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Dynamic Changes in Level Influence Spatial Coding in the Lateral Superior Olive

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Abstract

It is well established that the responses of binaural auditory neurons can adapt and change dramatically depending on the nature of a preceding sound. Examples of how the effects of ensuing stimuli play a functional role in auditory processing include motion sensitivity and precedence-like effects. To date, these types of effects have been documented at the level of the midbrain and above. Little is known about sensitivity to ensuing stimuli below in the superior olivary nuclei where binaural response properties are first established. Here we report on single cell responses in the gerbil lateral superior olive, the initial site where sensitivity to interaural level differences is established. In contrast to our expectations we found a robust sensitivity to ensuing stimuli. The majority of the cells we tested (86%), showed substantial suppression and/or enhancement to a designated target stimulus, depending on the nature of a preceding stimulus. Hence, sensitivity to ensuing stimuli is already established at the first synaptic station of binaural processing.

Keywords

Binaural; Sound Localization; Interaural Level Difference

Introduction

Interaural time differences (ITDs) and interaural level differences (ILDs) are important cues for encoding sound source locations in azimuthal space. Sensitivity to ITDs and ILDs is first established in the medial superior olive (MSO) and lateral superior olive (LSO), respectively (Boudreau and Tsuchitani, 1968; Caird and Klinke, 1983; Goldberg and Brown, 1968, 1969). The response properties established in the superior olive are then reiterated in auditory centres along the ascending neuraxis. However, numerous transformations take place which modify the basic response properties of olivary projections (Pollak et al, 2002; Pecka et al. 2007). In this regard, a great deal of attention has been focussed on the inferior colliculus which integrates a variety of both excitatory and inhibitory ascending inputs from various monaural

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and binaural brainstem nuclei including olivary inputs (Brunso-Bechtold et al., 1981; Oliver et al., 1995; Hutson et al., 1991). For example, inhibitory inputs onto collicular cells have been shown to narrow or shift the range of best sensitivity to binaural cues which are presumed to be established in the superior olive (Park and Pollak, 1993). Inhibitory inputs have also been shown to play an important role in shaping the responses of binaural collicular neurons to multiple stimuli and to dynamic stimuli (Spitzer and Semple, 1998; McAlpine et al., 2000; Yang and Pollak, 1994; Yin, 1994). Thus, a neuron's discharge rate to a specific binaural stimulus can change dramatically depending on the nature of a preceding stimulus. These effects have been suggested to play a role in echo suppression and in motion sensitivity (Pollak, et al, 2002; Spitzer and Semple, 1998).

Recent evidence has indicated that sensitivity to ensuing auditory stimuli can be established in the inferior colliculus. In one study, precedence-like effect in collicular neurons was blocked by reversibly inactivating the dorsal nucleus of the lateral lemniscus, a strong source of GABAergic inhibition to the inferior colliculus (Burger and Pollak, 2001). Similarly, Sanes et al. (1998) showed that collicular neurons displayed a paradoxical after-effect both from changing ILD and from a brief local application of inhibitory transmitter. Because the pharmacological manipulations were local, these experiments indicate that sensitivity to ensuing stimuli is at least partially shaped within the inferior colliculus via inhibitory circuits or by a specific shift of the balance of excitatory and inhibitory inputs (McAlpine and Palmer 2002). However, it is not clear whether these are emergent properties which are not seen below the midbrain, or whether similar response properties might be established in the superior olive as well.

The present study, we address this issue directly by characterizing sensitivity to ensuing stimuli in neurons in the gerbil LSO using a stimulus paradigm similar to the one used previously by Sanes et al (1998) on neurons in the gerbil inferior colliculus. Sanes, et al found that ILD-sensitive neurons in the inferior colliculus displayed prominent paradoxical after-effects from preceding stimulation. They termed these effects conditioned suppression and conditioned enhancement. In the present study, we found that most neurons in the LSO also show substantial conditioned suppression and/or enhancement, similar to that reported by Sanes and colleagues. Hence, sensitivity to ensuing binaural stimuli is established at the first synaptic station of the ascending ILD coding pathway prior to additional processing, and to some extent *de novo* establishment in the inferior colliculus.

Methods

All experiments were performed in conformity with the rules set by the EC Council Directive (86/89/ECC) and German German Tierschutzgesetz (AZ 211-2531-40/01 + AZ 211-2531-68/03).

Mongolian gerbils (*Meriones unguiculatus*) were anaesthetized with a mixture of ketamine (10mg/100g) and rompun (2%) throughout the experiment. Animals were placed on a heating cushion in a sound attenuated chamber and electrodes were inserted stereotaxically through the foramen magnum. Recording electrodes were tungsten or glass pipettes filled with 2 M sodium acetate (impedance 10–30 M Ω). Recording sites were anatomically confirmed by histological analysis of HRP injections (for details see Behrend et al. 2002) or electrolytic lesions (for details see Siveke et al. 2006).

Extracellular single cell recordings were performed using glass pipettes filled with 2 M sodium acetate (impedance 10–30 M Ω .) and an electrometer (Electro 705, World Precision Instruments). The recording electrode was advanced under remote control, using a motorized micromanipulator (Digimatic, Mitutoyo, Neuss, Germany) and a piezodriven (Inchworm

controller 8200, EXFO Burleigh Products Group Inc, USA). Recorded signals were fed into a 50/60 Hz noise eliminator (Humbug, Quest Scientific), a 0.7 to 3 kHz-band-pass filter (spike conditioner PC1, Tucker Davis Technologies, System II) and a spike discriminator (SD1, Tucker Davis Technologies, System II). Only action potentials from single neurons with a signal to noise ratio of >5 with stable shapes (visual inspection on a spike-triggered oscilloscope) were recorded. Action potentials were registered using an event timer (ET1, TDT; temporal accuracy: 2.5 μ s) and the DSP-Board (TDT, System II) and stored for offline analysis. Recording of action potentials and stimulus generation was controlled by custom-made software (Spike; D. Molter, Zoologisches Institut der LMU, München, B. Warren, University of Washington, Seattle). Data analysis was performed offline.

Acoustic stimuli were delivered using Tucker Davis Technologies (TDT) System II and two Beyer dynamics speakers (model DT 990), fitted to the ears via probe tubes (2 mm inner diameter). The stimulus delivering system and the speakers were calibrated using a ¼ inch microphone (Reinstorp VtS, Germany), a measuring amplifier (MV 302, Microtech, Gefell, Germany) and a waveform analyzer (Stanford Research Systems, model SR770 FFT network analyzer). After electrophysiological isolation of a single neuron, a frequency-tuning curve was measured and the best frequency and threshold determined. ILD functions were generated by simultaneously presenting tones at the neuron's best frequency to both ears. The intensity at the ipsilateral (excitatory) ear was set 20 dB above threshold while the intensity at the contralateral (inhibitory) ear was varied by ± 30 to 40 dB in a pseudo random order. Stimuli were delivered at a rate of 4/s with 10 repetitions at each ILD. An example ILD function generated in this way is shown in Figure 1a.

To test the effects of a preceding stimulus, we first selected a target ILD. The target ILD was the ILD that generated a spike-count that was approximately 50% of the peak spike-count. For preceding stimuli, we used the same intensity to the excitatory ear as that used for the target ILD, but the intensity to the inhibitory ear was 10–20 dB lower or higher than that used for the target ILD. Neurons were tested in three stimulus configurations. In one configuration, the preceding stimulus with a less intense signal to the inhibitory ear was alternated with the target ILD. In a second configuration, the preceding stimulus with a more intense signal to the inhibitory ear was alternated with the target ILD. In the third configuration, the ILD of the preceding stimulus and the target stimulus were identical. In each case, we presented the target and preceding stimuli 50 times. Most of the data were collected with 250 ms tones and no inter-stimulus-interval, but some neurons were tested with other stimulus durations and/or inter-stimulus-intervals, as indicated in the text. The rise/fall times were always 5 ms.

Results

We tested 37 LSO neurons and found that the majority (32/37) showed conditioned suppression, enhancement, or both depending on the nature of a preceding stimulus. The basic response properties in response to single, binaural stimuli of the neurons we studied were consistent with previous reports on the gerbil LSO (Sanes and Rubel, 1988). The best frequencies among the neurons in our sample ranged from 1.0 to 39.0 kHz, and the majority of the neurons responded throughout the stimulus duration with a primary-like temporal response pattern, although we also recorded from 3 onset cells. All of the neurons were excited by ipsilateral stimulation and inhibited by contralateral stimulation. Hence, spike-counts were highest for ILDs favouring the ipsilateral (excitatory) ear, and lowest for ILDs favouring the contralateral (inhibitory) ear. The example ILD function presented in Figure 1a shows the typical sigmoidal shape of the ILD functions we measured.

For each neuron, we selected a target ILD from the steep portion of the ILD function, near 50% suppression. For the example function in Figure 1a, the target ILD, indicated by the gray arrow,

was generated by presenting a 40 dB tone to the excitatory ear and a 50 dB tone to the inhibitory ear. To test the effect of a preceding stimulus on a neuron's response to the target, we used three stimulus configurations. In one configuration, the preceding stimulus was an ILD with a lower intensity at the inhibitory ear compared to the target (black arrow in Figure 1a). In the second configuration, the preceding stimulus was an ILD with a higher intensity at the inhibitory ear compared to the target (open arrow). In the third configuration, the level at the inhibitory ear was the same as in the target ILD. For all stimulus configurations, the intensity to the excitatory ear was kept constant.

The results for the example neuron in Figure 1a are presented as raster plots in Figure 1b-d. Each plot shows responses for 50 stimulus repetitions. As expected, this neuron responded with different spike-counts to the different preceding stimuli. More importantly, spike-counts also differed for the target ILD, depending on the preceding ILD. The middle panel (Figure 1c) shows the response to the preceding and target stimuli when the two stimuli were identical. The response to the target in this situation was used as a control to compare to responses when the preceding stimulus had a different ILD. When the target stimulus was preceded by an ILD with a less intense signal at the inhibitory ear, the target stimulus evoked a weaker response than in the middle panel (conditioned suppression) (Fig. 1b). The lower panel (Figure 1d) shows that when the target stimulus was preceded by an ILD with a more intense signal at the inhibitory ear, the target stimulus evoked a stronger response compared to the control condition (conditioned enhancement).

We used the data from the raster plots to construct peri-stimulus time histograms where spikes were binned into 20 ms bins (Figure 1e-g). To evaluate the effect of a change in response rate due to the preceding ILD, the control spike-counts from stimulus conditions where preceding and target ILD were the same, are indicated in grey in each panel. Figure 1e shows the suppression generated from the preceding stimuli that had a lower intensity to the inhibitory ear. The spike-counts for each bin during presentation of the target stimulus (white bars) are lower than the spike-counts generated by the target stimulus when it was paired with itself. Figure 1g shows the enhancement generated from the preceding stimuli that had a higher intensity to the inhibitory ear. In this case the spike-counts for each bin during presentation of the target stimulus (white bars) are higher than the spike-counts generated by the target stimulus paired with itself. Note that the neuron in Figure 1 displayed some degree of spike reduction across progressive trials, the first trial corresponding to the bottom row of dots in each dot raster plot and the last trial corresponding to the top row (Figure 1b-d). Testing for a correlation between trial number and spike-count revealed an average correlation co-efficient of 0.207 (s.e. = 0.019). There was no difference in the average correlation coefficient for trials where the target was preceded by itself ($R^2 = 0.237$) versus a different stimulus ($R^2 = 0.191$), suggesting that spike reduction was an effect of stimulus repetition and not related to the nature of the preceding stimulus.

To quantify conditioned suppression and enhancement, we calculated the percentage decrease and percentage increase in spike-counts for the entire stimulus duration in response to the same target stimulus when it was preceded by different ILDs. For the neuron in Figure 1, conditioned suppression corresponded to a 39% decrease and conditioned enhancement corresponded to a 67% increase in the spike-count. We found varying degrees of suppression and enhancement across the population of LSO neurons, but no systematic relationship or correlation between suppression and enhancement occurring within individual neurons. For example, the neuron in Figure 2a showed both substantial suppression (57%) and enhancement (63%). The neuron in Figure 2b showed a substantial degree of suppression (74%) but a much greater degree of enhancement (142%). The neuron in Figure 2c showed substantial suppression (43%) but little enhancement (17%). Note that the transition from the first binaural stimulus to the second, the

ramping off and on between stimuli, caused a transient response which is evident in the second row of histograms in Figure 2 (4th bin).

The distribution of suppression and enhancement values for our population of neurons is shown in Figure 3a. The average percentage decrease corresponding to suppression was $29\% \pm 4.14$ and the average percentage increase corresponding to enhancement was $49\% \pm 9.63$. Twenty-five of the neurons (68%) showed a suppression greater than 20%; 24 of the neurons (65%) showed an enhancement greater than 20%; and 17 of the neurons showed both suppression and enhancement greater than 20%. Only 5 neurons (14%) failed to show either suppression or enhancement, meaning that the majority of neurons (86%) showed a substantial effect, either suppression, enhancement, or both, from a preceding stimulus. Within individual neurons, there was no correlation between the magnitude of suppression and the magnitude of enhancement ($R^2 = 0.0008$), as indicated by the regression line in Figure 3a. We also found no significant correlation between suppression or enhancement with characteristic frequency, excitatory threshold, inhibitory threshold, slope of rate-level function or slope of ILD function (R values < critical values for Pearson R with $df=35$). To quantify the overall effects of a preceding stimulus, we combined the percentage increase corresponding to enhancement and the percentage decrease corresponding to suppression. For the neuron in Figure 1, this resulted in a value of 105 (67% increase plus 39% decrease). Figure 3b presents these values for each cell in rank order of effect size to illustrate the wide range of overall effects from a preceding stimulus.

To assess the contributions of inter-stimulus interval (ISI) and stimulus duration, we tested a subset of neurons using the standard condition (ISI=0 ms; duration=250 ms) as well as with a longer ISI (2750 ms; $N=7$) or a longer stimulus duration (3000 ms; $N=5$). These neurons showed a substantial effect under standard conditions (Fig. 4a,b). However, with an ISI of 2750 ms (triangles) the effect of the preceding stimulus on the response to the target stimulus disappeared (Fig. 4a). The difference in effects from the two stimulus configurations was significant (paired t-test, $t = 2.9$, $df = 6$, $p < 0.05$). In contrast, there were substantial effects with both the short (250 ms) and the long (3000 ms) stimulus durations (Fig. 4b), and there was no significant difference between the values (paired t-test, $t = 1.52$, $df=4$, $p=0.2031$).

So far we have described only effects due to changes of level at the inhibitory ear. However, we found that changes in the level of the preceding stimulus at the excitatory ear also evoked suppression and enhancement. Figure 5a and b presents the results from one of these neurons. The data in Figure 5a show how the neuron responded to the standard paradigm in which the level to the excitatory ear was fixed and the level to the inhibitory ear was varied for the preceding stimulus compared to the target stimulus. As shown in previous examples, under these conditions the neuron demonstrated suppression (top panel) and enhancement (bottom panel) – suppression following a preceding stimulus that had a less intense signal to the inhibitory ear compared to the target. The data in Figure 5b show how the same neuron responded when the level to the inhibitory ear was fixed and the level to the excitatory ear was varied for the preceding stimulus. The neuron again demonstrated suppression (top panel) and enhancement (bottom panel). Note that in both stimulus paradigms (Figure 5 a,b), suppression followed a preceding stimulus that generated a relatively high spike-count, while enhancement followed a period of relatively low spike activity.

The summary data for the 10 cells tested in the two stimulus paradigms described above is shown in Figure 5c, again displayed as percent difference between enhancement and suppression. Some of the neurons showed a greater effect from preceding stimuli when the level to the inhibitory ear was varied (circles) while others showed a greater effect when the level to the excitatory ear was varied (triangles). There was no significant difference between the values generated by the 2 stimulus paradigms (paired t-test, $t = 1.424$, $df = 9$, $p = 0.1881$).

We also tested 5 neurons with stimulation to just the excitatory ear and again found suppression and enhancement when we decreased or increased the overall stimulus level. Data from an example neuron are presented in Figure 6a which shows that the response to a monaural target stimulus was suppressed when the target was preceded by a more intense signal (top panel). Responses were enhanced when the target was preceded by a less intense signal (bottom panel). The summary data from 5 neurons tested in the monaural paradigm are shown in Figure 6b. Four of the 5 neurons showed substantial effects from preceding stimuli (triangles). For comparison, the value for each neuron obtained with the standard stimulus configuration (level to the excitatory ear fixed, level to the inhibitory ear varied) is also plotted (circles). The values did not differ significantly (paired t-test, $t = 2.02$, $df = 4$, $p = 0.1135$).

Discussion

The main finding of the present study is that neurons in the LSO display a robust sensitivity to ensuing stimuli. This sensitivity is presumably relayed to ascending targets, notably the inferior colliculus, where Sanes et al (1998) have reported conditioned suppression and enhancement for ILD-sensitive neurons in that structure.

The stimulus regiment in the Sanes study differed from ours in that they used continuous tones and changed ILDs by trapezoidally modulating the intensity to the inhibitory ear. In our study, due to technical reasons, we used discrete tone bursts. Nevertheless, the degree of suppression and enhancement displayed by collicular neurons appears to be qualitatively very similar to that reported here for LSO neurons (see Sanes Figures 1 and 3). Also, the proportion of neurons displaying enhancement was similar in both the collicular and the LSO samples (65%), while the collicular sample had a higher proportion of neurons that displayed suppression (80% vs 68%). In an additional experiment, Sanes, et al used local application of a mixture of glycine and GABA instead of acoustically stimulating the inhibitory ear and they found that the discharge rate was enhanced following inhibitory transmitter application as it was following acoustically driven inhibition. This pharmacological result indicates that sensitivity to ensuing stimuli in the inferior colliculus is at least partially shaped within the colliculus via inhibitory circuits. Therefore, it seems likely that sensitivity to ensuing stimuli is established in the LSO and modified and/or established again in the inferior colliculus, which is true for basic ILD sensitivity (Faingold et al, 1993; Li L and Kelly, 1992; Park and Pollak, 1993; 1994; Vater et al, 1992).

This is not the first report of dynamics in the SOC or the LSO. Using a forward masking paradigm, Finlayson and Adam (1997a,b) showed that probe tones reduce response to a second tone in the majority of rat SOC cells. They also found that recovery occur in the range of about 100 ms. The magnitude of effects and the time course of recovery, however, were significantly less in the SOC compared to the IC. For LSO cells, roughly half of the neurons showed an enhanced response after binaural probing but the authors argued that, in about one third of the LSO cells, changes in the inhibitory strength basically counterbalanced this effect. Therefore, the representation of the ILD code should be stable for those cells. This is in contrast to our finding that the majority of neurons the absolute response to a given ILD changes depending on the recent history of binaural stimulation. Our present data, together with the data from the inferior colliculus (Sanes, et al, 1998) argues that the ILD code is dynamic. Two questions therefore arise: what are the mechanisms underlying the observed dynamics and how does that affect the encoding of sound localization.

A number of different mechanisms can underlie “adaptation” and therefore may account for the extraordinary plasticity and dynamics of network functions. We did not assess the mechanisms underlying the dynamic changes in this study, but results from other experiments

and the fact that the changes occur within a few hundred milliseconds at least narrow the possible explanations down to a few candidates.

There are various categories of “adaptation” observed in the nervous system and almost all of them can be found within the mammalian ascending auditory system. Long term plasticity has been found in the adult auditory cortex. For example, Bao et al (2003) could induce long-lasting changes in the responsiveness of neurons in the primary auditory cortex which were probably based on long-term changes in synaptic weights or even changes in the connection patterns. Long lasting effects at lower stages have been induced by lesions, for instance of one cochlea, leading to an altered balance of excitation and inhibition (McAlpine et al. 1997). This may be due to a permanent decrease in the efficacy of inhibitory connections as, for instance, glycine receptors are permanently down regulated in the IC opposite to a cochleaeectomy (Suneja et al. 1998; Argence et al. 2006).

On an intermediate time scale, reversible changes in ILD sensitivity in the gerbil’s brainstem lasting several days can be induced by noise exposure (Siveke et al. 2007), which may cause homeostatic adaptation to the overall driving force or changes in the turnover and trafficking of receptors, vesicles, and proteins in the postsynaptic machinery (reviews: Bruneau et al. 2006, Chen et al. 2007). Such explanations only occur over the time course of several hours and are therefore unlikely mechanisms underlying the plasticity observed in this study.

Mechanisms on the timescale of only a few milliseconds can be observed even at the level of the first synapse in the auditory system, the hair-cell ribbon synapse (Nouvian, et al, 2006 for review) which are reflected in the rapid but mild adaptive behavior of auditory nerve fibers (Loquet et al, 2003 for review). Such adaptations would, most likely, affect the inhibitory and excitatory pathways to the LSO rather equally and it is difficult to imagine that they could cause such strong and stable influences as those observed in the present study. As mentioned earlier, Finlayson and Adam (1997a,b) argued that adaptive behavior of both excitatory and inhibitory LSO inputs should cancel each other out, leading to a stable ILD-specific output. However, Sanes and colleagues (Sanes et al, 1998) provided evidence and argued convincingly that a more specific change in the balance of excitation and inhibition is responsible for the effects in their study. Comparably, manipulating the strength of GABAergic inhibition can influence the way ITD-sensitive IC neurons adapt to excitatory inputs and thereby influence their response to dynamic sounds (McAlpine and Palmer 2002). This finding raises the possibility that specific modulation of synaptic inputs or postsynaptic weighting of these inputs may account for the conditioned suppression and enhancement reported by Sanes et al and in the present study.

There is increasing evidence that several efferent and/or modulatory mechanisms are present in the auditory brainstem. For example, cortical activity can influence the ascending inputs even at the level of the cochlear hair cells (Xiao and Suga, 2002), or augment frequency tuning at the level of the inferior colliculus (Yan, et al, 2005). Therefore, influences on the LSO or its inputs via efferent projections would be one possible source for short-term adaptations in the early binaural system. However, such effects would require activation of specific cortical regions in the auditory cortex. Since the study by Sanes et al, as well as the present study, was performed in anesthetized animals and no cortical stimulation was used, the efferent system seems an unlikely explanation for the observed effects. Moreover, the LSO, as well as the MSO, is particularly sparsely innervated by efferent inputs (Thompson and Schofield, 2000), further making descending inputs an unlikely candidate. Another potential mechanism might involve olivocochlear feedback circuits. In a recent study, Darrow et al (2006) showed that feedback via the olivocochlear system may be involved in fine adjusting the excitability of both ears and could, therefore, help to balance the binaural inputs. It is also possible that adaptation, in a binaural context, could already occur at the level of the cochlear nucleus. It

has been shown that a commissural connection between the left and right cochlear nuclei provides a fast, onset inhibition. It is a relatively weak inhibition and only a minority of bushy cells (the primary source of inputs to the LSO and MNTB) receive these commissural inputs (Needham and Paolini, 2007; Schofield and Cant, 1996). However, these inhibitory inputs could still affect the onset portion of responses in the LSO.

A likely candidate mechanism to explain the conditioned suppression and enhancement we observed may involve neuromodulatory systems that act on a time scale of tens of milliseconds. For instance, noradrenalin has been shown to enhance the temporal precision of response onsets in the cochlear nucleus (Kössl and Vater 1989), and serotonin has short term effects on the tuning functions of inferior colliculus cells (Hurley and Pollak, 2001). Hence modulatory systems may well effect binaural processing in the SOC as well. One potential, but by no means the only possible contributor, may be the GABA_B system. The principal binaural nuclei of the SOC - MNTB, LSO, and MSO - show pronounced GABA_B receptor staining in the cat (personal communication, Winer JA and Larue DT) and the gerbil (Magnusson, Koch and Grothe, unpublished results). In fact, blockade of GABA_B receptors in the gerbil LSO leads to a shift of the ILD functions *in vivo* (Magnusson, et al, 2006). The direction of the shift indicates either an enhancing effect on the excitatory drive or a reducing effect on the inhibitory drive, suggest to us that prior to drug application GABA exerts a greater inhibitory effect on excitatory than on inhibitory inputs. These effects could be confirmed with *in vitro* recordings which also indicate that GABA is released from the dendrites of LSO neurons themselves. Hence, the LSO may adjust the balance of excitation and inhibition, and thereby its ILD sensitivity, dynamically via activity dependent release of GABA. The GABA mainly affects (reduces) the excitatory inputs and thereby reduces the overall excitability of the cells (Magnusson et al, 2006). This is in agreement with the findings of the present study, that a preceding stimulation with a lower intensity at the inhibitory ear (associate with greater spike activity), reduces a neuron's response to the following target ILD, and that a preceding stimulation with higher intensity at the inhibitory ear (associate with less spike activity) increases the response to the target ILD.

Whatever the mechanisms underlying the dynamics of ILD sensitivity in the gerbil LSO might be, the fact that ILD coding is dynamic supports recent speculations that stable ILD coding at the single cell level is not required for stable sound source perception. Traditionally, binaural processing had been discussed in the conceptual framework of labeled line coding. Therefore, stable ILD and ITD processing has been assumed at the earliest level of binaural coding in the SOC. At higher levels, dynamics had been assumed to be related to motion direction selectivity (Spitzer and Semple, 1993; 1998). However, a recent study challenged the explanation that dynamics in ITD processing of IC neurons is related specifically to motion detection, and argued instead that dynamics might be a result of general adaptation to overall firing rate (McAlpine, et al, 2003). Changes in absolute ITD sensitivity would therefore be an epiphenomenon of adaptation to other stimulus statistics or absolute stimulus intensity. Similarly, we found in a previous study that overall intensity has a profound impact on ILD coding of single LSO and IC cells (Park, et al, 2004). However, the data also indicated that the overall population code was affected very little by absolute intensity. Therefore we argue that response dynamics as observed in the present study of the LSO may not substantially affect the overall population code. Moreover, it might be advantageous for single cells to adapt to overall stimulus amplitude and statistics in order to optimize ILD coding in the sense of keeping the steep slope of the ILD function close to the actual ILD. However, it remains to be shown that the dynamics observed here are in fact helpful in adapting ILD sensitivity to the actual spatial stimulus context.

At other levels of auditory processing, dynamic adaptation in order to adapt to environmental changes or, more specifically, to changed statistics of sounds are well known. For instance

preceding stimuli dynamically narrow the receptive field of A1 cells in anesthetized cats. As a result, selectivity for binaural conditions that elicited maximal spike rates to single stimuli was enhanced (Nakamoto, et al, 2006). Moreover, acoustic filter properties of A1 neurons can dynamically adapt to stimulus statistics, classical conditioning, instrumental learning and the changing of amplitude (Fritz, et al, 2005; 2007) and IC neurons can adapt to the actual statistics of the temporal structure of sounds (Lesica and Grothe, 2006). Since most sounds occur not in isolation but in sequences or in a complex context (Bregmann, 1993), such adaptations might be crucial for extracting behaviorally relevant signals in a noise background. In fact a recent study from the bird auditory system convincingly showed that such adaptations can be of considerable advantage for processing biologically relevant sounds in a natural environment (Nagel and Doupe, 2006).

There is clearly a growing body of evidence that many forms of adaptation take place at multiple levels of the auditory system and via multiple mechanisms. The data we present in the present manuscript indicate that this is also true for the LSO where the first stages of binaural processing take place, possibly mediated by a GABA_B modulatory system.

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List of Abbreviations

A1	primary auditory cortex
IC	inferior colliculus
ILD	interaural level difference
ITD	interaural time difference
LSO	lateral superior olive
MSO	medial superior olive
MNTB	Medial Nucleus of the Trapezoid Body
SOC	superior olivary complex

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Figure 1.

Effects of preceding stimuli on the responses to a standard target stimulus for an example LSO neuron. **A.** Preceding and target stimuli were ILDs selected from the dynamic portion of the neuron's ILD function. ILD functions were generated with 250 ms tones presented at the neuron's best frequency. For this neuron, the intensity to the ipsilateral, excitatory ear was held fixed at 40 dB, SPL and the intensity to the contralateral, inhibitory ear was varied from 20–70 dB, SPL. The curve shows that spike number decreased as a function of increasing contralateral intensity. **B–D** Raster plots showing spike activity during presentation of a preceding stimulus and a following target stimulus (50 presentations). The ILD of the target stimulus is the same as the ILD indicated by the grey arrow in **A**. **B** shows responses for a

preceding stimulus with a less intense signal to the inhibitory ear (corresponding to the ILD indicated by the black arrow in **A**). **C** shows the responses for a preceding stimulus that was the same as the target. **D** shows responses for a preceding stimulus with a more intense signal to the inhibitory ear (corresponding to the ILD indicated by the open arrow in **A**). **E–G** Peristimulus time histograms corresponding to the raster plots (spikes binned into 20 ms bins). The first three bars corresponds to the last 60 ms with the preceding stimulus. The remaining 12 bins correspond to the first 240 ms with the target. In each of the tree histograms, the grey bars show spike-counts for the target stimulus when it was preceded by itself. The open bars show spike-counts for the target when it was preceded by an ILD with a less intense signal to the inhibitory ear (**E**) or an ILD with a more intense signal to the inhibitory ear (**G**).

Figure 2. Peri-stimulus time histograms for three neurons (A–C) tested with preceding stimuli as described in Figure 1. See text for detail.

Figure 3.

Magnitude of effects for the 37 neurons tested. **A.** Suppression values along the x-axis correspond to the percentage decrease in spike-count for the target stimulus preceded by an ILD with a less intense signal to the inhibitory ear. Enhancement values along the y-axis correspond to the percentage increase in spike-count for the target stimulus preceded by an ILD with a more intense signal to the inhibitory ear. The regression line and correlation coefficient indicate no correlation between magnitude of suppression and enhancement. **B.** The combination of the percentage increase corresponding to enhancement and the percentage decrease corresponding to suppression is plotted for each neuron as an index of overall effects of preceding stimuli. The values are in rank order of effect size.

Figure 4.

Effects from preceding stimuli are lost with a relatively long inter-stimulus-interval but not with a relatively long stimulus duration. **A.** The percentage difference between suppression and enhancement for seven neurons tested with the standard 0 ms inter-stimulus-interval (circles) and a relatively long inter-stimulus-interval of 2,750 ms (triangles). **B.** The percentage difference between suppression and enhancement for five neurons tested with the standard stimulus duration of 250 ms (circles) and a relatively long stimulus duration of 3,000 ms (triangles). Each neuron shows substantial effects for both durations.

Figure 5.

Effects of changing excitation versus inhibition in generating the preceding stimulus. **A.** Peri-stimulus time histograms from a neuron tested with the standard stimulus paradigm where the intensity to the inhibitory signal was manipulated. **B.** Peri-stimulus time histograms from the same neuron when the intensity of the excitatory signal was manipulated. Both stimulus paradigms induce suppression and enhancement. **C.** The percentage difference between suppression and enhancement for ten neurons tested with both stimulus paradigms.

Figure 6.

Effects of stimulating only the excitatory ear. **A.** Peri-stimulus time histograms from a neuron tested with monaural, excitatory stimuli. This neuron showed suppression to the monaural target when it was preceded by a more intense monaural stimulus (top) and enhancement when the target was preceded by a less intense monaural stimulus (bottom). **B.** The percentage difference between suppression and enhancement for five neurons tested with monaural stimuli.