

Binaural Interactions in the Auditory Brainstem

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Binaural cues for sound localization

- Two main binaural cues are available for localizing sounds in the horizontal plane: Interaural time differences (ITD) and interaural level differences (ILD).
- ITD depends primarily on the distance between the ears. In cats, ITD varies with azimuth from about $-400 \mu\text{sec}$ to $+400 \mu\text{sec}$. In humans, the ITD range is about $\pm 700 \mu\text{sec}$.
- The ILD cue is strongest at high frequencies ($> 5 \text{ kHz}$ in cats, $> 2 \text{ kHz}$ in humans). In cats, ILD at high frequencies can vary with azimuth by as much as $\pm 30 \text{ dB}$.
- Sound localization also depends on spectral features (peaks and notches) introduced by the filtering action of the pinna.

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Please see: Tsuchitani, C., and D. H. Johnson. "Binaural cues and signal processing in the superior olivary complex." In *Neurobiology of Hearing: The Central Auditory System*. Edited by R. A. Altschuler, R. P. Bobbin, B. M. Clopton, and D. W. Hoffman. New York: Raven, 1991.

Cell groups in superior olivary complex (SOC)

- Nissl-stained cross sections of the cat brainstem at the level of the superior olivary complex.
- Three principal cell groups are visible: The **medial nucleus of the trapezoid body** (MNTB, the most medial), the **medial superior olive** (MSO), and the S-shaped **lateral superior olive** (LSO). Surrounding these nuclei are loosely-defined **periolivary cell groups**.
- The **trapezoid body** is a fiber bundle largely consisting of axons of AVCN cells.

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Principal nuclei of the SOC

- Schematic cross section showing the 3 principal superior-olivary nuclei (MNTB, MSO, and LSO) surrounded by periolivary nuclei (PON).
- The layout and nomenclature of the PON varies between species and investigators. In rodents a large PON called Superior Paraolivary Nucleus (SPN) occupies the position of the DMPO in cats.
- Whereas the principal nuclei get most of their inputs from the AVCN, the PON get ascending inputs from the PVCN and descending inputs from the inferior colliculus. Some PON (VNTB and VMPO) contain the cell bodies of medial olivocochlear (MOC) efferents.

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Please see: Hefert, R. H., and A. Aschoff.
“Superior olivary complex and nuclei of lateral lemniscus.” In *The Central Auditory System*. Edited by G. Ehret, and R. Romand. Oxford: Oxford University Press, 1997, pp. 193-258.

Basic circuitry of SOC

- Spherical bushy cells in AVCN project via the trapezoid body (TB) to the ipsilateral LSO and the MSO on both sides.
- Globular bushy cells in AVCN project, also via the TB, to the contralateral MNTB. MNTB neurons project to the ipsilateral LSO as well as some PON.
- Thus, MSO and LSO get inputs from both sides (via MNTB for LSO), while MNTB receives only monaural (contralateral) inputs.
- MSO projects to the ipsilateral inferior colliculus (IC) and dorsal nucleus of lateral lemniscus (DNLL).
- LSO projects primarily to the contralateral IC and DNLL, with a minor ipsilateral projection.

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Please see: Hefert, R. H., and A. Aschoff.
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Major projections from AVCN to SOC

- Physiologically-identified axons in the trapezoid body were labeled with HRP and their cells of origin in the AVCN identified.
- Spherical bushy cells (which have primary-like response patterns) project to the ipsilateral LSO, MSO on both sides and some periolivary nuclei (VNTB/LNTB).
- Globular bushy cells (which have primary-like-with-notch response patterns) project to the contralateral MNTB and some periolivary nuclei on both sides.

Figure removed due to copyright reasons.
Please see: Smith, P. H., P. X. Joris, and T. C. T. Yin. "Projections of physiologically characterized spherical bushy cell axons from the cochlear nucleus of the cat: Evidence for delay lines to the medial superior olive." *J. Comp. Neurol.* 331 (1993): 245-260.

Cell shapes and axonal plexus in SOC

- A. Afferents to the SOC form an orderly plexus. Note the calyces of Held in MNTB, and the segregation of inputs from each side in MSO. In both LSO and MSO, the plexus runs orthogonal to the long axis.
- B. LSO principal neurons are disk-shaped (nearly planar) with dendrites perpendicular to the long axis of the LSO.
- C. MSO neurons have a bipolar shape with their two dendrites oriented along the afferent axons and orthogonal to the main axis.

Figure removed due to copyright reasons.
Please see: Irvine, D. R. F.. *The Auditory Brainstem*. Berlin: Springer-Verlag, 1986.

All three principal SOC nuclei are tonotopically organized

- In MNTB, low frequencies are represented dorso-laterally and high frequencies ventro-medially.
- In MSO, low frequencies are represented dorso-medially and high frequencies ventro-laterally.
- In LSO, low frequencies are represented in the lateral limb, and high frequencies in the medial limb.
- In MSO, there is an over representation of the low frequencies, while high frequencies are over represented in MNTB and LSO. This is significant because ITD and ILD are most effective for sound localization in different frequency regions.

Figure removed due to copyright reasons.
Please see: Guinan, J. J., Jr., B. E. Norris, and S. S. Guinan. "Single auditory units in the superior olivary complex. II: Locations of unit categories and tonotopic organization." *Int. J. Neurosci.* 4 (1972): 147-166.

Cellular specializations for precise timing in auditory brainstem

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EPSCs recorded with
voltage clamp technique are
much shorter in VCN bushy
cells than in hippocampal
neurons

Trussell (1997, 1999)

Calyces of Held on MNTB principal neurons

- The axons of AVCN globular bushy cells form giant synaptic terminals called **calyces of Held** onto MNTB principal neurons. These calyces cover a large fraction of the MNTB cell surface.
- These specialized synapses, together with the thick, myelinated axons of globular bushy cells ensure rapid, secure transmission of spikes from the AVCN to the contralateral MNTB and, ultimately, to LSO.

Figure removed due to copyright reasons.
Please see: Morest, D. K. "The growth of synaptic endings in the mammalian brain: A study of the calyces of the trapezoid body." *Z. Anat. Entwickl.-Gesch.* 127 (1968): 201-220.

Pre-potential spikes in MNTB

- Metal electrodes inserted into MNTB record complex spike waveforms consisting of two components, often of opposite polarity, that are separated by ~0.4 msec.
- These complex spikes resemble those recorded from spherical bushy cells in the AVCN. Both spherical bushy cells and MNTB principal cells receive huge synapses called end bulbs and calyces of Held, respectively.
- As in bushy cells, the first component of complex spikes (the pre-potential) is presynaptic (from the end bulb), while the second component is postsynaptic.
- Intracellular recordings from labeled MNTB principal cells show the same response to sound as pre-potential units, confirming that these units are the MNTB principal cells.

Figure removed due to copyright reasons.
Please see: Smith, P. H., P. X. Joris, and T. C. T. Yin. "Anatomy and physiology of principal cells of the medial nucleus of the trapezoid body." *J. Neurophysiol.* 79 (1998): 3127-3142.

MNTB neurons have low-threshold, outward-rectifying K⁺ conductance

- AVCN bushy cells have two specializations for precisely relaying temporal discharge patterns: (1) inputs via end bulbs of Held which ensure secure synaptic transmission, and (2) a low-threshold K⁺ conductance that rapidly resets the membrane voltage after each spike or EPSP.

Figure removed due to copyright reasons.
Please see: Banks, M., and P. H. Smith.
“Intracellular recordings from neurobiotin-labeled cells in brain slices of the rat medial nucleus of the trapezoid body.” *J. Neurosci.* 12 (1992): 2819-2837.
- Principal cells of MNTB resemble bushy cells in that they have the first of these specializations, inputs from calyces of Held. *In vitro* intracellular recordings show that MNTB cells also have a low-threshold K⁺ conductance similar to that found in bushy cells. When membrane voltage is measured in response to step current pulses, hyperpolarizing currents cause a nearly linear change in membrane voltage, while depolarizing currents cause a nonlinear change consistent with a very low membrane resistance. Bath application of 4-aminopyridine, a K⁺ channel blocker, makes the I-V curve linear (not shown), confirming that the nonlinear drop in resistance is due to a K⁺ conductance similar to that found in bushy cells.
- As expected from these specializations, MNTB neurons show both precise phase locking to low-frequency tones and Pri-notch PST histograms for high-frequency tone bursts, just like their inputs from globular bushy cells (not shown).

MNTB principal cells project to MSO and LSO

- Reconstruction of intracellularly-labeled MNTB principal cells (here in the big brown bat) show that their axons have an extensive pattern of projections including not only the ipsilateral LSO, but also periolivary nuclei. In some species, MNTB neurons also project to the ipsilateral MSO.
- Inputs from MNTB neurons make bouton endings on the cell bodies and proximal dendrites of LSO principal cells. In contrast, inputs from ipsilateral AVCN terminate on the distal dendrites.
- There is strong evidence that MNTB projections to LSO are inhibitory based on the shape of synaptic vesicles, the presence of the inhibitory neurotransmitter glycine, and physiological responses *in vivo* and *in vitro*.

Figure removed due to copyright reasons.
Please see: Zook, J. M., and R. A. DiCaprio. Intracellular labeling of afferents to the lateral superior olive in the bat, *Eptesicus*. 1988.

LSO neurons are excited by ipsilateral stimuli and inhibited by contralateral ones

- LSO neurons are excited by stimulation of the ipsilateral ear, and inhibited by stimulation of the contralateral ear. This is consistent with their excitatory inputs from the ipsilateral AVCN and their inhibitory input from the contralateral AVCN (via an inhibitory interneuron in MNTB). The more intense contralateral stimulation, the more the response to a fixed ipsilateral stimulus is inhibited.
- Tuning curves for ipsilateral excitation and contralateral inhibition closely match.
- For most neurons, latencies of ipsilateral excitation and contralateral inhibition also match, despite the additional distance and intervening synapse for contralateral inhibition.

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Please see: Boudreau, J. C., and C. Tsuchitani.
“Cat superior olive S-segment cell discharge to tona stimulation.” In *Contributions to sensory physiology*. Vol. 4. Edited by W. D. Neff. New York: Academic, 1970, pp. 143-213.

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Please see: Caird, D., and R. Klinke.
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LSO neurons are sensitive to ILD

- A consequence of the ipsilateral excitation and contralateral inhibition on LSO neurons is that they are highly sensitive to interaural level differences (ILD).
- To a first approximation, the discharge rate of an LSO neuron depends primarily on ILD, regardless of overall level. Response is small when the ILD is zero, as would occur on the midline.
- Closer examination shows that, for this neuron, response for a given ILD decreases with increasing overall level., i.e. inhibition becomes relatively more effective than excitation at high sound levels.

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Please see: Irvine, D. R. F. *The Auditory Brainstem*. Berlin: Springer-Verlag, 1986.

Classification of binaural interactions

Simple scheme (Goldberg and Brown, 1968)

- Two letter code, indicating the *predominant* effect of each ear on neural response, either E (excitation), I (inhibition) or O (no effect). Usually, the contralateral ear comes first.
- **Examples:**
 - OE Responds to ipsilateral ear only (e.g. VCN)
 - EO Responds to contralateral ear only (e.g. MNTB)
 - IE Ipsilateral ear excites, contralateral ear inhibits (e.g. LSO)
 - EE Binaurally excited (e.g. MSO)

Detailed scheme (Irvine, 1986)

- Two letters followed by slash and third letter (e.g. EO/S). First 2 letters characterize the predominant effect of each ear alone (contralateral first). Third letter gives the type of interaction observed when both ears are stimulated: facilitation (F), suppression (S), or no interaction (O)
- **Examples:**
 - EO/S Responds to contralateral ear , NR to ipsilateral ear, binaural response smaller than contra.
 - EE/F Responds to each ear alone. When both ears are stimulated, response is facilitated (greater than both monaural responses)
 - OO/F Responds only to binaural stimulation

LSO neurons are sensitive to ITD of AM tones

- LSO neurons respond better to amplitude-modulated (AM) tones when the modulations are out of phase at the two ears (B) than when they are in phase (A). Thus, LSO neurons are sensitive to interaural time differences of stimuli having modulated waveforms.
- This form of ITD sensitivity is a consequence of the IE binaural interactions in LSO neurons, as well as the specializations in the LSO circuit (thick axons of globular bushy cells terminating on calyces of Held) which allow contralateral inhibition to arrive to LSO at the same time as ipsilateral excitation despite the longer pathway and additional synapse in MNTB.

Figure removed due to copyright reasons. Please see: Joris, P. X., and T. C. T. Yin. "Envelope coding in the lateral superior olive. I. Sensitivity to interaural time differences." *J Neurophysiol.* 73 (1995): 1043-1062.

MSO receives excitatory and inhibitory inputs from both sides

- MSO principal cells receive excitatory inputs from spherical bushy cells in AVCN bilaterally.
- MSO cells also receive inhibitory inputs from the ipsilateral MNTB and LNTB (one of the periolivary nuclei). Since the primary inputs to MNTB are from the contralateral AVCN, and inputs to LNTB are from the ipsilateral AVCN, MSO receives inhibitory inputs from both sides.
- The function of these inhibitory inputs is a topic of considerable current interest.

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Please see: Grothe B. "New roles for synaptic inhibition in sound localization." *Nat Rev Neurosci.* 4, no. 7 (Jul 2003): 540-50.

Bipolar dendrites of MSO cells allow segregation of inputs from the two sides

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Stotler, W. A. “An experimental study of the cells and connections of the superior olivary complex of the cat.” *J. Comp. Neurol.* 98 (1953): 410-432.

AND

Smith, P. H. “Structural and functional differences distinguish principal from nonprincipal cells in the guinea pig MSO slice.” *J Neurophysiol* 73, no. 4 (Apr 1995): 1653-67.

- MSO principal neurons are bipolar in shape, with both dendrites largely covered by excitatory synaptic terminals from spherical bushy cells.
- Lesion of the contralateral CN results in degeneration of most afferents on the medial dendrite, but leaves inputs on the lateral dendrite intact. This finding shows that inputs from the two AVCNs are segregated, each one ending on one of the two dendrites of MSO cells.
- MSO neurons project to the ipsilateral central nucleus of the inferior colliculus (ICC) and dorsal nucleus of the lateral lemniscus (DNLL).

Inputs to MSO show enhanced phase locking

- Spherical bushy cells show better phase locking than AN fibers at low frequencies
- This enhanced phase locking is thought to reflect coincidence detection between similar AN inputs occurring in bushy cells
- The enhanced phase locking is likely to aid processing of ITD in MSO

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MSO neurons contain low-threshold K⁺ conductance

- A. MSO cells, like AVCN bushy cells and MNTB principal cells, fire a single spike or brief burst of spikes in response to step current injections *in vitro*
- B. Bath application of 4-aminopyridine (4-AP) a selective blocker of low-threshold K⁺ channels causes the MSO cell to fire spikes throughout the current step

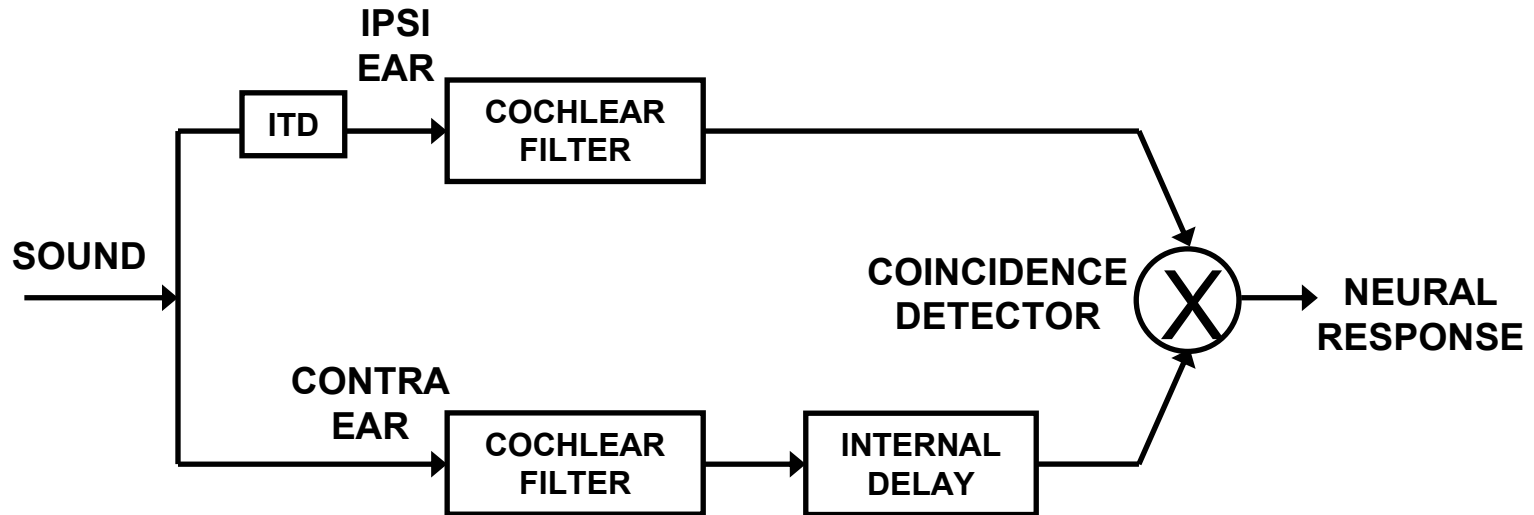
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Please see: Smith, P. H. "Structural and functional differences distinguish principal from nonprincipal cells in the guinea pig MSO slice." *J Neurophysiol* 73, no. 4 (Apr 1995): 1653-67.

MSO neurons create sensitivity to ITD via binaural coincidence detection

- MSO neurons best respond to a particular ITD for tone stimuli. For pure tones, introducing an ITD results in an interaural phase difference (IPD).
- MSO neurons phase lock for both monaural and binaural stimulation. The best IPD corresponds approximately to the difference in response phases for monaural stimulation of the ipsilateral and contralateral ears. This result shows that **MSO neurons act as binaural coincidence detectors**.
- At the least favorable IPD, the binaural response is smaller than responses to monaural stimulation of either ear. This is consistent with, but not necessarily evidence for, inhibitory binaural interactions.

Figure removed due to copyright reasons.
Please see: Yin, T. C. T., and J. C. K. Chan.
“Interaural time sensitivity in medial superior olive of cat.” *J Neurophysiol* 64 (1990): 465-488.

Crosscorrelation (coincidence) mechanism for ITD tuning in MSO



- Jeffress model (1948):
- Coincidence detector neuron best responds when external ITD matches internal delay.
- Array of coincidence detectors having different internal delays provides a place code for ITD.

Evidence for inhibition in MSO responses

- The coincidence detection model of MSO neurons does not account for all aspects of the responses: When the ILD of a binaural tone stimulus is varied at a constant ITD, responses of some MSO neurons vary non-monotonically.
- Since the excitatory inputs to the MSO (AVCN spherical bushy cells) have largely monotonic responses, the nonmonotonicities in MSO responses suggest an effect of inhibitory inputs, which are known to exist anatomically.
- The function of inhibitory inputs to the MSO in binaural processing is an active area of research.

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Please see: Yin, T. C. T., and J. C. K. Chan.
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ITD map in MSO?

- There is some evidence for a map of best ITD running along the long (anterior to posterior) axis of MSO, consistent with the Jeffress model. The most contralateral ITDs tend to be represented posteriorly, and the most medial ITDs anteriorly.
- Only ITDs favoring the contralateral ear are represented in each MSO. Both MSOs are necessary to represent the entire physiological range of ITDs.
- The ITD map runs orthogonal to the tonotopic map, where low frequencies are represented dorsally, and high frequencies ventrally.
- The excitatory inputs from both AVCNs run orthogonal to both the frequency map and the ITD map.

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Please see: Yin, T. C. T., and J. C. K. Chan. "Interaural time sensitivity in medial superior olive of cat." *J Neurophysiol* 64 (1990): 465-488.

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Please see: Yin, T. C. T., P. X. Joris, P. H. Smith, and J. C. K. Chan. "Neuronal processing for coding interaural time disparities." In *Binaural and Spatial Hearing*. Edited by R. H. Gilkey, and T. R. Anderson. Mahwah, NJ: Erlbaum, 1997.

Diversity in SOC nuclei among mammals

The relative sizes and layout of the three principal SOC nuclei and periolivary nuclei varies a great deal among mammals. In general, larger mammals with good low-frequency hearing such as humans have a large MSO, but small LSO and MNTB. Small mammals with good high-frequency hearing such as mice and bats show the opposite pattern. Cats are well balanced in that they have good hearing over a wide frequency range and show well-developed LSO and MSO.

Figure removed due to copyright reasons.
Please see: Schwartz, I. R. "The superior olivary complex and lateral emniscal nuclei."
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Sound localization performance correlates with SOC anatomy

The performance of 4 mammalian species in discriminating two sound sources placed symmetrically with respect to the midline is shown as a function of pure-tone frequency. Cats, tree shrews and rats have good lateralization performance at both low and high frequencies, while the hedgehog has poor performance at low frequencies. Unlike the other 3 species, the hedgehog lacks an MSO. These results support the idea that MSO plays an essential role in localizing low-frequency stimuli.

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Please see: Masterton, B., G. C. Thompson, J. K. Bechtold, and M. J. RoBards.
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Barn owls excel at sound localization

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Barn owls can detect a 1-msec ITD and catch mice in complete darkness. Their external ears are highly asymmetric, allowing them to utilize ILD for localizing in the median vertical plane. Their localization along the horizontal plane is largely based on ITD even for frequencies as high as 8 kHz.

Two separate auditory pathways in the barn owl

The barn owl's auditory system processes ITD and ILD in separate parallel pathways. Each auditory-nerve fiber (nVIII) divides into two branches, one innervating cochlear nucleus angularis (NA) and the other cochlear nucleus magnocellularis (NM). These two nuclei are the starting points of the two pathways as indicated by blue and yellow boxes and arrows. Nucleus laminaris (NL), which receives inputs from both NMs is the first site for processing ITD. NL projects contralaterally to one of the lemniscal nuclei (VLVa) and the core of the central nucleus of the inferior colliculus (ICc). The core projects to the lateral shell (LS) on the contralateral side where the two pathways meet as shown by green. Both pathways and different frequency bands converge in the external nucleus of the inferior colliculus (ICx). This area contains a map of auditory space which is composed of neurons selective to combinations of ITD and ILD. This map projects to the optic tectum (OT) to form a bimodal map of space. The inferior colliculus projects to nucleus ovoidalis (OV) in the thalamus which in turn projects to Field L in the forebrain.

Figure removed due to copyright reasons. Please see: Konishi, M. "Study of sound localization by owls and its relevance to humans." *Comp. Biochem. Physiol. Part A* 126 (2000): 459-469.

Barn owls are specialized for phase locking at high frequencies

- Barn owl auditory-nerve fibers show a much higher upper frequency limit of phase locking (as measured by the vector strength) than any other species of birds or mammals.
- High-frequency phase locking in the barn owl resembles that in the electrically-stimulated auditory nerve of the cat, a condition which bypasses lowpass filtering by the inner hair-cell synapses.

Figure removed due to copyright reasons.
Please see: Köppl, C. "Phase locking to high frequencies in the auditory nerve and nucleus magnocellularis of the barn owl." *J. Neurosci.* 17 (1997): 3312-3321.

Nucleus laminaris receives excitatory and inhibitory inputs from both sides

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Please see: Grothe, B. “New roles for synaptic inhibition in sound localization.”
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Axonal delay lines in Nucleus Laminaris

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Please see: Carr, C. E., and M. Konishi.
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- In the barn owl, afferent inputs from the two NMs interdigitate within Nucleus Laminaris (NL): Inputs from ipsilateral NM run dorso-ventrally, while inputs from contralateral NM run ventro-dorsally. This arrangement resembles the Jeffress model.
- Intra axonal recordings from NM fibers inside NL show a systematic variation of response phase along the dorso-ventral dimension, providing evidence for neural delay lines.
- NL neurons act as coincidence detectors much like mammalian MSO cells (not shown).

Spaced-tuned neurons in the barn-owl auditory midbrain

- Neurons in the barn owl's external nucleus of the inferior colliculus (ICx) are tuned to a specific azimuth and elevation. Unlike neurons in the central nucleus (ICc), they have broad frequency tuning.
- Azimuth tuning of ICx neurons depends primarily on ITD, whereas elevation tuning depends primarily on ILD (not shown).

Figure removed due to copyright reasons.
Please see: Knudsen, E. I., and M. Konishi. "A neural map for auditory space in the owl." *Science* 200 (1978): 795-797.

The barn owl's IC contains a map of auditory space

- The barn owl's ICx (the region which contains space-tuned neurons) forms a neural map of acoustic space. Contralateral azimuths are represented caudally within ICx, and medial azimuths rostrally (C). Low elevations are represented ventrally, and high elevations dorsally.
- There are also maps of auditory space in both mammalian and avian superior colliculi. On the other hand, no convincing space map has been found in the mammalian IC.

Figure removed due to copyright reasons.
Please see: Knudsen, E. I., and M. Konishi. "A neural map for auditory space in the owl." *Science* 200 (1978): 795-797.

Separate pathways process ITD and ILD in the barn owl brainstem

- Cochlear *nucleus magnocellularis* (NM) contains almost entirely neurons resembling mammalian bushy cells, while *nucleus angularis* (NA) contains stellate neurons.
- Top: The local anesthetic lidocaine (which blocks spike conduction) was injected into NM. This greatly altered ITD tuning of neurons in the space-mapped region of ICx, but had relatively little effect on ILD tuning.
- Bottom: Injection of lidocaine into NA had the opposite effect, altering ILD tuning much more than ITD tuning.

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Please see: Takahashi, T., A. Moiseff, and M. Konishi. "Time and intensity cues are processed independently in the auditory system of the owl." *J. Neurosci.* 4 (1984): 1781-1786.

Specializations for sound localization in the barn owl

- Barn owls show specializations for sound localization that distinguish them from mammals and other birds:
 - Asymmetric arrangement of the external ears allows ILD to code elevation
 - Neural phase locking at high frequencies
 - Separate pathways for ITD and ILD processing
 - Orderly arrangement of axonal delay lines as in the Jeffress model
 - Spaced-tuned neurons with broad frequency selectivity
 - Neural map of auditory space in the IC
- In other respects, ITD processing in the barn owl resembles that in mammals in that the basic circuit involves neural delay lines and coincidence detectors to perform an interaural crosscorrelation in each frequency band.

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