). To reduce acoustic reflections all surfaces were lined with 4-in. reticulated wedged foam (Sonex). The skin overlying the skull was dissected, and a stainless steel rod was secured to the skull on the side opposite to the recording site with dental acrylic and/or screws, depending on the thickness of the skull. The rod was attached to an animal holder which maintained the head in a secure position for the duration of the experiment. After exposure of the IC, the skin was sutured back so that the ears assumed a natural position while still allowing access to the brain. The electrode manipulator was also attached to the head holder to increase stability during recording. The animal holder was anchored to the floor of the room such that the head was positioned in the center of a circle with a 90 cm radius defined by the loudspeaker array. Thirteen loudspeakers (Realistic 3-in. midrange tweeter) were positioned along the horizontal axis in the frontal hemifield at 0° elevation with loudspeakers every 15° (see Fig. 1A). Positive angles refer to sounds in the contralateral hemifield. The loudspeakers were carefully matched for frequency response by monitoring their outputs to clicks and to tone bursts delivered from 100 to 25 000 Hz in steps of 100 Hz. All speakers were matched to within 2 dB at octaves spanning 250–8000 Hz.

Auditory stimuli were digitally stored in a general waveform buffer for delivery by a digital stimulus system. The CF of each cell was defined as the frequency with the lowest threshold to tonal stimuli at +45° on the horizontal axis. In a small proportion of cells that preferred the ipsilateral hemifield, CF was obtained at −45°. Thresholds for clicks and noise bursts were also obtained at +45°. Azimuthal response
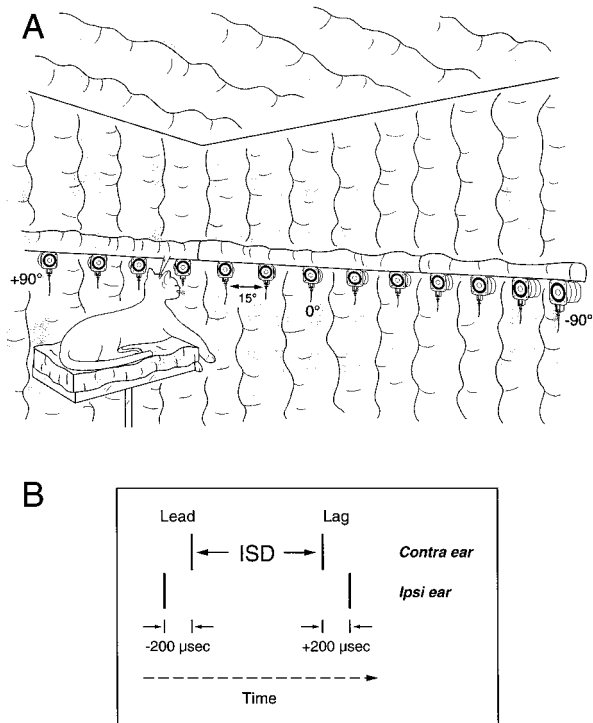
FIG. 1. Stimulus configuration in free field (A) and under dichotic conditions (B). A: A cat is placed in an anechoic chamber in the center of a semicircular array of loudspeakers positioned every 15° along the horizontal axis from +90° on the right (contralateral) to −90° on the left. B: Two pairs of clicks are delivered dichotically, separated by an inter-stimulus-delay (ISD); each click pair contains an interaural time delay, e.g., −200 and +200 msec as diagrammed. Positive ITDs refer to the convention of the contralateral stimulus presented first.

area curves were obtained by presenting 50 repetitions of either clicks or noise bursts from each loudspeaker at 5–20 dB above threshold. Finally, the PE was simulated by presenting two sounds from different loudspeakers with one sound delayed relative to the other by a variable ISD.

D. Dichotic experiments

The animal was placed in a double-walled, sound insulated chamber (IAC). Both pinnae were dissected away and the external ear canals were transected so that the tympanic membrane was visible. Acoustic stimuli were delivered independently to each ear through hollow ear-pieces which were connected to the earphones (Telex 140) and tightly sealed into the ear canals with Audalin ear impression compound. A small hole was drilled in each bulla and polyethylene tubes (0.9 mm internal diameter and 30 cm in length) were inserted into the hole to equalize middle ear pressure during the experiment. Acoustic stimuli were generated by a digital stimulus system which was calibrated in amplitude and phase for each animal. A 0.5-in. Bruel and Kjaer condenser microphone was coupled to a probe tube which was positioned inside the ear canal 1–2 mm away from the tympanic membrane, and 50 ms tone bursts were delivered from 100 to 42 000 Hz in 50-Hz steps. The CF of each cell was defined as the frequency with the lowest threshold for the contralateral ear. By convention positive ITDs refer to the

contralateral ear leading. As in the free field experiments, thresholds were estimated for clicks and noise, but they were obtained either for the contralateral ear alone or for binaural stimuli with an ITD of zero. Stimuli with a PE configuration were simulated by presenting two dichotic pairs of clicks or noise separated by an ISD of several ms; ITDs were imposed separately for each stimulus pair (Fig. 1B). The ISD was defined as the time difference between the onset of the two stimuli delivered to the contralateral ear.

E. Normalizing the lagging responses in recovery curves

Data were analyzed by comparing the lagging response in the presence of the leading stimulus with the lagging response in absence of the leading stimulus. For each neuron, the number of spikes in response to the leading and lagging stimuli at each ISD was counted during discrete time windows (chosen to accommodate the latency and duration of each neuron's response). In cases where the leading and lagging stimuli were identical, such as under dichotic conditions with the same ITDs imposed, at each ISD the lagging responses were divided by the leading responses within the discrete time windows. In free field the leading and lagging stimuli never occurred at the same location and were thus never identical. The lagging responses were therefore normalized in one of two ways: (a) by the response to the lagging stimulus presented in isolation; or (b) by the lagging response at a large ISD where there was no apparent effect of the leading stimulus. When the analysis time windows for the leading and lagging response overlapped, such as when ISD was very short (see Fig. 5), we assumed that there was no variation in the response to the leading stimulus as a function of ISD and subtracted the mean leading responses at the five longest ISDs from the total number of spikes at the ISDs with overlap. In the resulting normalization recovery to 1.0 represents a lagging response that equals the response obtained in the absence of a leading stimulus.

II. RESULTS

Results from recordings made in kitten ICC are compared with those reported by Litovsky and Yin (1998a, b) in the ICC of adult cats. Results were obtained from 57 neurons recorded from the ICC of 16 kittens, ages 8–29 days. Table I shows the distribution of units recorded from animals at various ages, under free field or dichotic conditions. Once encountered and isolated, each neuron was studied for 1–6 hours. Since the survival time of most kittens was 12–18 hours, each animal yielded data from a small number of neurons.

A. Sensitivity to stimulus location in free field

Free field experiments always began by measuring a neuron's receptive field, i.e., sensitivity to clicks or noise varying in azimuth. Sensitivity is defined by the neuron's response to stimuli presented 5–10 dB above threshold; if measurements were obtained at more than one level, sensitivity was defined at the lowest level. Threshold is defined as the neuron's response to clicks at 45 deg to the left or right,

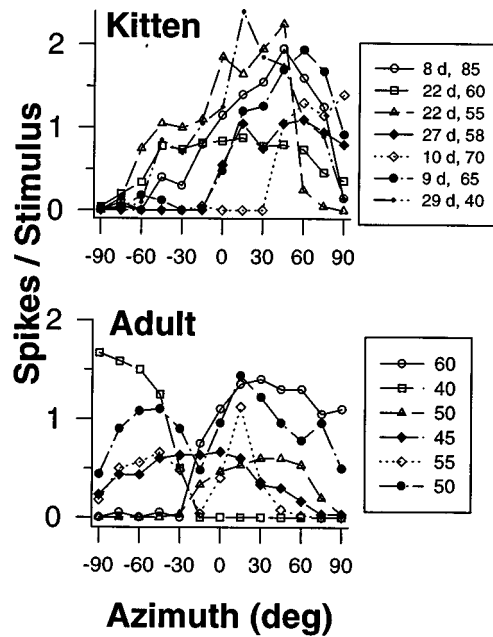| Expt. #	Age (days)	#Neurons
049 F	8	5
164 F	9	9
089 F	10	2
099 D	10	4
008 D	11	3
039 F	12	5
109 D	13	1
103 F	14	4
165 F	15	5
018 F	15	5
105 D	20	2
009 D	20	2
056 F	22	2
096 D	24	2
086 F	27	7
030 F	29	4

FIG. 2. Effect of varying the location of single clicks along the azimuthal plane in free field. Top: 7 representative neurons studied in kittens; Bottom: 6 representative neurons studied in cats. Each curve represents the response (number of spikes per stimulus) of one neuron to 50 repetitions of the stimuli. The legends contain the ages of the kittens and the threshold of each neuron.

whichever is lower. There does not seem to be any differences in azimuthal sensitivity to noise or clicks, thus measurements with those two stimuli are shown together.

At 5–10 dB above threshold, most neurons show sensitivity to locations along the horizontal dimension, defined by a modulated response with a difference >0.5 in spike rate (number of spikes per stimulus) between the azimuthal locations that results in the maximal and minimal spike rates. For the population of kitten neurons studied, ranging in age from 8 to 29 days, 85% (29/34) of neurons exhibit maximal responses to stimuli presented in the contralateral hemifield. A minority of neurons (15%; 5/34) are omni-directional, i.e. show no preference for either hemifield; these neurons are found in animals aged 14 and 27 days. No neurons respond maximally to stimuli presented in the ipsilateral hemifield. Figure 2 shows the azimuthal receptive field for several representative neurons studied in kittens (top) and cats (bottom). In cats 60% of neurons prefer the contralateral hemifield, 35% are omni-directional, and 5% prefer the ipsilateral hemifield.

The receptive field profiles of many ICC neurons depend on the level of presentation. In all neurons but one there is increased discharge rate with increased level. In addition, most neurons show a widened receptive field at higher levels, extending into the opposite hemifield. Responses from four neurons at several levels are shown in Fig. 3, at 8 days, 10 days, 29 days, and adult age. The lowest levels at which neurons were tested were usually near or at threshold. In all four cases the receptive fields at the lowest levels are restricted to the contralateral hemifield, and in three cases the receptive fields extend out to the ipsilateral hemifield at the higher levels, thereby reducing the neuron's spatial sensitivity. In the omni-directional neurons higher stimulus levels result in increased discharge rate, but no changes in receptive field sensitivity are observed. In summary, a neuron that showed an omni-directional response at 5 dB above threshold is not likely to gain receptive field sensitivity at higher

levels; a neuron that shows sensitivity at low levels is likely to lose that sensitivity at higher levels.

Of the 15 neurons studied with the level manipulation, nine (60%) show decreased azimuthal sensitivity at higher levels, and 5/15 neurons (36%) show no azimuthal selectivity at any level. The 8-day-old neuron shown in Fig. 3 is the only one that does not lose azimuthal sensitivity at higher levels. The corresponding values in the adult data are: 31/60 (52%) of neurons show decreased spatial sensitivity with level, 8/60 (13%) of neurons show no shift into the ipsilateral
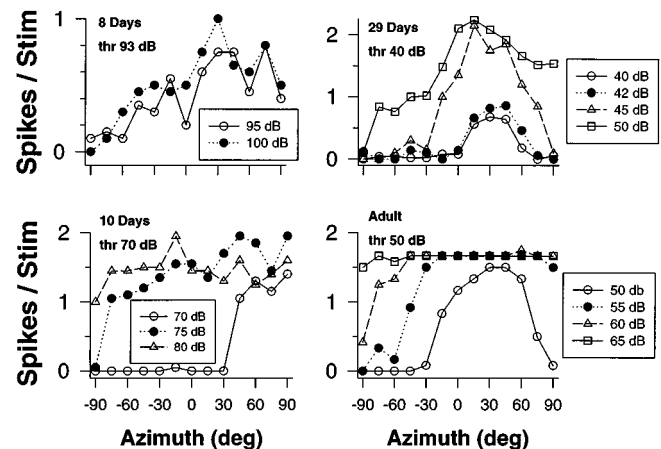

FIG. 3. Effect of varying overall stimulus level on receptive fields. Neurons from four animals are shown, at ages 8-days (CF 3 kHz), 10-days (CF 3 kHz), 29-days (CF 2.5 kHz), and adult (CF 6 kHz). Each panel shows the responses of one neuron to 50 clicks presented at ±90° in 15° steps, and at several levels. The threshold for responding to the stimulus at 45° is shown below the age.
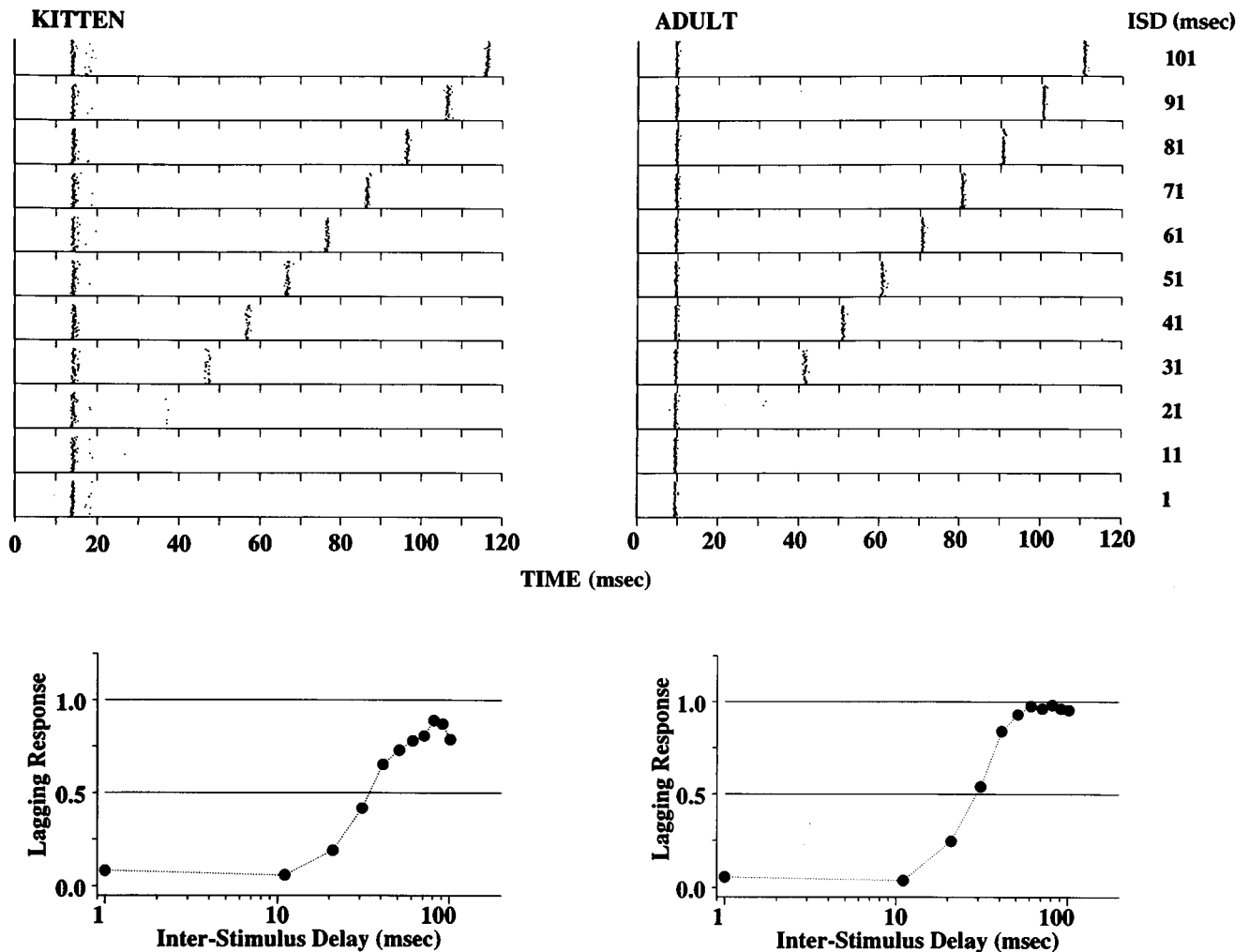
FIG. 4. Echo suppression for two neurons studied in free field, one in a 12-day-old kitten (left; CF=2.3 kHz) and one under in an adult cat (right; CF=2.4 kHz) conditions. Top: Dot rasters showing the responses to the leading and lagging stimuli, with ISDs ranging from 1 (bottom) to 101 (top) ms. The leading and lagging stimuli were placed at locations along the horizontal plane that elicited robust responses by each neuron, +30° and 0°, respectively. Each row of dots represents responses to 50 repetitions of the stimuli. The leading response occurs in each row at a latency of 14 ms, and the lagging response occurs with greater latency which depends on the ISD. For example, at ISDs of 91 and 101 ms, the lagging responses occurs at 105 and 115 msec, respectively. Bottom: Recovery curves for the dot rasters shown above. The normalized (see Sec. I) response to the lagging stimulus is plotted as a function of ISD. The delay at which the horizontal lines at 0.5 meets the function represents the *half-maximal ISD*, which is 35 ms and 29 ms, for the kitten and adult neurons, respectively.

hemifield with level, and 21/60 (35%) show no directional selectivity at any level tested.

From the kitten data it is difficult to determine whether all response types exist at 8 days of age, since only one neuron was studied at that age. The next youngest neuron, studied at 10 days, does show a decrease in azimuthal sensitivity with increased level. It is important to note that both response types can be found in the adult data.

B. Precedence and neural echo thresholds (half-maximal ISD)

Results presented below describe responses of ICC neurons to PE stimuli. Figure 4 shows examples from a 12-day-old kitten (left) and a cat (right), with the ISDs varied from 1 to 101 ms. In both cases the leading and lagging stimuli, when presented in isolation, elicit robust neural discharges. When the ISDs are long (41–101 ms), each neuron responds vigorously to both the leading and the lagging stimuli. As the ISDs are decreased, the delayed response is diminished, al-

most disappearing completely by 21 ms. The bottom panels in the figure show recovery functions for the lagging responses of each neuron. The neural correlates of echo threshold, or *half-maximal ISDs* (delays at which recovery functions reach 50% of the un-suppressed response) are 33 ms and 30 ms, for the kitten and cat, respectively. These particular examples were chosen to reflect the similarity between recovery functions observed in kitten and cat.

Figure 5 shows responses from populations of neurons in kittens (top) and adult cats (bottom). Since no differences were observed between free field and dichotic data, Fig. 5 contains results from both procedures. Each neuron was studied at a level 5–10 dB above threshold. Leading and lagging stimuli were both selected so that each produced a robust response when presented in isolation, i.e. within the neuron's receptive field in free field or at an ITD that produced a robust response under headphones. The left panels (A and C) each contain recovery functions from 20 neurons, demonstrating that within each population there is tremen-
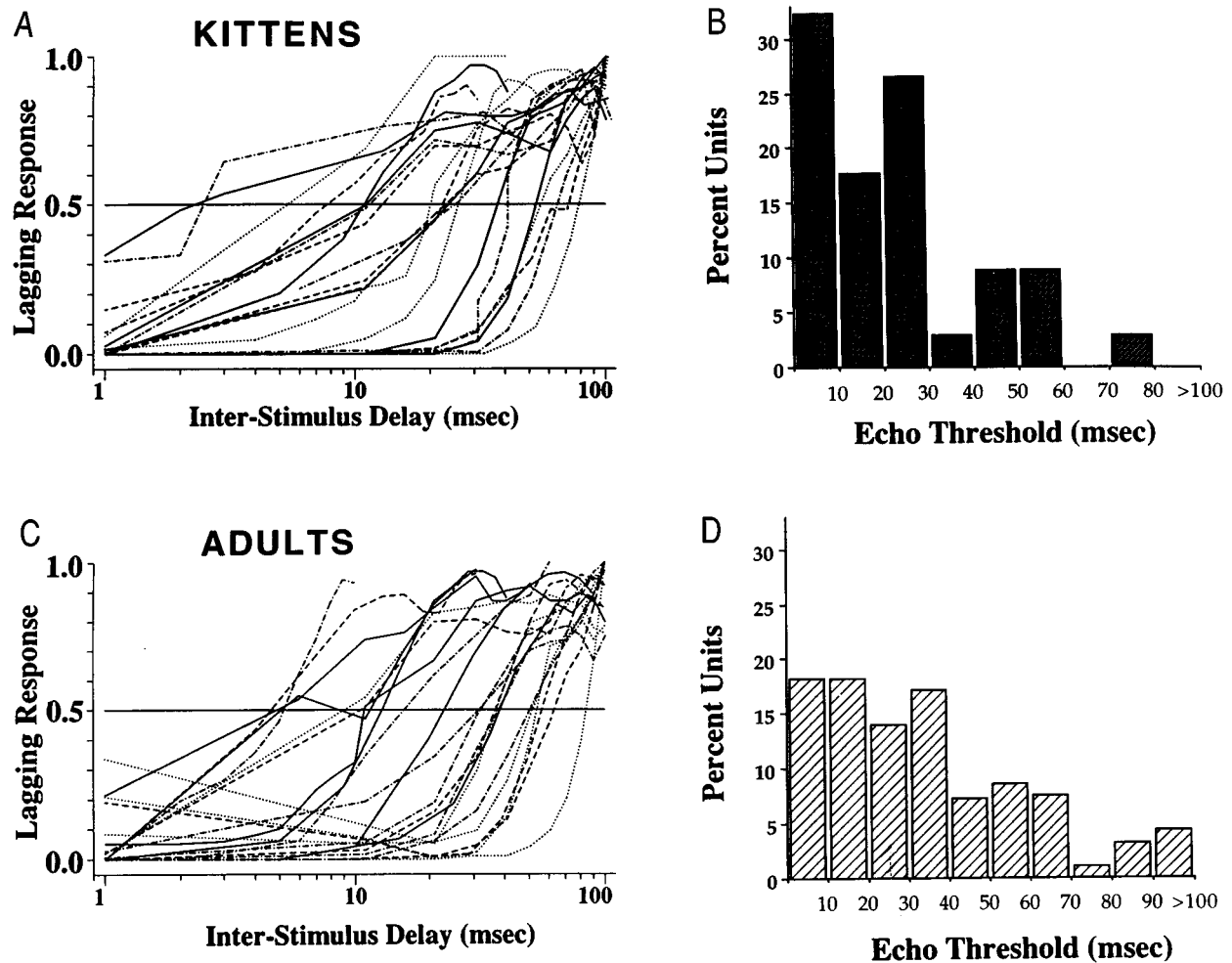
FIG. 5. Exemplary recovery functions (left) and population histograms (right) of neural echo thresholds, or *half-maximal ISDs,* plotted for kittens (top) and adults (bottom). For all neurons, both leading and lagging stimuli were at locations or ITDs which elicited robust responses with single stimuli. The recovery functions (left) represent the normalized lagging responses as a function of ISD. Although the recovery functions only include 22 sample neurons from each population, the histograms on the right are based on the entire populations of neurons studied (N=94 for adults and N=34 for kittens). Adult data are from Litovsky and Yin (1998a).

dous variability in the delays at which the *half-maximal ISD* is reached. The right panels (B and D) compare histogram distributions for *half-maximal ISDs* of 34 kitten neurons (20 free field and 14 dichotic), and 94 cat neurons (49 in free field and 45 dichotically). In both populations these values have wide ranges (2–80 ms for kittens and 2 to over 100 for adults); means and standard deviations are 21 ± 18 ms and 36 ± 32 ms for kittens and cats respectively. In addition, for the entire population the proportion of neurons with echo thresholds less than 10 ms, which approximates the range for perceptual echo thresholds in humans (Blauert, 1997; Freyman *et al.*, 1991) and cats (Cranford, 1982), is 32% (11/34) in kittens and 24% (23/94) in cats. Statistically, *half-maximal ISDs* are significantly lower in the kitten population than in the cat population (p=0.02).

A closer look at the data suggests that in the adult population many of the neurons with high *half-maximal ISDs* had either very low CFs (<1 kHz) or very high CFs (>16 kHz). Since the CFs of neurons in the kitten population were restricted to 1–16 kHz (perhaps due to a sampling bias), a further t test between all the kitten neurons and only cat

neurons with CFs between 1 and 16 kHz (N=67) revealed a lack of significant difference (p=0.08).

Figure 6 shows a correlation plot between *half-maximal ISDs* and age for the kitten data; the low correlation value (r=0.058) suggests that, within the kitten group, the distribution of neural echo thresholds is not age-dependent. Finally, Fig. 7 shows a scatter plot of neural echo thresholds as a function of CF for the kitten (top) and adult (bottom) populations. There is no apparent relationship between these variables for either the adult group (r=0.06) or the kitten group ($r=-0.12$). Within the adult population, if the analysis is restricted to the 67 neurons with CF 1–16 kHz the correlation is higher (0.2488), but still not significant.

C. Effects of varying level and duration

In addition to investigating a mechanism for suppression of responses to a lagging source, this study investigated additional correlates of psychophysical effects. In everyday listening environments various stimulus parameters associated with the original source (lead) and its echo (lag) change dy-
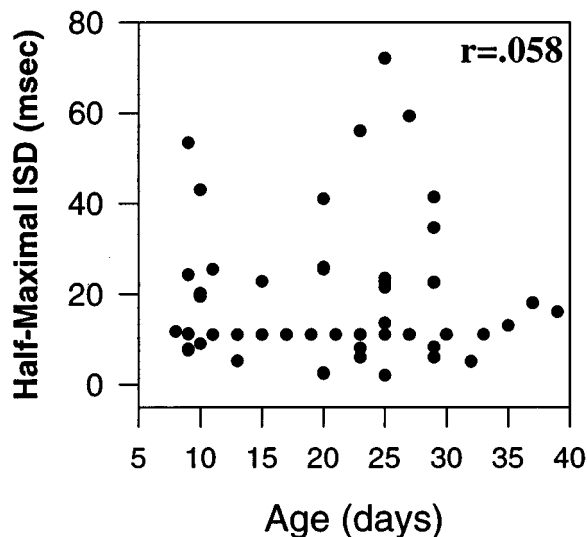
FIG. 6. Correlation plot of neural echo thresholds, or *half-maximal ISDs,* and number of days postnatal for the population of kittens neurons studied.

namically. Some examples are the level and duration of the stimuli, which are modulated in cases of ongoing dynamic stimuli such as speech or music. One approach to studying effects of level and duration is to co-vary the lead and lag, i.e., to change the overall level or duration of a stimulus, which is congruent with realistic changes that occur in a reverberant environment. In fact, the PE is reportedly weaker at higher overall stimulus levels (e.g., Shinn-Cunningham *et al.*, 1993), and stronger when the overall stimulus duration is longer (Damaske, 1971). A second approach is to vary only the level or duration of the leading source, while holding constant that of the lag. Although such stimulus manipulations may not reflect phenomena that occur in real listening environments, they are geared towards understanding the neural mechanisms that might be involved in mediating the
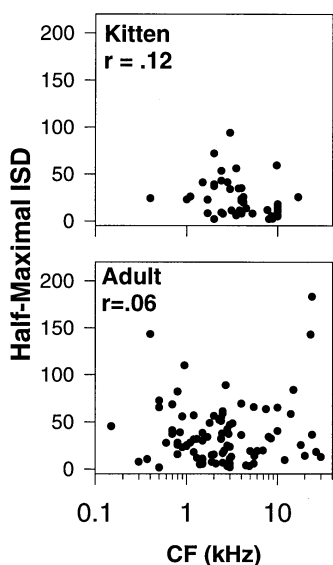

FIG. 7. Correlation plots of *half-maximal ISD* and CF for kittens (top) and adults (bottom).

PE (Yin, 1994; Litovsky and Yin, 1998b). Psychophysical data using this approach have shown that the PE is significantly stronger when the level of the lead alone is increased (Blodgett *et al.*, 1956; Thurlow and Parks, 1961; Babkoff and Sutton, 1966). Similar studies on duration have not been conducted. Comparisons made below between kitten and adult cat refers to adult data reported by Litovsky and Yin (1998a, b).

While one can expect leading stimuli of increasing level to generate more suppression, it is not obvious what to expect when the lagging stimulus level is raised concomitantly. Plotted in Fig. 8 are results from six neurons, all studied with click stimuli. The four neurons at the top show an effect of increased suppression at lower overall stimulus level at ages 10 days, 13 days, 20 days, and adult. The majority of kitten neurons (87%; 13/15) show this effect, which is consistent with findings in adult neurons (72.5%; 29/40). The two neurons at the bottom show the opposite effect, of decreased suppression at lower levels, an effect that is observed in 13% (2/15) of kitten neurons and 10% (4/40) of adult neurons.

The effect of varying the level of the leading stimulus alone was also measured. Although only 8 kitten neurons were studied, they all show a strong effect of increased suppression with increased lead level. The same effect was also seen by Litovsky and Yin (1998b) in all neurons studied ($N=17$). Figure 9 shows examples from a 12-day-old kitten neuron (9A and 9B) and from an adult neuron (9C). There is an interesting interaction between delay and lead level: In 9A at a delay of 20 ms the lead at 40 dB produces a very weak response, but the lagging response is completely suppressed. At a longer delay of 40 ms the lead at 40 dB produces weaker suppression, and finally, at a 60 ms delay the lead at 40 dB produces almost no suppression. Hence, increasing the delay compensates for the suppressive effect of the lead. Note that once the lead is above threshold the neuron only responds to the lagging sound at 60 ms, but even at that long delay the lag response is suppressed when the lead level reaches 50 dB.

The effect of stimulus duration was tested using short noise bursts rather than clicks, which allows changes in duration that do not compromise the frequency bandwidth of the stimulus. Figure 10 shows data from one 27-day old neuron (left) and one adult neuron (right), each tested under conditions in which either the overall duration (top) or lead duration alone (bottom) were varied. In the overall duration cases shown here, increasing the stimulus duration results in increased suppression in both kitten and adult neurons. In kittens this trend was observed in all neurons studied (8/8), although in adult cats the effect had been reported for only 56% of neurons (Litovsky and Yin, 1998a). In the bottom plots the lag was held constant at 10 ms (kitten) or 5 ms (adult), while the lead duration was varied. In both examples shown here the suppression increases as the durations are increased. This trend was observed in 75% (6/8) neurons studied in kittens, with no effect of duration in 25% (2/8) neurons. In adult cats longer duration produced stronger suppression in 86% (12/14) of neurons, with no effect in 14% (2/14).
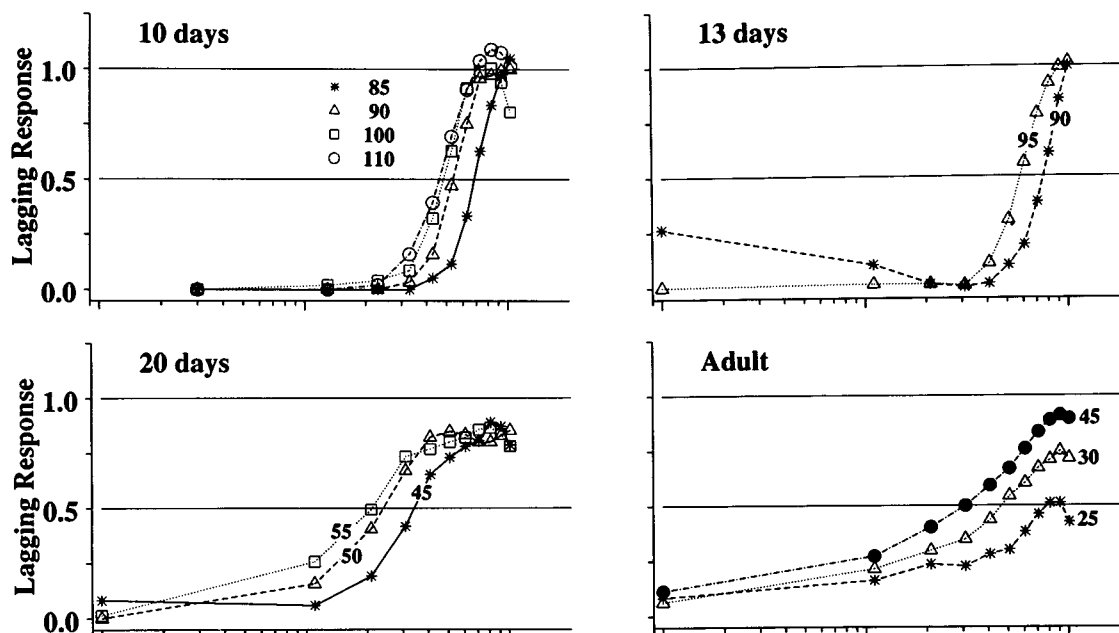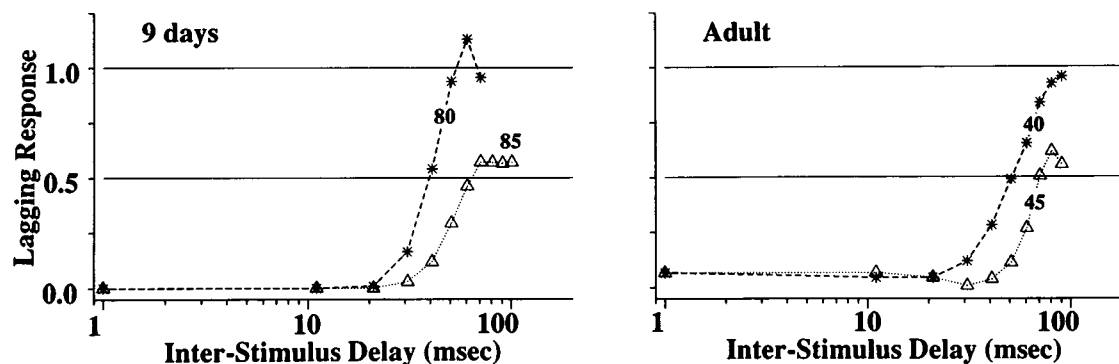
FIG. 8. Effect of overall level is shown for 6 neurons. The stimulus level of both leading and lagging sounds was always equal and co-varied between conditions. In each plot, *half-maximal ISDs* are marked by the ISD at which the normalized lagging response recovers to 0.5. The top four neurons, at 10 days (CF 2.4 kHz; threshold 80 dB), 13 days (CF 8.6 kHz; threshold 90 dB), 20 days (CF 3.7 kHz; threshold 40 dB), and adult (CF 5.5 kHz; threshold 25 dB) are examples in which lower levels resulted in *stronger* suppression. The bottom two neurons, at 9 days (CF 2.4 kHz; threshold 60 dB) and adult (CF 3.0 kHz; threshold 35 dB), are examples in which lower levels resulted in *weaker* suppression.

D. Effect of lead stimulus position on suppression

Echoes occurring in a normal listening environment naturally appear from many different locations. Since a well known feature of ICC neurons is their sensitivity to stimulus direction along the azimuth, a natural question is whether the location of the leading sound influences the degree of echo suppression. In the experimental setup the locations of the leading or lagging source could be independently varied in free field. The paradigm in this experiment consisted of varying the location of the leading stimulus while holding constant that of the lagging stimulus. Hence one can compare the amount of suppression that each leading stimulus exerts on the same lagging response. Figure 11A and B show responses to click stimuli in the form of dot rasters of a repre-

sentative ICC cell in a 27-day-old kitten, in which the ISDs were 10 ms and 20 ms, respectively. In both cases, the leading stimulus was varied along the azimuth from −90° to +90° while the lagging stimulus was held constant at +45° (black arrow in Fig. 11B). At both 10 and 20 ms delays the response to the leading sound, which occurs at a latency of about 10–13 ms, is strongest on the contralateral side between 0° and 30°; responses is weaker at negative azimuth values on the side ipsilateral to the recording site.

These data are summarized by plotting the responses to the leading (Fig. 11C) and lagging (Fig. 11D) stimuli separately. Figure 11C shows the neuron's response to the leading sound when presented as a single click in isolation, i.e., with no lagging stimulus (dark circles), and when followed
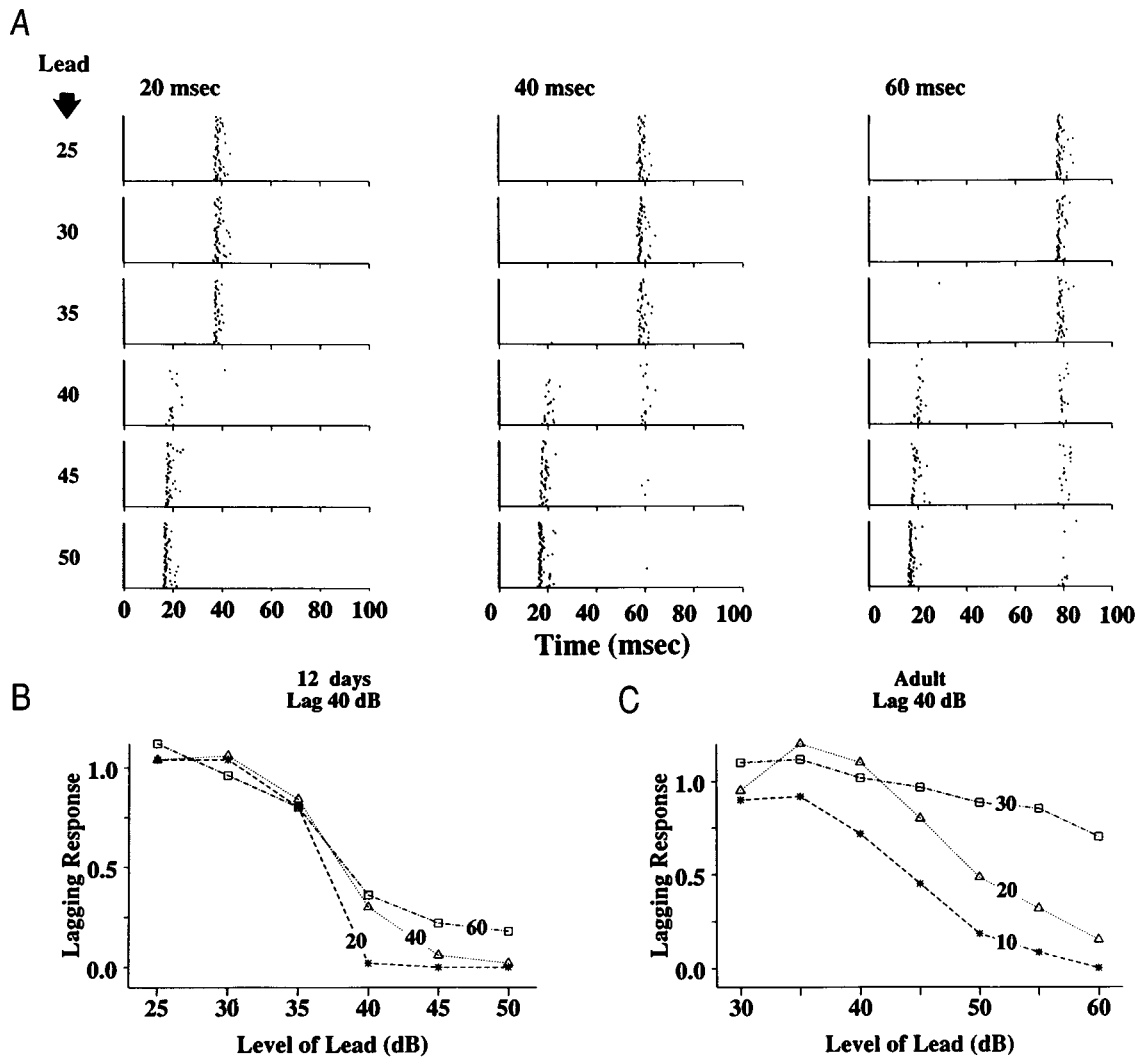
FIG. 9. Effect of the SPL of the lead. A: Data from one neuron in a 12-day-old kitten studied in free field (CF=9.8 kHz; threshold 40 dB). Both lead and lag locations were chosen such that when presented in isolation they elicited a robust response; the lagging response is slightly more robust than the leading response at 40 dB. Leading click SPL was varied from 25 to 50 dB in steps of 5 dB, while the SPL of lagging click was held constant at 40 dB. Results are shown at ISDs of 20, 40, and 60 ms (from left to right). B: Data from A are summarized, showing normalized lagging response as a function of lead level. C: Data from one neuron in an adult cat studied in free field (CF=2.65; threshold 40 dB). Lag level was held constant at 40 dB, lead level varied from 30 to 60 dB in steps of 5 dB, and measurements were conducted at ISDs of 10, 20, and 30 ms.

by a lagging stimulus at 5, 10, and 20 ms delays (stars, triangles and squares, respectively). Under all conditions the lead response shows a peak in the contralateral hemifield. In the single click condition the neuron also responds to a stimulus at $-90°$, but for unknown reasons that response does not occur in the other conditions. Figure 11D shows the response to the lagging stimulus at 5, 10, and 20 ms, as a function of the location of the leading stimulus, as well as the response to single clicks (filled circles). For all delay conditions the lagging sound was placed at $+45°$, which elicited maximal response to the lead. If the leading source has no suppressive effect then all lagging responses should approximate the neuron's response to a single click at $+45°$; any reductions in responses reflect a suppressive effect. At positive angles suppression is maximal when response to the lead is maximal, at 0° to $+60°$. Suppression is also strongest at the shortest delays (5 and 10 ms) and weak at the long delay (20 ms). At negative angles, where the neuron does not

respond to the leading source, there is no suppression (11C).

The effect of lead location on suppression was observed in kittens as young as 9 days and as old as 29 days. Figure 12A and B shows an effect of lead location in 9-day-old and 27-day-old neurons, respectively. In 12B suppression is strongest at the shortest delays, as well as when the leading source exerts maximal responses. In 12A, the youngest animal for which these data were obtained, the effect of lead location is quite strong, although the effect of delay is somewhat weak. No examples with strong effects of both delay and location are available at the youngest ages studied. Figure 12D shows an effect of both delay and lead location in an adult neuron. The response types shown in Figs. 11, 12A, B, and D are termed SMAX (Litovsky and Yin, 1998, b), since suppression is strongest when the lead response is maximal. These responses were seen at all ages studied and represent 73% (11/15) of neurons; this proportion is consistent with proportions found in the adult data (62%; 24/39).
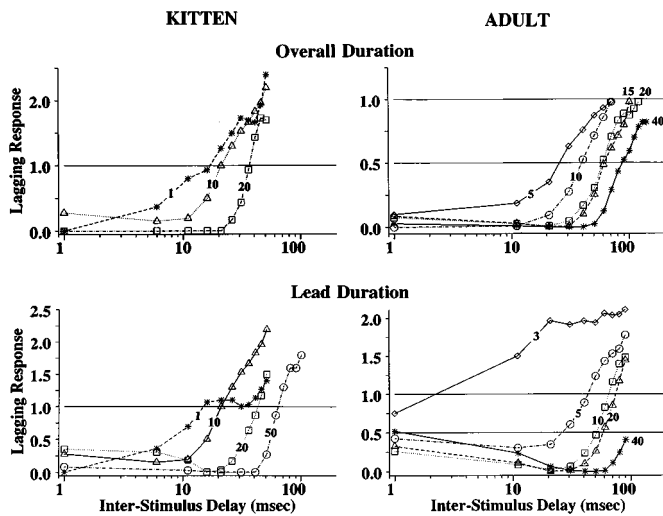
KITTEN **ADULT**

FIG. 10. Effect of stimulus duration. Top: Effects of co-varying the lead and lag durations. Responses of one kitten neuron (27 days, CF=4 kHz) and one adult neuron (CF=10 kHz), each tested using narrow-band noise bursts at CF. Bottom: Effects of varying lead duration for a constant lag duration. Responses of the same two neurons shown above; lag duration were 10 ms and 5 ms, for the kitten and adult neurons, respectively. Both lead and lag locations were chosen such that when presented in isolation they elicited a robust response.

In the adult data there exist an additional, much smaller (13%; 5/39), category of neurons termed SMIN, in which suppression is minimal when the lead response is maximal. In the kitten data 13% (2/15) of neurons exhibited a similar response type as well. For example, in Fig. 12C when the lead produces maximal excitation (+30° to +90°) the lag response is high; the lag response is weaker when the lead response is weaker at −15° to −45°. However, this neuron is not completely SMIN, since at the locations which produce minimal lead excitation (−90° to −60°), suppression of the lag at 5 ms is weak. Finally, the proportion of neurons with no effect of lead location on suppression is 13% (2/15) in kitten neurons, compared with 25% (10/39) in adult cats.

III. DISCUSSION

The principal finding is that cells in the ICC exhibit an adult-like physiological correlate of the PE. This occurs as early as 8–9 days of age, before the full maturation of the structure or function of the auditory system and before the time that a kitten functions behaviorally in its auditory environment.

A. Azimuthal sensitivity

The data presented here suggest that azimuthal sensitivity is well developed early in life. One difference between kitten and adult neurons is the lack of kitten neurons that prefer stimuli presented in the ipsilateral hemifield. However, given that ipsilateral neurons only represent 5% of the adult population (Litovsky and Yin, 1998a), this difference could be due to a sampling bias; adult data were based on almost 70 neurons, whereas kitten data were based on 34 neurons. A second difference is that the youngest neurons studied (8 days) did not show changes in azimuthal sensitivity with increased levels. The effect of level was studied in

several other very young neurons (9, 10, 15, and 20 days of age), all of which did show decreased azimuthal sensitivity at higher levels (i.e., Fig. 3, 10 day neuron). Any developmental effects would thus have to occur between 8 and 10 days. A more likely explanation is that, given the small number of neurons studied for this effect (N=15) the difference may be attributed to a sampling bias.

B. Physiological correlates of precedence

The general finding that most cells in the IC show a suppressed response to the lagging stimulus is consistent with previous reports using stimuli that mimic the PE (Yin, 1994; Yin and Litovsky, 1995; Fitzpatrick *et al.*, 1995; Keller and Takahashi, 1996; Litovsky *et al.*, 1997; Litovsky and Yin, 1998a, b). The results presented here also show that many perceptual phenomena related to the PE exhibit correlates in responses of IC neurons. It is notable that, whereas neural echo thresholds range from 2 to 100 ms, the PE is psychophysically strongest at delays that are below 10 ms (Wallach *et al.*, 1949; Blauert, 1997; Zurek, 1987; Freyman *et al.*, 1991). However, the physiological results are consistent with the idea that perceptual thresholds are generated by those neurons with the lowest thresholds, rather than by mean behavior of the population (Elliot *et al.*, 1960; Liberman, 1978; Yin, 1994). The proportion of neurons with *half-maximal ISDs* (neural correlate of echo thresholds) less than 10 ms is quite substantial: 32% (11/34) and 24% (23/94) in kittens and adults, respectively. Fitzpatrick *et al.* (1995) have also argued that several aspects of the PE, such as accurate localization of the lag at its respective position, and equal-loudness perception of the lead and lag, are not fully in place until the delays are in the tens of milliseconds, which may account for the neurons whose *half-maximal ISDs* are long.

Responses in kitten neurons showed further correlates of psychophysical findings. First, using noise stimuli, half-maximal ISDs were longer (i.e., suppression stronger) with more excitable stimuli having longer durations, which is consistent with findings in adult cats (Litovsky and Yin, 1998a), and with human behavior (Damaske, 1971). Second, *half-maximal ISDs* varied with stimulus level, however, in this case a more excitatory stimulus at higher levels resulted in reduced suppression in most neurons, which is consistent with psychophysical reports (Shinn-Cunningham *et al.*, 1993). These findings suggest that the strength of suppression is not always predictable from the amount of excitation that a stimulus produces when presented in isolation. Rather, there seems to be a more refined interaction between the excitability of the lag and the suppression produced by the lead, which may be independent of spike rate (Yin, 1994). Third, our findings on the effect of varying the leading source level are consonant with psychophysical results in humans: an increase in the level of the lagging stimulus reduces echo thresholds, and an opposite effect occurs when the lag level is decreased (Blodgett *et al.*, 1956; Thurlow and Parks, 1961; Babkoff and Sutton, 1966). Yin (1994) has previously reported similar results in the ICC of adult cats.

Finally, the ICC is thought to be an important structure for encoding auditory cues that are used in sound localization (Yin and Kuwada, 1983; Yin and Chan, 1988). Most neurons
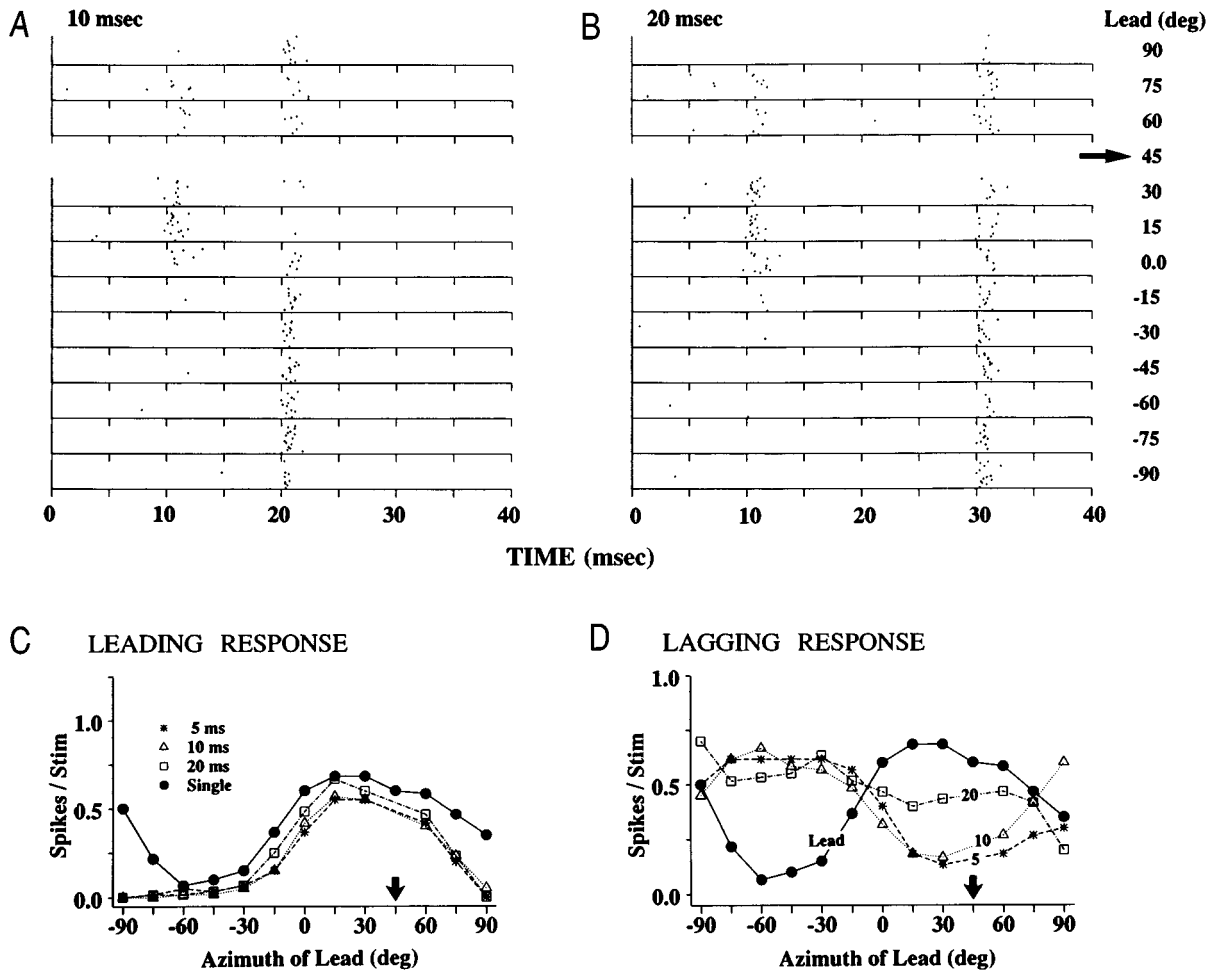
27 DAYS

FIG. 11. Modulation of echo suppression by azimuthal location of the leading stimulus in response to clicks in one 12-day neuron (CF=3 kHz). A and B: Dot rasters with an ISD of 10 ms (A) and 20 ms (B). Responses to the leading stimuli occur at a latency of 10–14 ms, and varies with location from +90° (top) to −90° (bottom). The responses to the lagging responses occur later in time with the stimulus always at +45°. These responses are summarized in C and D. C: Responses to the leading stimulus from A and B (triangles and squares), to the lead at 5 ms (not shown above) and to single clicks (closed circles). The maximum lead/single response occurs at +15° to +60°, in the contralateral hemifield. D: Responses to the lagging stimuli from A and B, as a function of the azimuthal location of the leading stimulus. Responses to single clicks from panel C are shown again in dark circles for comparison. If no suppression occurs then the lagging response should approximately equal the response of the neuron to a single click at 45°. Open symbols represent responses to the lagging clicks at ISDs of 5, 10, and 20 ms.

in the ICC are sensitive to stimulus locations along the azimuth (Semple *et al.*, 1983; Aitkin *et al.*, 1985, 1984; Litovsky and Yin, 1994; Delgutte *et al.*, 1995), hence the importance of stimulus location for physiological correlates of the PE was studied. For most neurons, suppression of response to the lagging source occurred when the leading stimulus was presented from the same locations as the lagging source. Since those locations were most excitatory for the neurons, it may seem that these results are related to the phenomenon of forward masking, whereby the excitability of a signal is reduced by a stimulus that precedes it in time. However, in several neurons suppression of the lagging response could occur even when the response to the leading source is weak (see Fig. 12C). The SMAX neurons might be related to the auditory system's ability to separate the signal from its echo; an echo that arrives from a nearby location is potentially less confusing than one arriving from further locations, hence the

further echo is less likely to be suppressed. Our results are insufficient for resolving this issue; however, it should be noted that psychophysically, the PE and forward masking are considered to reflect different mechanisms in the auditory system (Zurek, 1987).

C. Developmental issues

During the first few weeks after birth the central auditory pathway of mammals undergoes remarkable structural changes, hence it is quite surprising to find that many basic elements of responses to auditory stimuli emerge very early in postnatal life (Brugge, 1992). In the kitten, the pattern of innervation of hair cells stabilizes at around three weeks after birth (Pujol *et al.*, 1978), but myelenation of the auditory nerve is not completed until 3–6 months postpartum (Romand *et al.*, 1976; Walsh *et al.*, 1985). During the neonatal
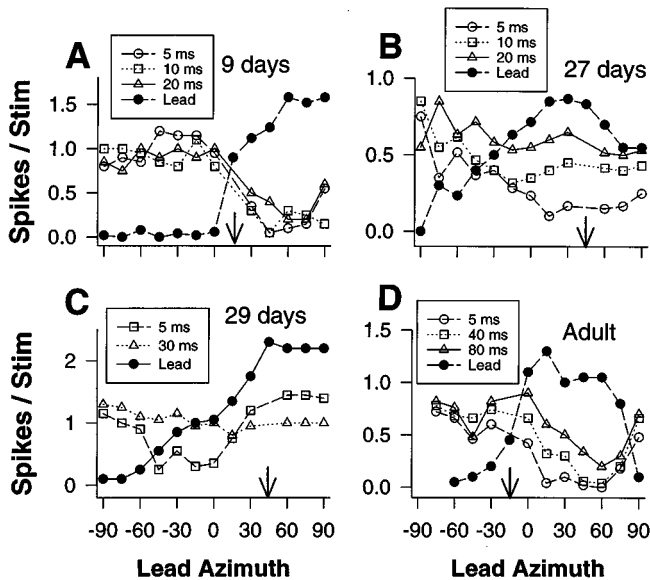
FIG. 12. Responses from four neurons whose echo suppression is modulated by the leading stimulus location. Responses to the leading stimulus by itself (filled circles) and to the lagging stimulus at various ISDs (unfilled symbols) are plotted as a function of the location of the leading stimulus. The arrows in each panel point to the azimuthal location of the lagging stimulus, which was held constant. Neurons in panels A–C are examples from kitten neurons, at 9 days (CF=11 kHz), 27 days (CF=4 kHz) and 29 days (CF=3.7 kHz), respectively. The fourth example in D is from an adult neuron (CF=0.85 kHz).

period significant structural changes also occur in the superior olivary complex (Schwartz, 1972, 1977), which is the first site of binaural interaction in the auditory pathway.

Physiological changes in stimulus coding also undergo significant changes during development. The response latency to sound sources appears to decrease with age at all levels of the auditory pathway (Moore, 1983). In the lateral superior olive (LSO), where neurons encode interaural differences in level, the resolution of single cells is poor in young gerbils tested immediately after ear canal opening (Sanes and Rubel, 1988). This functional immaturity is also found in the IC of kittens (Moore and Irvine, 1981; Blatchley and Brugge, 1990). As Sanes (1992) points out, decreased resolution in single cells at higher levels in the system cannot be accounted for simply by changes at the level of the cochlea.

In spite of all the changes that occur in the auditory system of developing animals, our data show that neurons in the ICC of kittens display a physiological correlate of the PE that is remarkably similar to effects found in the ICC of adult animals (Fitzpatrick *et al.*, 1995; Yin, 1994; Litovsky and Yin, 1998a, b). In fact, the only potential difference in the data was that of lower *half-maximal ISDs* in the kitten population than adult population, a difference which disappeared once the neurons being compared had the same range of CFs. Other than *half-maximal ISDs* (neural correlate of echo threshold), quantitative comparisons between kittens and adults are difficult to make due to the small number of kitten neurons studied. However, our results show that for every effect studied, i.e., varying stimulus level, duration, or lead location, kitten neurons responded in a similar fashion to

adult neurons. Thus, the qualitative similarity between kitten and adult neurons appears to be strong.

Although the site of generation of the PE in the auditory pathway is not known, there is strong evidence to suggest that the IC is an important station in the initial stages of the pathway (Yin, 1994; Fitzpatrick *et al.*, 1995). Studies conducted on kittens in the IC have shown that the neural circuitry involved in sensitivity to ITD and IID (Blatchely and Brugge, 1990) as well as amplitude-modulation (Brugge *et al.*, 1993) is well-developed before the binaural system is matured, and before the cochlea is even capable of responding to those stimuli. Thus, it is not surprising that the responses of ICC neurons to PE stimuli is also fully matured at birth.

How do these findings relate to the behavioral data which suggest that newborn mammals do not experience the PE in a similar fashion to adult mammals (Clifton *et al.*, 1981; Muir *et al.*, 1989; Burnham *et al.*, 1993)? The auditory cortex has been implicated as an important structure in the behavioral manifestation of the PE. Cats with lesions in their auditory cortex are impaired in their ability to localize PE stimuli at the leading source, however, their localization of a single sound remains intact (Cranford *et al.*, 1971; Cranford and Oberholtzer, 1976; Whitfield *et al.*, 1972). In addition, children with temporal lobe epilepsy (Hochster and Kelly, 1981) and adults with cerebrovascular damage (Cornelisse and Kelly, 1987), whose localization of single sounds is nearly perfect, show marked decrease in their ability to localize PE stimuli. It has been suggested (Clifton, 1985) that the auditory cortex provides sensory inhibition of the lagging source, which produces the perception of a fused auditory event at the leading source location. This inhibition presumably unfolds during the first few months of life when the auditory cortex is undergoing significant changes (Dekaban, 1970; Yakovlev and Lecours, 1967). Further research is needed in order to link developmental changes in the cortex with the late onset of the PE in mammals. In particular, behavioral studies in kittens demonstrating a similar time course to that observed in dogs and humans are important.

In summary, this study provides the first measurement of physiological correlates of the PE in the IC of kittens. Our finding that most single-unit physiological observations made in adult cats can be replicated in young kittens is consistent with the notion that the behavioral manifestation of the PE is mediated at higher levels in the auditory pathway than the IC (e.g., Clifton *et al.*, 1994; Clifton and Freyman, 1997). Thus, the neurons in the brainstem are ready to carry relevant information concerning sounds and their echoes at a very young age, much before higher centers are capable of processing that information and using it effectively for behavioral purposes.

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