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Conditioned enhancement and suppression in the developing auditory midbrain

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Abstract

Neural responses in the adult central auditory system to binaural stimuli can be altered by preceding acoustic events, including auditory motion. To determine whether the juvenile auditory system also exhibits this feature, we have examined interaural level difference (ILD) processing in the developing gerbil. A long binaural stimulus was followed without interruption by modulation of the level difference (virtual acoustic motion), which in turn was followed smoothly by a new steady state ILD. Auditory responses of single neurons in the inferior colliculus (IC) were assessed for sensitivity to the final steady state ILD. The response of EI neurons (excited by contralateral stimulation and inhibited ipsilaterally) was examined at postnatal (P) days 17–18, P24–25, and in adult animals. In adult animals, a sudden reduction of the inhibitory stimulus level resulted in a long-lasting (median = 4.3 s) enhanced discharge rate (conditioned enhancement). In P17–18 animals, conditioned enhancement only lasted for 1.2 s. When the inhibitory stimulus level was suddenly increased, adult neurons often displayed a conditioned suppression of discharge rate (median = 4.5 s), whereas P17–18 neurons remained suppressed for a much briefer period (median = 1.2 s). Moreover, the difference between conditioned responses and control discharge rates was three–four times greater in adult neurons compared to those recorded in P17–25 animals.

Because conditioned responses are sensitive to the relative balance of contralateral excitation and ipsilateral inhibition, we examined the relationship between excitatory and inhibitory thresholds. In adult animals, excitatory thresholds were an average of 12 dB lower than inhibitory thresholds, while at P17–25 excitatory and inhibitory thresholds were roughly the same. These results indicate that computational properties of juvenile and adult IC neurons differ quantitatively, and this may reflect an imbalance between excitation and inhibition. The developmental differences described herein may limit the ability of young animals to locate a sound source with the latency and accuracy of an adult.

Introduction

Auditory response properties mature rapidly during the third postnatal week in the gerbil. The cochlea first responds to sound around postnatal day 12 (P12), when a microphonic is first elicited (Harris & Dallos, 1984), and adult-like input–output functions are achieved by P18 (Woolf & Ryan, 1984). The lateral superior olive (LSO) is the first location within the central nervous system (CNS) that responds selectively to interaural level differences (ILDs), and LSO neurons are typically excited by sound at the ipsilateral ear and inhibited by sound at the contralateral ear (Boudreau & Tsuchitani, 1970). In young gerbils (P13–16), LSO neurons exhibit a change in discharge rate with ILD, and the range of level differences that is represented suggests that the inhibitory pathway is relatively stronger than the excitatory pathway, as compared to neurons in adult animals (Sanes & Rubel, 1988). Similarly, ILD functions in the juvenile cat inferior colliculus (IC) are irregular and shallow compared to those obtained from neurons in adult cats (Moore & Irvine, 1981).

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The IC receives bilateral inhibitory and excitatory afferents from multiple brainstem nuclei (Beyerl, 1978; Adams, 1979; Brunso-Bechtold *et al*., 1981; Nordeen *et al*., 1983; Saldaña & Merchán, 1992). The balance between excitation and inhibition arising from these converging afferents is apparently quite sensitive to use, because acute or chronic hearing loss lead to long-term changes in excitability (Kitzes & Semple, 1985; Mogdans & Knudsen, 1993; Bledsoe *et al*., 1995; Szczepaniak & Møller, 1995; Palombi & Caspary, 1996; Wang *et al*., 1996; McAlpine *et al*., 1997). For example, one consequence of monaural deafening is an increase in the magnitude of ipsilaterally evoked excitation (Kitzes & Semple, 1985). Although there is no direct behavioural data, one might suppose that this balance is also critical for auditory processing, particularly for computations of sound location. In contrast to the many studies that have now been performed on the plasticity of excitatory–inhibitory interactions in the IC, there is almost no information on the development of this balance.

Our current knowledge of the development of ILD sensitivity derives from the application of brief static stimuli. However, recent studies in adult animals show that a preceding acoustic event, including auditory motion, can evoke discharge rates that are not predicted by responses to brief stimuli (Spitzer & Semple, 1993). For example, when an IC neuron is pre-exposed to a decreasing inhibitory sound pressure level (SPL), the discharge rate is larger than expected

from the response to a constant stimulus at the same dichotic sound levels (Sanes *et al*., 1998). Therefore, our aim was to determine the responses of young IC neurons to both dynamic and static ILDs.

In summary, we show that dynamic conditioning effects are produced in many young IC neurons. However, these responses are often curtailed in time and diminished in magnitude compared to adults. An increased efficacy of synaptic inhibition reflected in low discharge rates and lower relative inhibitory thresholds may contribute to the cellular immaturities observed. The findings as a whole are considered in relation to a young animal's ability to process complex acoustic stimuli, including its ability to locate a sound source.

Materials and methods

All experiments were performed on surgically anaesthetized Mongolian gerbils (*Meriones unguiculatus*). There were two groups of young gerbils (P17–18 and P24–25), and one adult control group. All young gerbils were anaesthetized with 2 mL/kg i.m. Hypnorm® (fentanyl, 0.3 mg/mL and fluanisone, 10 mg/mL) and 2 mL/kg i.p. Midazolam (5–10 mg/mL). Adults were anaesthetized with one of three protocols: (i) 50 mg/kg ketamine and 350 mg/kg choral hydrate ($n = 9$); (ii) 50 mg/kg ketamine and 50 mg/kg pentobarbital ($n = 18$); or (iii) 0.3 mg/kg fentanyl, 10 mg/kg fluanisone and 5 mg/kg Midazolam ($n = 2$). Supplementary doses were delivered i.m. when the animal responded to a noxious stimulus (cf. paw pinch). All protocols were reviewed and approved by the New York University Animal Welfare Committee. Animals were positioned on a heating blanket in a sound attenuated room and the temperature was maintained at 37 °C. Tracheotomies were performed on some P24–25 and all adult animals. The pinnae were removed, and the external ear canals transected. Speculae for sound delivery were positioned close to the tympanic membrane and seated on the temporal bone; agar was applied to ensure a tight seal. A craniotomy above the occipital cortex provided access to IC from a dorsorostral approach. Tungsten in glass (Ainsworth, London, UK) or parylene (Microprobe, Clarksburg, MD, USA) microelectrodes were used to record the extracellular responses of single neurons in 17 animals at P17–18, eight animals at P24–25 and 29 animals > P90.

Neural signals were amplified, filtered and monitored on an oscilloscope and loud speaker. Unit location in IC was based on physiological criteria of tonotopicity and response reliability (e.g. Aitkin *et al*., 1975). A MALab system (Kaiser Instruments, Irvine, CA, USA) was used for stimulus generation and data acquisition. Stimuli were transduced by Beyer DT-48 earphone elements and calibrated for SPL re 20 μPa. Spike events were time stamped relative to stimulus events with a resolution of 1 μs. Initially, responses were characterized using short static tone pips (200 ms duration, presented once per 700 ms trial period). Inhibitory and excitatory characteristic frequencies (CF) were determined from the relevant frequency tuning curves. Excitatory and inhibitory threshold SPLs were extracted from excitatory rate-level and ILD functions, respectively. Excitatory rate-level functions were defined as discharge rate plotted as a function of excitatory SPL. ILD functions were defined as the discharge rate plotted as a function of inhibitory SPL at a fixed excitatory SPL. To produce a family of ILD curves, the average discharge rate of a neuron to 10 repetitions of the same stimuli was calculated. The contra SPL was fixed initially at the lowest SPL (near threshold) and the ipsilateral SPL was increased stepwise (often in 10 dB steps), contra SPL was then increased by 10 dB and ipsi SPL was again increased stepwise.

Time-varying ILD stimuli were generated by trapezoidally modulating the SPL of a tone delivered to the ipsilateral 'inhibitory' ear, in the presence of an unmodulated tone of the same frequency and duration delivered to the contralateral ear. Thus, the stimulus began with an initial steady-state ILD (origin), which was ramped linearly to a second steady-state ILD (target) and then ramped back to the origin. This complete trapezoidal cycle was reiterated for the duration of the stimulus trial. A common configuration comprised 1 s steady-state components and 250 ms (or 375 ms) dynamic components (depths of 20 or 30 dB at 80 dB/s), presented for three–four modulation cycles. A range of ILDs was explored by systematically adjusting the ipsilateral (and sometimes contralateral) SPL to generate different origin ILDs. In some instances, the depth and rate of modulation was also varied. Responses during the target steady-state 'conditioning' period were compared with control static stimuli containing no dynamic components. For the configurations that were associated with the largest observed differences between the conditioning period and its control, a 12 s pip (14 s trial length) with a single ILD ramp and a single 10 s target steady-state component was used to assess the duration over which the conditioned effect was maintained. The duration of the conditioned response was delimited by the time points at which the spline fit of the histogram intersected with the spline fit from control trials. The spline fit is a set of third degree polynomial segments spliced together such that the resulting curve is continuous and smooth at the splices.

In general, the parametric distributions obtained from these recordings were not normally distributed, and non-parametric global tests for significance were utilized (ANOVA; Kruskal–Wallis). The Mann–Whitney test was employed for pair-wise comparisons.

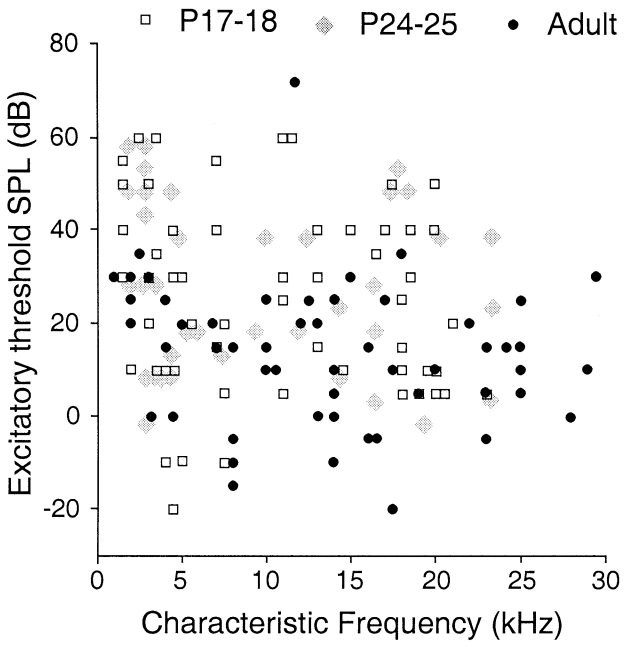

FIG. 1. The threshold at characteristic frequency is plotted for single neurons recorded at the three age ranges. Higher excitatory thresholds and a confined range of CFs were apparent in neurons from animals < P25.

Results

All responses reported here were recorded in neurons that could be excited by stimuli presented at the contralateral ear and inhibited by stimuli delivered to the ipsilateral ear (EI neurons). The data in this study derive from 62 neurons recorded in P17–18 animals, 39 neurons recorded in P24–25 animals and 79 neurons at $P > 90$. A plot of CF versus excitatory threshold is shown for each age group in Fig. 1.

Conditioned response of developing IC neurons

As described previously for adults (see fig. 3 in Sanes *et al*., 1998), one can observe an enhanced response to a specific binaural level stimulus when it is preceded by a conditioning stimulus (consisting of a stationary binaural stimulus followed by a downward modulation of sound level at the ipsilateral inhibitory ear). As illustrated in Fig. 2, decreasing the ipsilateral sound level (Ipsi) in the presence of a constant contralateral sound level (Contra) resulted in a much larger discharge rate (dynamic, open bars) than was observed when an identical binaural level stimulus was delivered for the entire trial period (static, grey bars). As shown in the two poststimulus time histograms (PSTH) from young neurons (P17–18 and P24–25), the period of time during which discharge rate was elevated was less than 1 s, whereas the histogram from an adult neuron shows an elevated response that persisted for over 6 s. Median values for each age group are shown next to each representative histogram (Fig. 2). A significant difference in duration of enhanced spike rates was found between P17–18 and the other age groups ($P = 0.0005$ and 0.008 for adults and P24–25, respectively). The P24–25 group was not significantly different from adults, $P = 0.3$ (Mann–Whitney pair-wise comparisons).

Conditioned suppression refers to the depressed response to a specific binaural level stimulus when it is preceded by a conditioning stimulus consisting of a stationary binaural stimulus followed by an upward modulation of sound level at the ipsilateral inhibitory ear. As illustrated in Fig. 3, increasing the ipsilateral sound level (Ipsi) in the presence of a constant contralateral sound level (Contra) resulted in a much smaller discharge rate (dynamic, open bars) than was observed when an identical binaural level stimulus was delivered for the entire trial period (static, grey bars). As shown in the two representative PSTHs from young neurons (P17–18 and P24–25), discharge rate was suppressed for about 1 s, whereas the histogram from an adult neuron shows a response that persisted for about 5 s. A wide range of suppression periods was observed, but the mean duration of conditioned suppression was shorter in the younger animals (medians = 1.2 s, 2.8 s and 4.5 s; $P = 0.0495$, ANOVA; Kruskal–Wallis).

As reported previously for neurons in the adult IC, only a limited range of ipsilateral sound levels produced conditioned enhancement or suppression. To determine which stimulus conditions produced the largest amplitude response, each cycle of the conditioning stimulus consisted of a 1 s steady-state ILD plus the modulated ILD period. Response magnitude was measured during the 1 s period immediately following the modulation. Figure 4 shows the responses of four neurons, each examined with a range of target ipsilateral sound levels. The magnitudes of conditioned enhancement and suppression can be compared to the discharge rate obtained in response to a constant binaural stimulus delivered for the full trial period.

Pooled data from all such functions indicated that the magnitude of conditioned enhancement was often smaller during the 1 s after modulation in young animals compared to adults (medians = 2.4, 2.2 and 9 spikes/s, and $n = 25$, 31 and 23, at P17–18, P24–25 and adult ages, respectively: $P < 0.0001$ ANOVA; Kruskal–Wallis). Similarly, although the disparity was not so pronounced, in many young cells fewer spikes were suppressed compared to responses recorded in adult animals (medians = 1.2, 1.4, 3.1 spikes/s, and $n = 21$, 24 and 23, at P17–18, P24–25 and adult ages, respectively: $P = 0.03$ ANOVA; Kruskal–Wallis). Note that for each cell only the largest difference between dynamic and static spike rates was chosen from the ILD function.

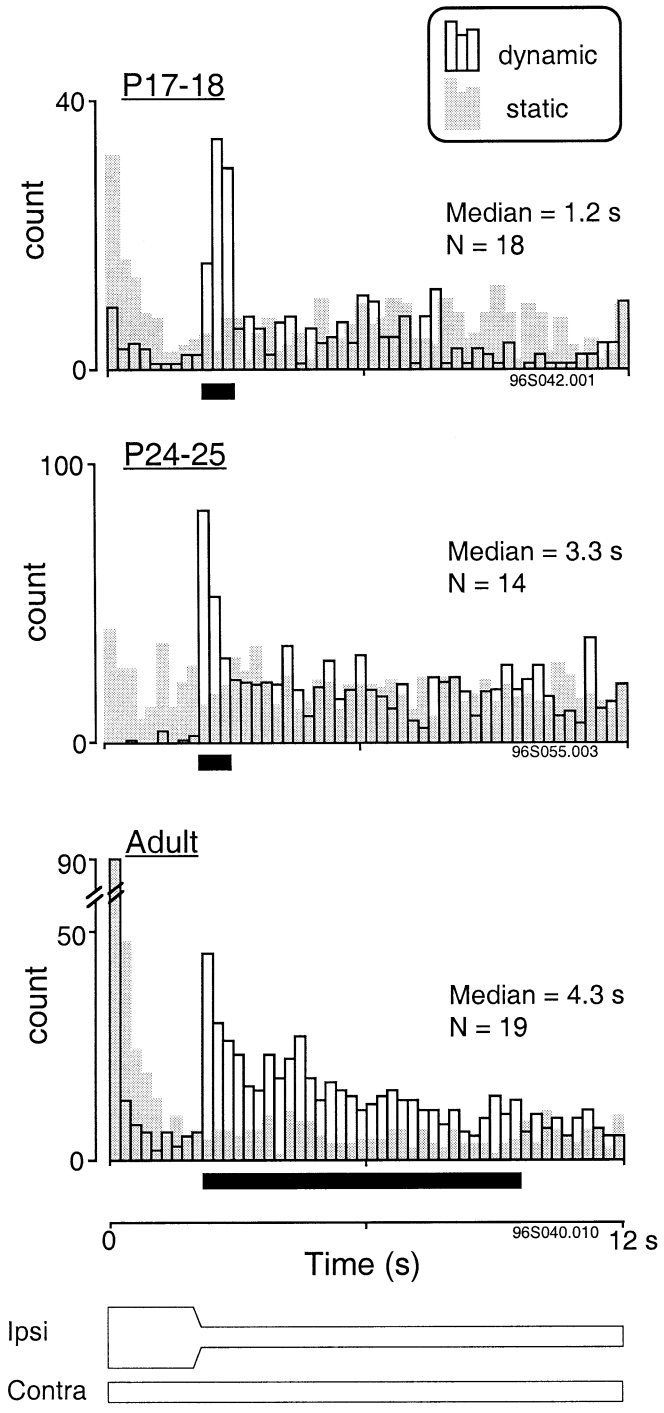

FIG. 2. Representative PSTHs of conditioned enhancement (dynamic) and control (static) trials at three postnatal ages. The specific stimulus conditions were: (P17–18) ipsilateral SPL decreasing from 50 to 30 dB, and contralateral remaining constant at 70 dB; (P24–25) ipsilateral SPL decreasing from 70 to 40 dB, and contralateral remaining constant at 20 dB; and (adult) ipsilateral SPL decreasing from 50 to 30 dB, and contralateral remaining constant at 30 dB. The ipsilateral (Ipsi) and contralateral (Contra) stimulus levels are schematized for the conditioned enhancement (dynamic) trial beneath the histograms. A schematic of the static stimulus conditions is not shown, but the levels were identical to the postmodulation levels in the dynamic stimulus (i.e. during the final 10 s of the trial). The median duration of enhancement is shown for each age group along with the number of neurons recorded. The bar beneath each histogram indicates the period during which enhancement occurs. Cell identification number is indicated beneath each histogram.

Balance between excitatory and inhibitory pathways

One measure of the balance between ipsilateral inhibition and contralateral excitation is the threshold of each pathway. As shown in Fig. 5, there is no correlation between excitatory and inhibitory threshold in neurons from P17–18 animals. Approximately the same number of neurons have lower inhibitory thresholds as those having lower excitatory thresholds. A similar trend exists at P24–25. In contrast, the excitatory threshold of most adult neurons is lower than the inhibitory threshold. To quantify this relationship, the difference between excitatory and inhibitory threshold was computed for each neuron and analysed by age. On average, the excitatory threshold is 4 dB lower at P17–18, the inhibitory threshold is 1.5 dB lower at P24–25, and excitatory threshold is 12 dB lower in adults. The adult value was significantly larger than that for neurons at P24–25 ($P < 0.05$, ANOVA; $P < 0.01$, *t*-test).

A second measure of inhibitory and excitatory balance was the slope and midpoint of ILD functions. Figure 6 shows representative ILD functions along with the median slope values for each age group. The slopes of ILD functions were taken from the linear portion of the ILD functions (grey dashed lines in Fig. 6), and these were shallower in young gerbils of both age groups compared to those in adults ($P < 0.001$, ANOVA; Kruskal–Wallis). However, an important factor in determining the slope of all ILD functions was the peak discharge rate in the absence of contralaterally driven inhibition (not shown): neurons from young animals that have relatively elevated discharge rates in the absence of inhibition (cf. > 30 spikes/s), are also found to have ILD slopes that are not significantly different from those of adult animals (ANOVA: Kruskal–Wallis; $P = 0.3$).

Finally, the midpoints of ILD functions were measured under comparable conditions (contralateral level at 20 dB above threshold). The excitatory–inhibitory response strength was almost equal in adults, whereas inhibition was relatively more powerful in P17–25 neurons (Fig. 7). On average, discharge rate was suppressed at a lower relative ipsilateral level (negative ILD values) in P17–25 animals (medians = – 10, – 10 and 3.75, and $n = 57$, 29 and 40 at P17–18, P24–25 and adult; $P < 0.0003$, ANOVA; Kruskal–Wallis).

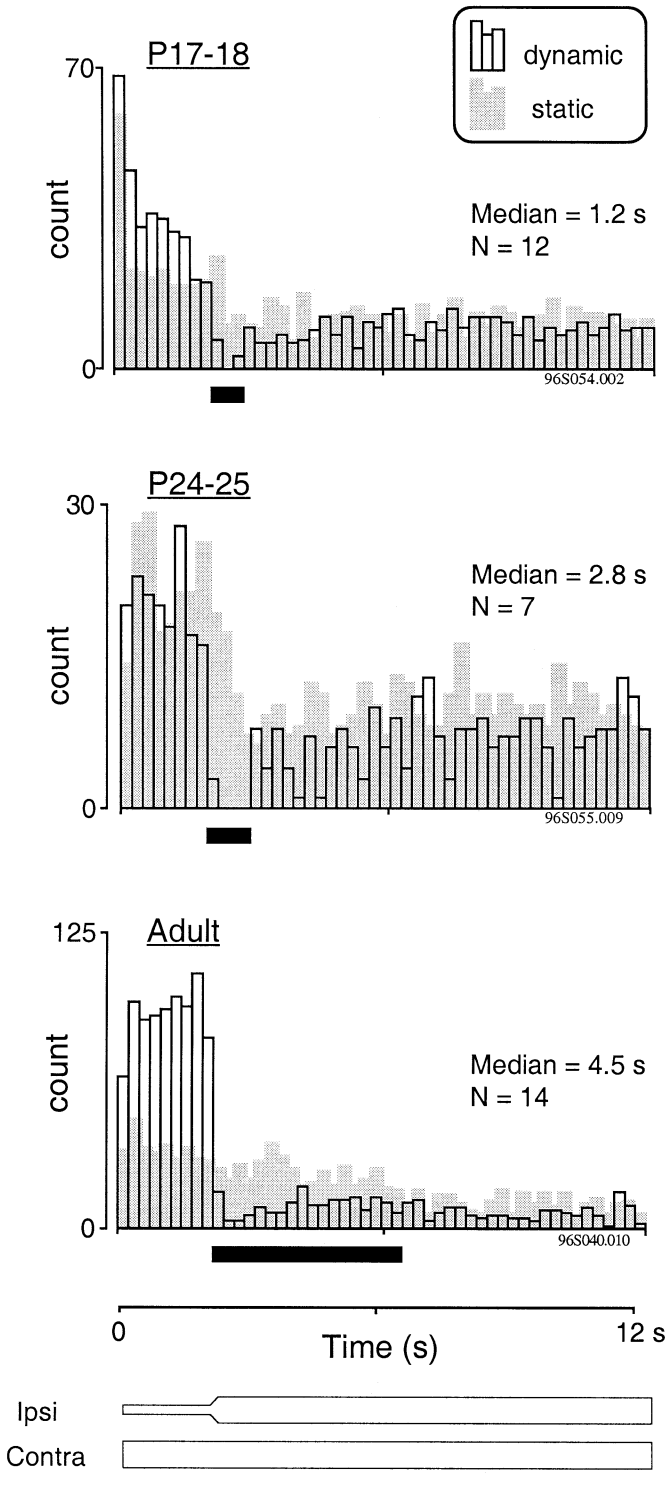

FIG. 3. Representative PSTHs of conditioned suppression (dynamic) and control (static) trials at three postnatal ages. The specific stimulus conditions were: (P17–18) ipsilateral increasing from 30 to 60 dB, and contralateral remaining at 30 dB; (P24–25) ipsilateral increasing from 20 to 50 dB, and contralateral remaining at 40 dB; and (adult) ipsilateral increasing from 30 to 50 dB, and contralateral remaining at 10 dB. The ipsilateral (Ipsi) and contralateral (Contra) stimulus levels are schematized for the conditioned enhancement trial beneath the histograms. A schematic of the static stimulus conditions is not shown, but the levels were identical to the postmodulation levels in the dynamic stimulus (i.e. during the final 10 s of the trial). The median duration of suppression is shown for each age group along with the number of neurons recorded. The bar beneath each histogram indicates the period during which suppression occurs. Cell identification number is indicated beneath each histogram.

Discussion

The balance between excitation and inhibition in the IC can be altered dramatically following acute or chronic injury to one ear (Kitzes & Semple, 1985; Mogdans & Knudsen, 1993; Bledsoe *et al*., 1995; Szczepaniak & Møller, 1995; Palombi & Caspary, 1996; Wang *et al*., 1996; McAlpine *et al*., 1997). This balance can also be altered by a binaural conditioning stimulus, leading to an unexpected elevation or suppression of discharge rate (Sanes *et al*., 1998). In contrast, little is known about the maturation of excitatory and inhibitory balance (Moore & Irvine, 1981; Sanes & Rubel, 1988; Blatchley & Brugge, 1990). The present study was designed to assess this balance, particularly during exposure to conditioning stimuli that employ a virtual motion stimulus.

For many adult IC neurons, the response to a given ILD stimulus was enhanced if that stimulus was immediately preceded by a dynamic reduction in level at the ipsilateral inhibitory ear, and this was termed conditioned enhancement. When the sound pressure level at the ipsilateral inhibitory ear was suddenly increased, many IC neurons responded to the new binaural level with a smaller than expected response, called conditioned suppression (Sanes *et al*., 1998). This is

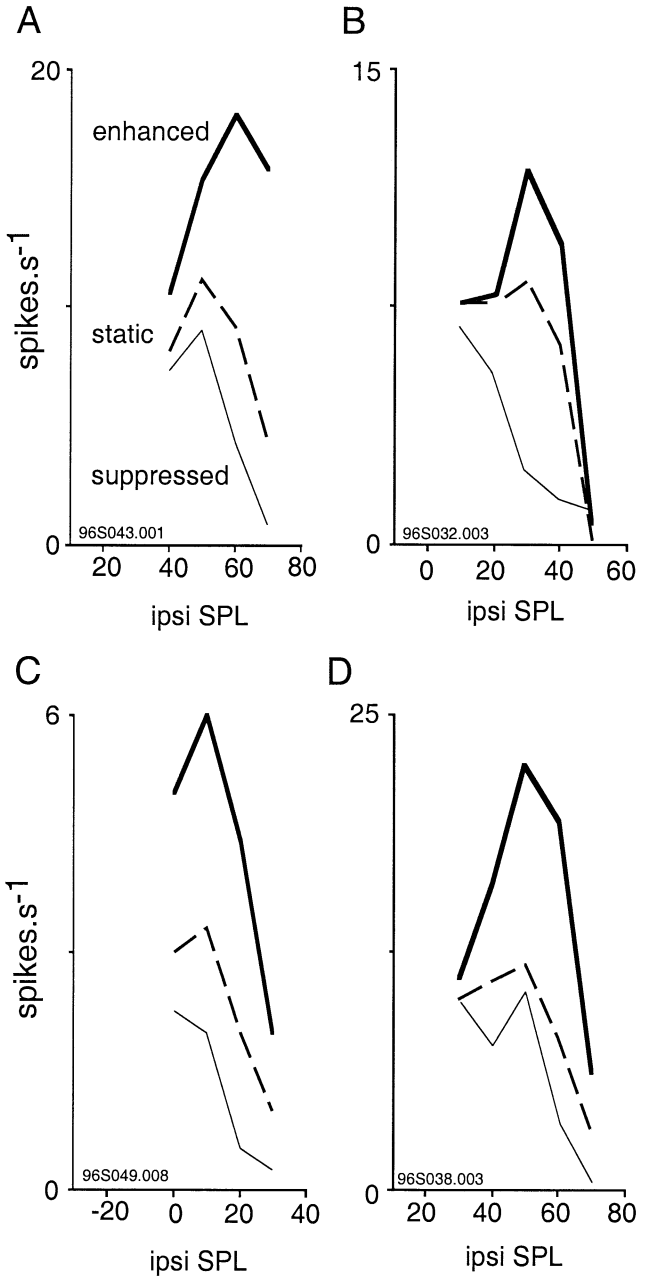

FIG. 4. Plots of the discharge rate following a conditioning stimulus or during control trials for four different neurons. In each case, the discharge rate was measured during the 1 s period that followed a conditioning stimulus (see Materials and methods). For control trials, the discharge rate was measured at the same point in time. The parameter being varied is the final ipsilateral sound level following the modulation. Static curves (dashed line) indicate control trials in which contralateral and ipsilateral sound level remained constant. Enhanced curves (thick line) indicate the response following decreased ipsilateral SPL. Suppressed curves (thin line) indicate the response following increased ipsilateral SPL. In each case, the neuron responds with maximum sensitivity to a specific ipsilateral modulation. (A) This P18 neuron displayed maximum conditioned enhancement when the ipsilateral level was modulated to 60 or 70 dB, and maximum conditioned suppression when the ipsilateral level was modulated to 60 dB. (B) This P17 neuron only displayed maximum conditioned enhancement or suppression when the ipsilateral level was modulated to 30 dB. (C) This P18 neuron displays maximum conditioned enhancement when the ipsilateral level was modulated to 10 dB. (D) This P18 neuron displayed maximum conditioned enhancement when the ipsilateral level was modulated to 50 dB, but did not exhibit conditioned suppression. Cell number is indicated beneath each plot.

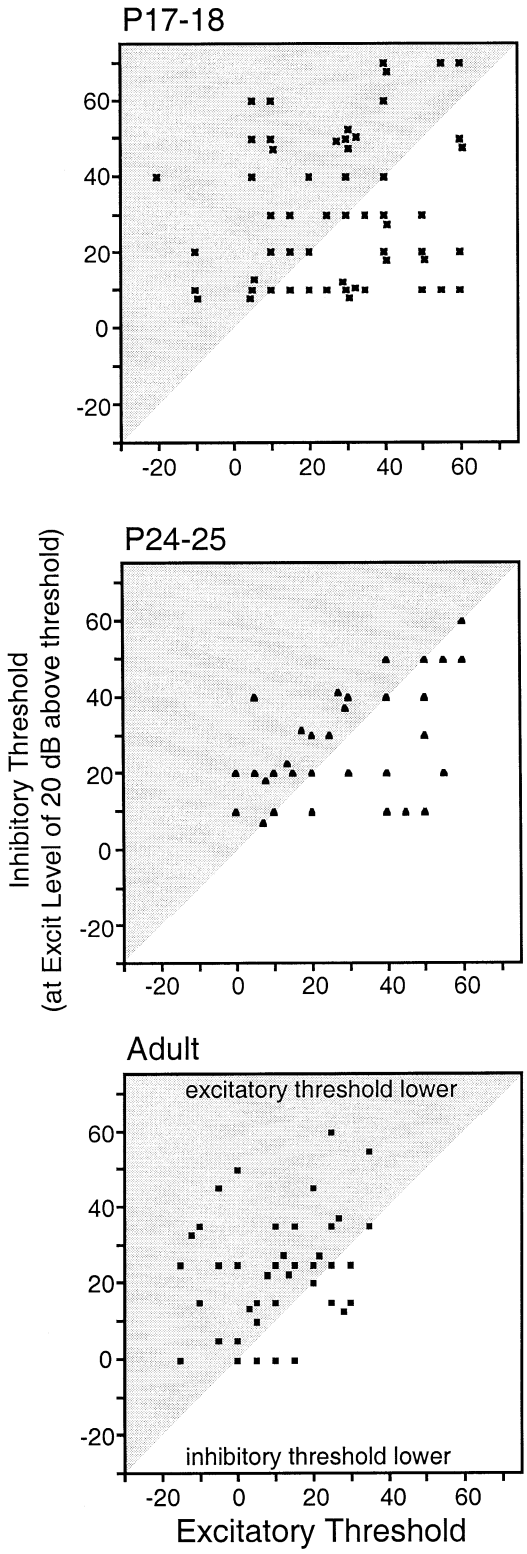

FIG. 5. Plots of excitatory versus inhibitory threshold of neurons recorded in each age group. Grey regions indicate that the excitatory threshold is lower than the inhibitory threshold. Inhibitory thresholds were determined with contralateral stimulus level at 20 dB above the threshold. (Top) At P17–18 there is no relationship between excitatory and inhibitory threshold. (Middle) At P24–25 the diversity of thresholds becomes more limited and clusters around the slope of one. (Bottom) In neurons from adult animals there is a clear bias towards lower excitatory thresholds.

consistent with previous studies demonstrating that neural sensitivity to a specific binaural stimulus may become altered by recent acoustic stimulation (Ahissar *et al*., 1992; Spitzer & Semple, 1993). Furthermore, it is thought that a change in the balance of excitation and inhibition in the IC may contribute to the special sensitivity to motion. Our present findings indicate a postnatal maturation of sensitivity to time-varying ILD stimuli. While neurons in P17–25 animals did produce a deviation from the static discharge rate following the conditioning period, the durations and magnitudes of conditioned enhancement or conditioned suppression were much smaller at P17–18 compared to adults (Figs 2 and 3). Although discharge rates are lower in young animals, the failure to produce long-lasting conditioned enhancement (or suppression) is not due to a general fatigue in the system. Rather, neurons continued to respond to sound stimuli at these low rates for several tens of seconds. Therefore, a specific mechanism may develop after P17–18 in order for IC neurons to become conditioned fully by an acoustic motion stimulus.

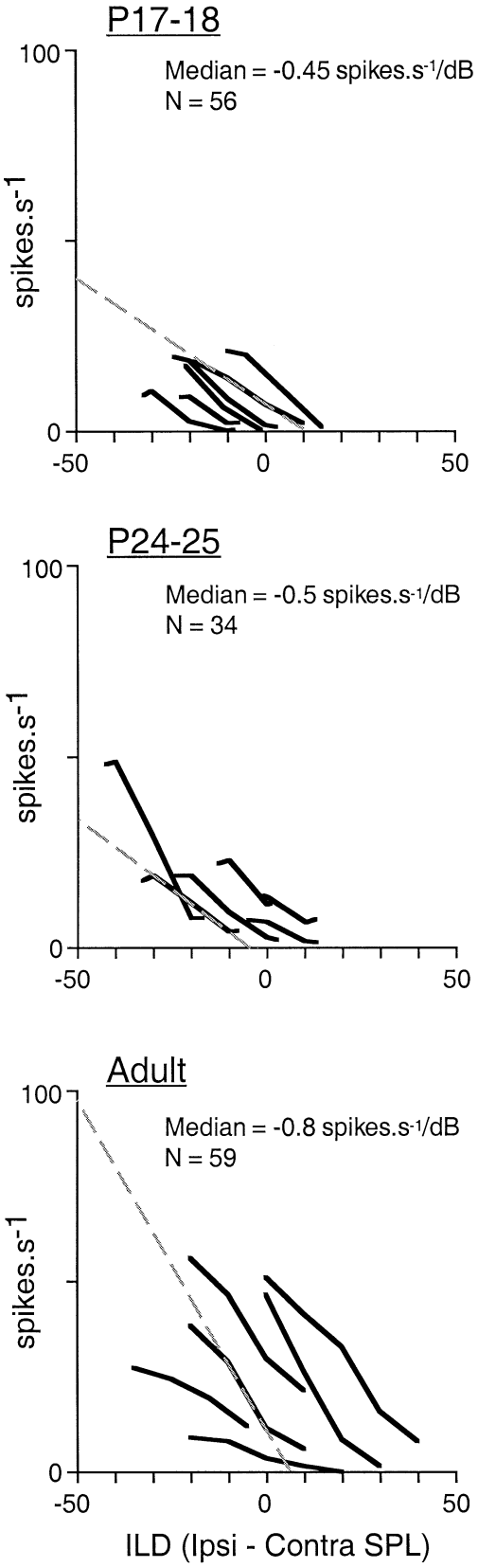

FIG. 6. Representative ILD functions for each age group. (Top) At P17–18 the ILD functions are quite shallow. (Middle) At P24–25 the ILD functions are both shallow and adult-like. (Bottom) In neurons from adult animals the ILD functions are relatively steep. The dashed grey lines indicate that ILD slope was measured from the linear portion of the curve. Median slope values for each of the three age groups are presented above the curves.

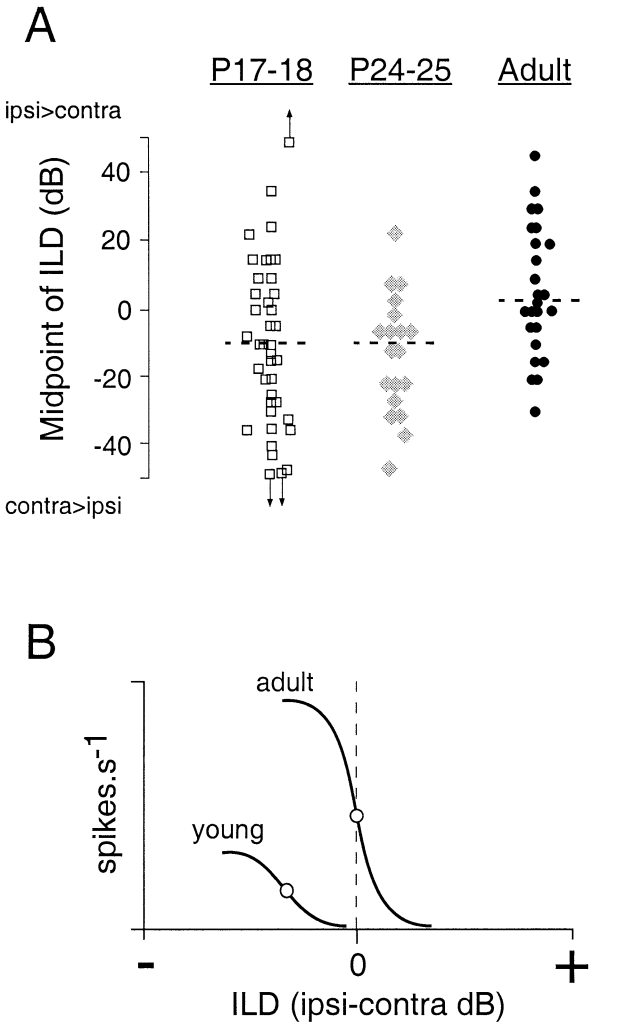

FIG. 7. Midpoints of ILD curves for each age group. (A) The midpoints of the linear portion of ILD functions at the three age groups display a greater variance at P17–18, and a significant shift towards a midpoint of 0 in adult neurons. Dashed lines indicate the median value for each age group. (B) A schematic summarizing the changes found for ILD curves.

One way to explore the potential interaction of excitation and inhibition of binaural inputs in the IC is through the use of ILDs. In the gerbil and other species, the ability to respond to binaural difference cues is present at a time when the auditory system is not yet structurally mature and when many monaural properties are still maturing (Moore & Irvine, 1980; Brugge, 1988; Sanes & Rubel, 1988). In the present study of gerbil IC, the shapes of the ILD and rate-level functions resembled those of adult animals, but the slopes of the functions were shallower and more irregular. In the younger age groups, both threshold and the midpoint of ILD functions show that the balance of inhibition and excitation is biased towards inhibition in young animals (Figs 5 and 7). Bruckner & Rubsamen (1995) observed that in adult gerbil IC, low frequency units have stronger ipsilateral inhibition than high frequency units (medians of midpoints of ILDs: – 3 dB and 4.3 dB, respectively). Although the lower relative inhibitory thresholds observed in juveniles could have been due to the proportion of low frequency neurons, if the analysis was restricted to neurons with CF above 4 kHz, a significant difference was still evident between midpoint positions in adult and P17–18 neurons (not shown). These findings complement observations made at the level of the gerbil LSO, indicating that the balance between inhibition and excitation favours inhibition in young animals (Sanes & Wooten, 1987; Sanes & Rubel, 1988).

A number of electrophysiological and behavioural studies have documented the protracted emergence of responses to other sound localization tasks. In gerbils, Kelly & Potash (1986) first observed approach responses at P16–19, and they further observed that binaural cues were used for sound localization at this time. If human infants are tested on a minimal audible angle task, significant improvements occur over a broad range of ages (18 months, 5 years and adult, Litovsky, 1997). It will be the work of future studies to elucidate the cellular basis of complex acoustic processing in the adult and young animal. Moreover, if complex acoustic tasks reflect higher order processing, then dynamic stimuli may provide a useful tool in determining the influences of early peripheral damage and delayed repair (cochlea damage, middle ear infections, cochlea implants) on development and plasticity of the CNS.

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Abbreviations

CF, characteristic frequency; CNS, central nervous system; IC, inferior colliculus; ILD, interaural level difference; LSO, lateral superior olive; P, postnatal; PSTH, poststimulus time histogram; SPL, sound pressure level.

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