

What's a cerebellar circuit doing in the auditory system?

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The shapes of the head and ears of mammals are asymmetrical top-to-bottom and front-to-back. Reflections of sounds from these structures differ with the angle of incidence, producing cues for monaural sound localization in the spectra of the stimuli at the eardrum. Neurons in the dorsal cochlear nucleus (DCN) respond specifically to spectral cues and integrate them with somatosensory, vestibular and higher-level auditory information through parallel fiber inputs in a cerebellum-like circuit. Synapses between parallel fibers and their targets show long-term potentiation (LTP) and long-term depression (LTD), whereas those between auditory nerve fibers and their targets do not. This paper discusses the integration of acoustic and the proprioceptive information in terms of possible computational roles for the DCN.

Hearing enables vertebrate animals to know what goes on around them even when they cannot see. Localizing the position of sound sources is thus an important biological function of the auditory system. Interaural time and intensity differences are used by reptiles, birds and mammals for localizing sounds in the horizontal plane [1]. However, these cues are not useful for localizing sounds in the vertical plane (i.e. low–high, front–back) or when hearing is lost in one ear. For vertical localization, mammals use spectral cues – modifications in the spectra that are produced by the interactions of sound with the external ear, or pinna. These modifications vary as a function of the direction from which sound emanates, so that the frequency content of the sound reaching the eardrum provides a cue for source location [2–4] (Box 1). In the cat, the dorsal cochlear nucleus (DCN) has been shown to be important for behavioral processing of spectral localization cues [5,6]. The cells whose axons convey signals from the DCN to the inferior colliculus provide a specific representation of these acoustic cues and integrate them with somatosensory information about the position or movement of the ears.

The DCN has a laminar, cerebellum-like organization

The output axons of the DCN originate from fusiform and giant cells (Figure 1). These cells integrate activity from two systems of inputs, auditory nerve fibers and parallel fibers. Auditory nerve fibers bring acoustic information

from the cochlea to smooth dendrites in the deep layer of the DCN [7]. Parallel fibers, the unmyelinated axons of granule cells, contact spines on dendrites of fusiform, giant and cartwheel cells in the superficial layer of the DCN [8]. Granule cells convey information they receive from widespread areas of the brain that are associated with multiple sensory modalities. Inputs to the granule cell area arise from the dorsal column nuclei [9], vestibular afferents [10], pontine nuclei [11], unmyelinated auditory nerve fibers [12], the octopus cell area of the ventral cochlear nucleus (VCN) [13], the inferior colliculus [14] and the auditory cortex [15].

The superficial layers of the DCN share many features with the overlying cerebellum (Figure 1); most importantly, both structures contain granule cells and associated interneurons. Cochlear nuclear and cerebellar granule cells develop from a common population of neurons [16]. Granule cells lie in clusters around the VCN and in the fusiform cell layer of the DCN [8]. Like the vestibulocerebellum, the DCN contains unipolar brush cells [17], Golgi cells [18] and superficial stellate cells [19].

Cartwheel cells are interneurons that occupy a similar position in the DCN circuit to that occupied by Purkinje cells in the cerebellum [20]. The two cells contain many of the same proteins and are similarly affected by genetic mutations [21], and both fire complex action potentials [19,22]. Unlike Purkinje cells, cartwheel cells terminate locally, contacting other cartwheel, fusiform and giant cells, and receive no input like that from climbing fibers. Although cartwheel cells contain GABA and glutamic acid decarboxylase, they are glycinergic [23].

Largely because of their granule cell systems, the DCN and the octavolateral nuclei in weakly electric fish are considered to be 'cerebellum-like' nuclei [24,25]. Like fusiform and giant cells of the DCN, the principal cells of these nuclei receive granule cell inputs on one set of dendrites and primary sensory inputs on another.

Synapses in the superficial DCN are adjustable

The strength of synapses between parallel fibers and their targets in the DCN, but not that of synapses between auditory nerve fibers and their targets, is modulated by activity (Figure 2) [26]. In fusiform and cartwheel cells, pairing of postsynaptic depolarization with stimulation of the parallel fibers in the molecular layer at high frequency (100 Hz) increases the amplitude of the synaptic current. After the high-frequency shocks, short-term potentiation

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Box 1. Spectral cues for localizing sound

When sound impinges on the external ear, it reflects off the irregular surfaces of the pinna. The reflections produce acoustic resonances in the cavities of the pinna and interference patterns at the entrance of the external ear canal [4]. These resonances and interference patterns differ as a function of the direction of the sound source. By placing a microphone near the eardrum of a cat, the spectra of sounds in the ear are compared with the spectra of the same sounds measured at the same place in the absence of the cat [2,61]. The ratio of the two spectra, the head-related transfer function, is shown in Figure 1 for sound originating at four elevations directly in front of the cat, as indicated by the different colors. The series of peaks and valleys at frequencies > 5 kHz varies strongly with the direction of the sound source. For reference, the green curve (for 0° elevation) is repeated at the other three elevations. Note in particular the notch at frequencies between 8 and 15 kHz; this notch is a particularly strong cue for sound localization in cats [62]. It moves from low to high frequencies as the sound source moves upward in elevation, from blue to red in Figure 1. It also moves consistently as the sound source moves away from the midline in azimuth (not shown).

The acoustic effects of the external ear depend on the size of the ear (see Ref. [63] for an interesting analysis of this point). Resonances and interference effects occur when the dimensions of cavities and distances between reflective surfaces are larger than one-quarter of the wavelength of sounds. In the cat ear, this places these effects at frequencies > 7 kHz; in the larger human ear, they are most prominent at frequencies > 3 kHz.

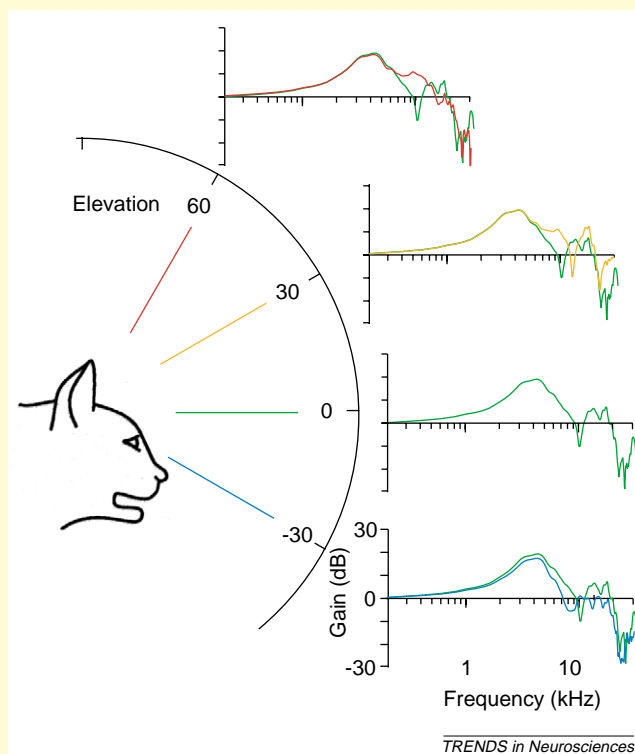


Figure 1. Head-related transfer functions for sounds at four elevations in the vertical plane. Transfer functions show gain – the dB ratio of the sound at the eardrum to the free field sound – as a function of frequency. Sound source directions, with respect to the head of the cat, are shown by the colored lines.

decreases over several minutes, leaving long-term potentiation (LTP). Stimulation at low frequency (1 Hz) produces long-term depression (LTD) of the synaptic current in both fusiform and cartwheel cells. Stimulation of auditory nerve fibers in the deep layer evokes synaptic

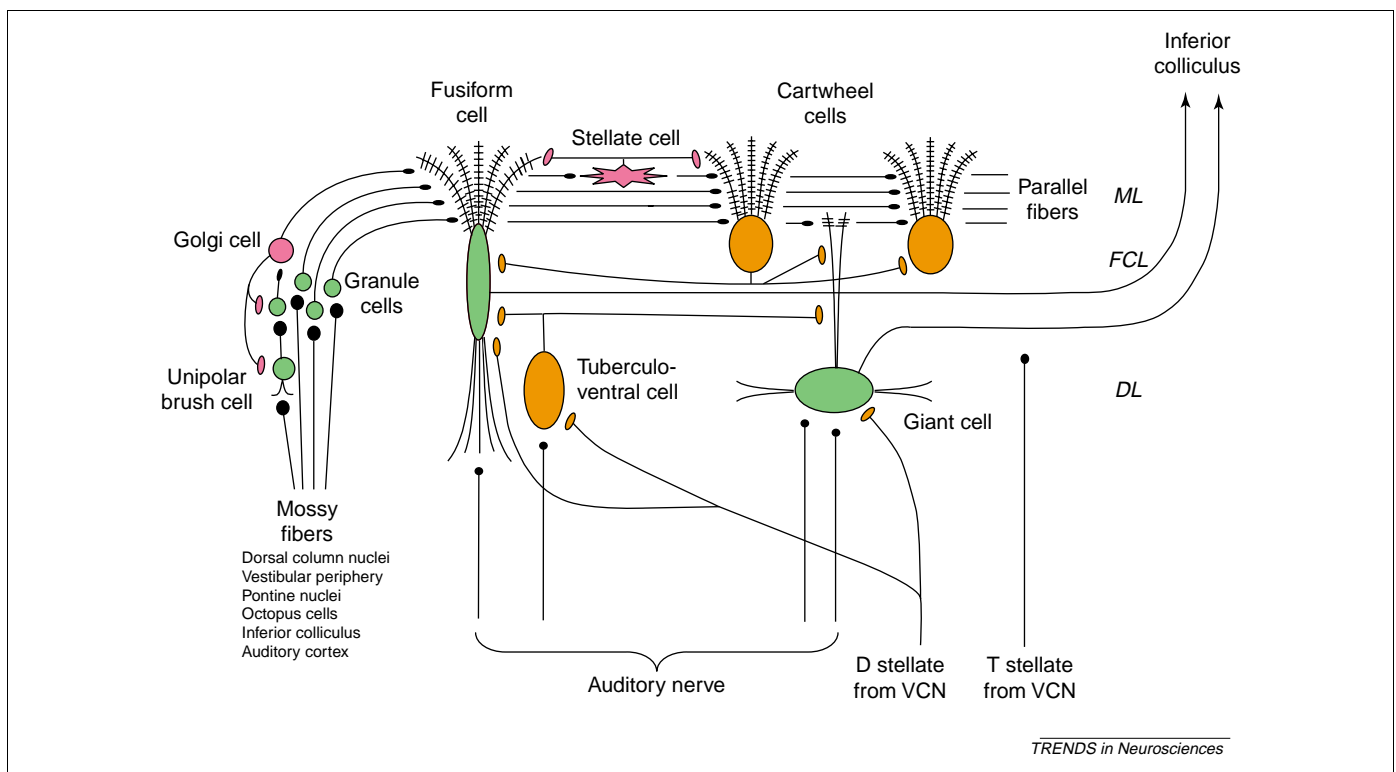
responses in fusiform cells but those synaptic responses show no plasticity.

Postsynaptic intracellular buffering of Ca^{2+} prevents LTP and LTD in fusiform and cartwheel cells, indicating that plasticity is initiated postsynaptically and involves changes in intracellular Ca^{2+} levels. Postsynaptic changes in intracellular Ca^{2+} concentration following parallel fiber stimulation are initiated by activation of neurotransmitter receptors and are mediated through signaling pathways that differ in fusiform and cartwheel cells (Table 1) [26]. Although AMPA receptors are activated by parallel fibers [27], these receptors contain GluR2 subunits on cartwheel dendrites and apical dendrites of fusiform cells [28] and therefore are not permeable to Ca^{2+} . AMPA receptors can, however, mediate the entry of Ca^{2+} through voltage-sensitive Ca^{2+} channels in fusiform and cartwheel cells [23,29]. NMDA receptors are also activated by parallel fiber stimulation [27]. Blocking these receptors with 2-amino-5-phosphono valerate (APV) prevents the induction of LTD in cartwheel cells but only reduces LTP in cartwheel cells and LTP and LTD in fusiform cells. Metabotropic G-protein-coupled glutamate receptors (mglu receptors) contribute to synaptic transmission in fusiform and cartwheel cells; Group 3 mglu receptors act presynaptically and Group 1 mglu receptors act postsynaptically and, in cartwheel cells, also presynaptically [26,30–32]. Although most of the synaptic current evoked by stimulating the molecular layer in fusiform and cartwheel cells can be blocked by antagonists of AMPA, NMDA and mglu receptors, a small current that is evoked by trains of shocks is insensitive to these blockers, indicating that additional, unidentified receptors contribute to synaptic transmission from parallel fibers [26].

Plasticity in fusiform and cartwheel cells requires the release of Ca^{2+} from intracellular stores [26]. Two families of ion channels, inositol trisphosphate [$\text{Ins}(1,4,5)\text{P}_3$] receptors and ryanodine receptors, regulate release of Ca^{2+} from intracellular stores. Both are sensitive to Ca^{2+} and mediate Ca^{2+} -induced Ca^{2+} release (CICR) but their distribution differs in fusiform and cartwheel cells (Table 1). The activation of these receptors has been shown in other cells to affect LTP and LTD differentially and to regulate the spatial distribution of plasticity [33,34]. LTP and LTD were blocked in fusiform and cartwheel cells when CICR was prevented [26]. Because intracellular ryanodine reduced plasticity, both fusiform and cartwheel cells contain ryanodine receptors. By contrast, $\text{Ins}(1,4,5)\text{P}_3$ receptors have been detected immunohistochemically in the dendrites of cartwheel, but not fusiform, cells [35] (Table 1). Vesicles have been observed in spines of cartwheel cells [36], indicating that regulation of release from intracellular stores could be at the level of individual dendritic spines.

DCN neurons convey information related to sound localization

The responses to sound of the fusiform and giant cells reflect the summation of multiple excitatory and inhibitory inputs (the two cell types cannot always be clearly distinguished and will be considered together) [37]. Responses to sound arise mainly through the deep layer; cartwheel cells, and by inference granule cells, respond



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Figure 1. Superficial layers of the dorsal cochlear nucleus (DCN) form a cerebellum-like structure. Granule cells lie in clusters around the ventral cochlear nucleus (VCN), as well as in the fusiform cell layer (FCL). As in the cerebellum, granule cells are excited through mossy terminals from unipolar brush cells and from other regions of the brain. Sources of terminals in the granule cell region are listed at lower left; not all of these have been shown to terminate as mossy fibers. The axons of granule cells (parallel fibers) contact spiny dendrites of cartwheel cells in the molecular layer (ML). They also contact other inhibitory interneurons, superficial stellate cells and Golgi cells. Cartwheel cell axons contact fusiform cells, which are themselves contacted by parallel fibers on spiny apical dendrites, and giant cells, which receive little or no parallel fiber input. Auditory nerve fibers innervate the deep layer (DL), contacting the smooth basal dendrites of fusiform and giant cells, as well as tuberculoventral neurons. Two groups of cells from the VCN, D- and T-stellate cells, provide auditory inputs to the deep layer. The targets of T-stellate cell axons in the DCN are not known. Fusiform and giant cells, the principal cells of the DCN, project to the inferior colliculus. Glutamatergic neurons are shown in green and their terminals in black, glycinergic neurons and their terminals are shown in orange, and GABAergic neurons are shown in pink.

weakly to sound and do not seem to affect the acoustic responses in DCN [38,39]. Responses to broadband sound stimuli are most easily understood by considering groups of cells as tonotopic arrays, as shown schematically in Figure 3. Each fusiform or giant cell is excited by a small group of auditory nerve fibers, and perhaps also by collaterals of T-stellate neurons from the VCN. These convey their sharp tuning so that the population of fusiform and giant cells also forms a tuned and tonotopically-organized array. The responses of fusiform and/or giant

cells are further shaped by inhibition from tuberculoventral cells of the deep layer of the DCN and D-stellate cells of the VCN. Tuberculoventral cells are also excited by a small number of auditory nerve fibers that make them sensitive to narrowband stimuli [40,41] and they inhibit fusiform and/or giant cells with similar tuning [42]. As a consequence of the strong inhibition from tuberculoventral cells, narrowband stimuli, such as tones that have a concentration of energy at one frequency, prevent firing in fusiform and giant cells, except when the sounds are very

Table 1. Excitatory synapses that feed into cartwheel and fusiform cells differ^a

Feature	Parallel fiber to cartwheel dendrite	Parallel fiber to fusiform apical dendrite	Auditory nerve to fusiform basal dendrite	Refs
Plasticity	LTP, LTD	LTP, LTD	No LTP, no LTD	[26]
AMPA receptors	Subunits GluR1, GluR2, GluR3	GluR2, GluR3	GluR2, GluR3, GluR4	[28,65–67]
NMDA receptors	Subunits NR1	NR1, NR2	NR1, NR2	[65–67]
mglu receptors	Effects of blocker (APV) ↓ LTP, no LTD, ↓ EPSC	↓ LTP, ↓ LTD, ↓ EPSC	↓ EPSC	[26,68]
	Receptor Postsynaptic Group 1 (mglu1 α)	Group 1	Group 1 (mglu1 α)	[26,31,32,65,66]
	Presynaptic Groups 1 and 3	Group 3		[26,32,65,66]
	Effects of blocker of Group 1, 2 and 3 mglu receptors (Ly341495) ↓ LTP, ↓ LTD	↓ LTP, ↓ LTD		[26]
Ca ²⁺ -induced Ca ²⁺ release	Receptor IP ₃ R, RyR	RyR		[26,35]
	Effects of blockers (caffeine and thapsigargin) No LTP, no LTD	No LTP, no LTD		[26]

^aAbbreviations: APV, 2-amino-5-phosphonovalerate; EPSC, excitatory postsynaptic current; GluR, ionotropic AMPA-subtype glutamate receptor subunit; IP₃R, inositol (1,4,5)-trisphosphate receptor; LTD, long-term depression; LTP, long-term potentiation; mglu receptor, metabotropic glutamate receptor; NR, NMDA-subtype glutamate receptor subunit; RyR, ryanodine receptor; ↓, decreased.

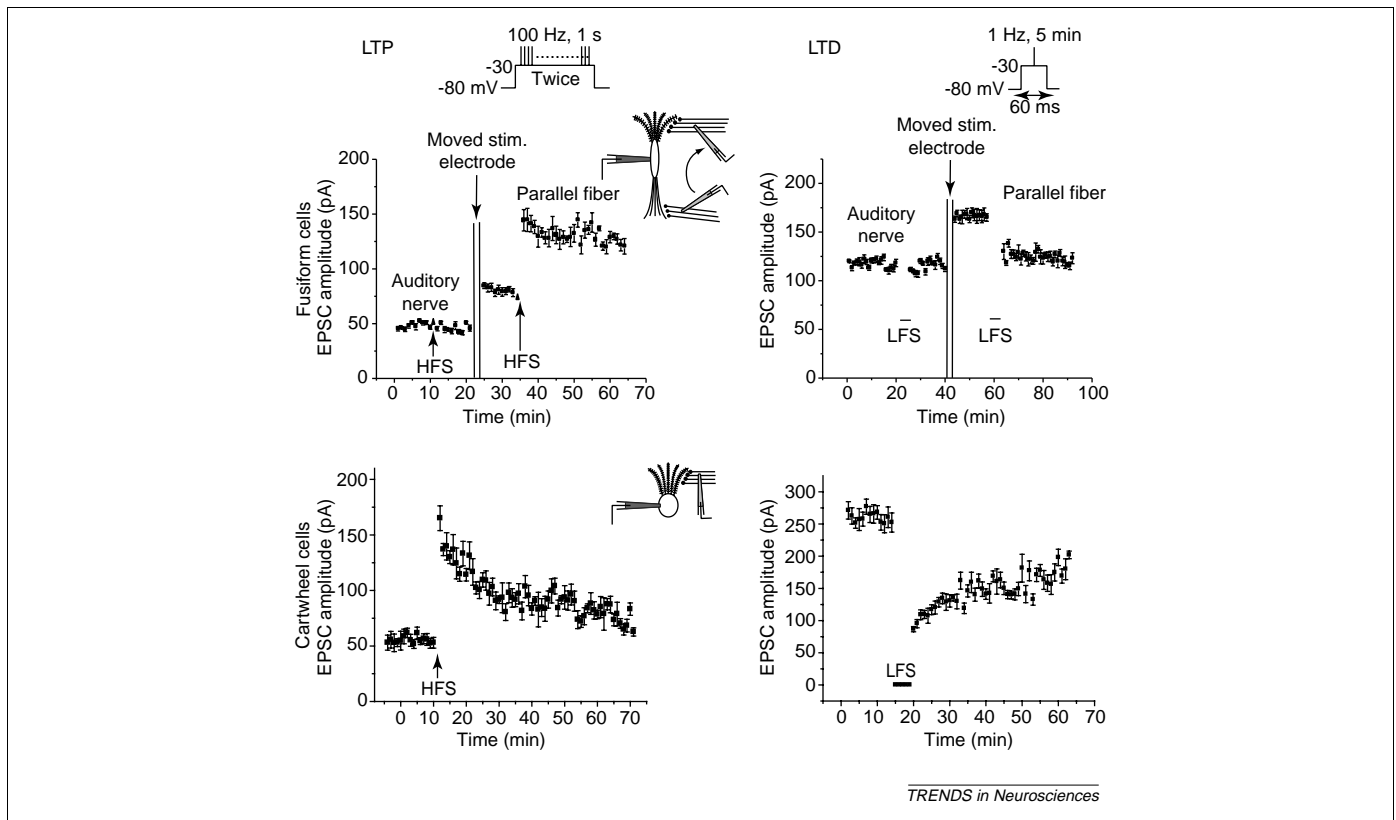


Figure 2. Long-term potentiation (LTP) and long-term depression (LTD) can be evoked at parallel fiber synapses but not at auditory nerve synapses. Excitatory postsynaptic currents (EPSCs) were recorded under voltage-clamp from the cell bodies of fusiform cells (top) or cartwheel cells (bottom). The recording arrangements are shown in the insets. Each plot shows EPSC amplitudes monitored at 0.1 Hz in a single cell. At the points marked HFS, a train of high-frequency shocks at 100 Hz for 1 s was applied twice while the cell was depolarized to -30 mV. At the points marked LFS, fibers were stimulated at low frequency (1 Hz for 5 min), also while the cell was depolarized. Upper panels: stimulating auditory nerve fiber inputs to fusiform cells with HFS or LFS resulted in no short-term or long-term changes in EPSCs. When the stimulating electrodes were moved to the molecular layer to stimulate parallel fiber inputs to the same cell, however, the amplitude of EPSCs was altered for a period of hours. HFS evoked LTP and LFS evoked LTD. Lower panels: similar experiments in cartwheel cells that receive only parallel fiber inputs reveal that HFS and LFS evoke LTP and LTD, respectively. We thank K. Fujino for contributing previously unpublished data in the lower panels of this figure. Upper panels are reproduced, with permission, from Ref. [26] © (2003) National Academy of Sciences, USA.

soft. The inhibition from tuberculoventral cells is itself shut down by inhibition from D-stellate cells in the presence of broadband sounds such as noise or cafeteria babble that have energy widely spread across frequency. D-stellate cells receive input from auditory nerve fibers that are tuned to a wide range of frequencies, making them sensitive to broadband sounds [43,44]; they strongly inhibit tuberculoventral cells [45]. Under such conditions, fusiform and/or giant cells are excited by their auditory nerve fiber inputs without also being inhibited. Fusiform and giant cells thus generally respond to broadband, but not to narrowband, stimuli. In the presence of spectral notches, when tuberculoventral cells tuned to notch frequencies are not excited, weak inhibition reveals a direct connection between D-stellate and fusiform and/or giant cells [46]. The confluence of these two inhibitory circuits on fusiform and giant cells thus allows the principal cells to detect sounds with peaks in their spectra and sounds with notches in their spectra, both through inhibition.

Spectral notches are important sources of acoustic information about the location of sounds (Box 1). In contrast with most neurons in the VCN, which sum linearly the acoustic energy that they detect near their best frequencies, the fusiform and giant cells of the DCN sum acoustic energy non-linearly and thus behave as feature

detectors [47]. The representation of spectral notches is qualitatively similar in VCN and DCN outputs. In both there is a dip in response rate when the notch is centered at the frequency to which the neuron is most sensitive [47]. The representations differ in that responses of fusiform cells are driven below the spontaneous firing rate by inhibition and in that, like their targets in the inferior colliculus [48], they have a specific response to the upper-frequency edge of the notch (L.A.J. Reiss and E.D. Young, unpublished) that is implicated in spectral sound localization [49]. Behavioral studies of animals in which output from the DCN to the inferior colliculus was severed support the conclusion that the DCN is required for orienting to sounds [5,6]. The DCN is not necessary for discriminating sounds from two different locations [50], which is not surprising because spectral cues for sound localization are contained in both DCN and VCN output neurons.

The superficial layers of the DCN provide fusiform and giant cells with multimodal inputs that are relevant to sound localization. As expected from what is known about the circuitry, somatosensory stimuli excite fusiform cells directly through the parallel fibers and inhibit them through cartwheel cells (Figures 1 and 3) [51]. In cats, stretching of the muscles attached to the pinna provide the strongest somatosensory stimuli to DCN neurons,

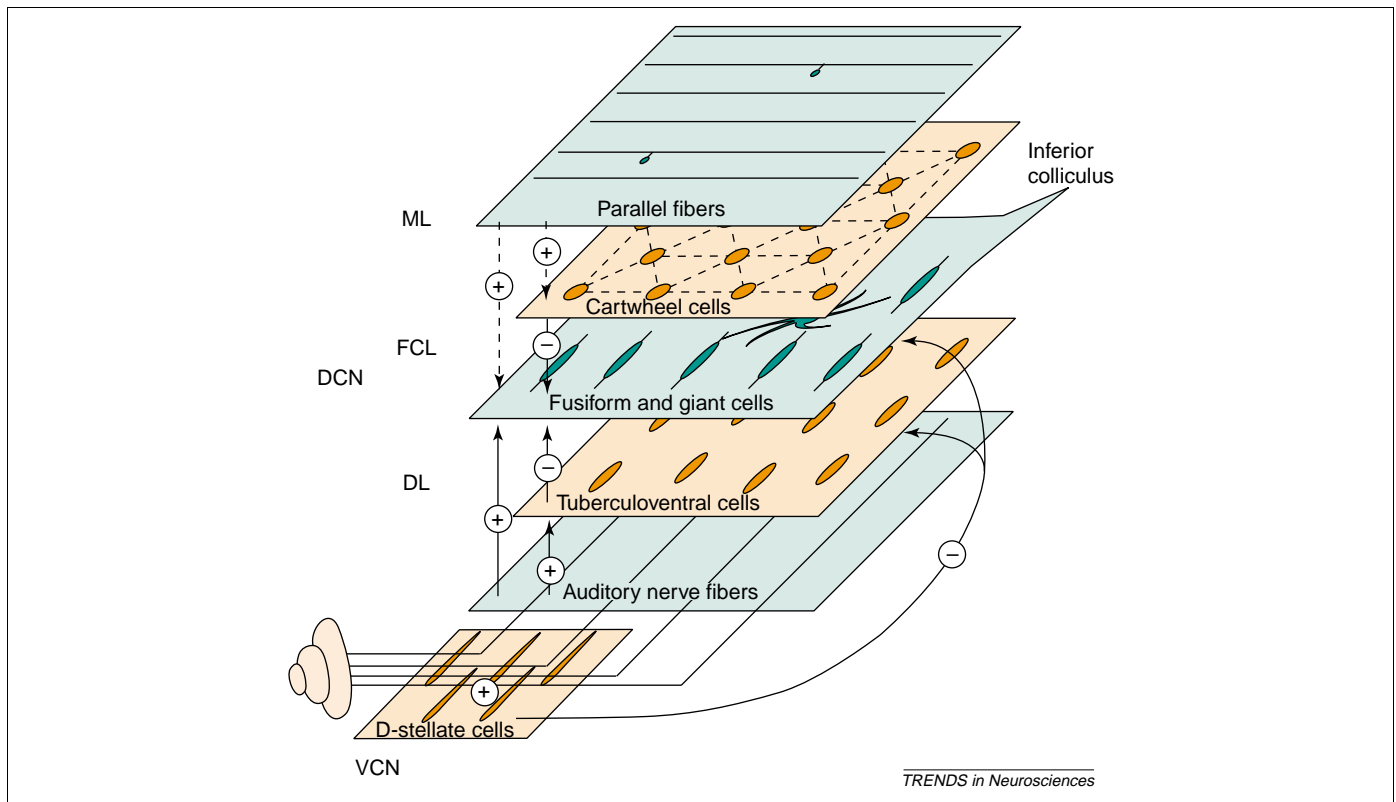


Figure 3. The neuronal circuits of the dorsal cochlear nucleus (DCN) can be considered as interacting arrays with orthogonal systems of inputs. Parallel fibers, the axons of granule cells, course dorsoventrally (from left to right in the figure) in the molecular layer (ML), exciting cartwheel cells and the apical dendrites of fusiform cells. The cartwheel cells form a network that is interconnected by weak excitation and inhibition and that inhibits the fusiform and giant cells in the fusiform cell layer (FCL) [23,64]. Auditory nerve fibers course caudorostrally in the deep layer (DL), exciting the basal dendrites of fusiform cells, giant cells and tuberculoventral cells. Fibers that encode low frequencies innervate ventral regions and those that encode high frequencies innervate dorsal regions, giving the DCN a tonotopic organization (from left to right in the figure). The deep layer also receives inhibition from D-stellate cells of the ventral cochlear nucleus (VCN) [45,46]. Glutamatergic, excitatory arrays are indicated in green and glycinergic arrays are indicated in orange; plastic synaptic connections are shown as dashed lines and stable connections as solid lines.

producing responses in DCN as large as those produced by sound stimuli [52]. Stimulation of the skin and hair on and near the pinna, by contrast, are ineffective as is stimulation of other parts of the body. Such stimulation produces evoked potentials in DCN but does not by itself activate DCN cells. Thus, the DCN shares a general characteristic of cerebellum-like nuclei: information from many sources is present in the parallel fibers, much of which is not effective in activating output cells. The information carried by vestibular and other inputs is not known, but it presumably provides information about the position and movements of the head.

A cerebellum-like function for the DCN?

A general feature of the cerebellum and cerebellar-like circuits associated with the eighth cranial nerve is that information conveyed by parallel fibers is used to achieve some aspect of sensorimotor coordination [53]. Often, this involves predicting the consequences of sensory events. Examples of cerebellar computations include correcting the gain of the vestibulo-ocular reflex [54] and producing an eyeblink reflex to avoid an unconditioned stimulus [55]. Essential to these calculations is adjusting the gain of the synapses made by parallel fibers on Purkinje cells, to select the appropriate signals from the mixture of inputs carried by the parallel fibers.

In the electrosensory lateral-line lobe of weakly electric fish, information carried in parallel fibers is used to predict

and cancel self-generated electric fields [56]. In that system, parallel fibers carry information about motor commands in addition to proprioceptive and descending electrosensory signals, which reach the apical dendrites of principal cells and inhibitory interneurons in a circuit similar to that described in Figure 1. The basal dendrites of principal cells receive sensory information from the electroreceptors. The electroreceptors are driven by large electric fields produced by the swimming and respiratory movements of the animal. By adjusting the gain of parallel fiber synapses, the responses to self-generated fields are cancelled in the principal cells, so that only electrical signals from external sources, which are not predictable from the parallel fiber activity, are transmitted.

In the electric fish, the cancellation occurs by creation of a 'negative image' of the excitation applied to the cell by the electroreceptor axons [57]. As currently understood, the negative image is constructed by decreasing the gain of parallel fiber synapses that are active immediately before invasion of the dendritic tree by a postsynaptic spike [58], an anti-Hebbian mechanism that decreases the excitatory input to the cell at a time when parallel fiber inputs predict an electrosensory event. A potentiation of parallel fiber synapses occurs when the synapses are active in the absence of postsynaptic activity; this balances the depression and provides the background of excitatory input needed by the anti-Hebbian mechanism. Computer simulations show that this learning rule accounts for much of

the plasticity observed in the electrosensory nucleus [59]. LTD and LTP in the DCN could reflect the same sort of spike-timing-dependent plasticity, but that remains to be demonstrated.

Unlike the cerebellum, cerebellar-like structures lack climbing fiber inputs. Climbing fiber spikes enable plasticity in the cerebellum. In the electrosensory system, the plasticity seems to be continuous, in that the system constantly constructs negative images of any ongoing electroreceptor activity that is correlated with parallel fiber activity.

How could a similar computation be useful in the DCN? This review summarizes evidence in support of the hypothesis that the DCN corrects spectral cues for the position of the head and pinnae. The hypothesis is not easy to test, however, because the DCN represents spectral cues tonotopically and not in terms of space, so it is not clear how such a correction would occur. It is possible that the granule cell system could modulate the sensitivity of DCN cells across the tonotopic array to optimize the use of spectral cues as the pinna moves or in response to variations in the signal-to-noise ratio in different frequency bands. However, such a calculation does not fit the current rubric of plasticity in cerebellar-like nuclei.

Several alternative hypotheses parallel more closely what is known from electric fish. One is that the DCN cancels neural activity associated with self-generated noise. Noise is produced when an animal moves or, especially, when the pinna moves. The noise could be predicted by inputs from motor nuclei and from vestibular and proprioceptive inputs. A second hypothesis that is more closely related to sound localization is suggested by the dramatic changes in external-ear transfer function that occur when the ears move [60]. While the pinna is moving, the sound at the eardrum from a fixed source in the environment is substantially amplitude-modulated by the changing direction of the ears. Somatosensory inputs could be important in smoothing or suppressing the responses to these modulations, which provide no useful information to the animal and could confuse sound localization. Both self-noise cancellation and movement suppression could be accomplished by autonomous mechanisms similar to those hypothesized for the electrosensory system.

The evidence surveyed here shows that the mammalian DCN has much in common with the cerebellum-like nuclei in the fish electrosensory system. Most important of the shared characteristics are the convergence of auditory and non-auditory signals in fusiform and giant cells, and the demonstration of LTP and LTD in the parallel fiber synapses. Exactly how the DCN uses non-auditory information to improve auditory performance is, however, not yet clear.

References

- 1 Yin, T.C.T. (2002) Neural mechanisms of encoding binaural localization cues in the auditory brainstem. In *Integrative Functions in the Mammalian Auditory Pathway* (Oertel, D. et al., eds), pp. 99–159, Springer
- 2 Musicant, A.D. et al. (1990) Direction-dependent spectral properties of cat external ear: new data and cross-species comparisons. *J. Acoust. Soc. Am.* 87, 757–781
- 3 Middlebrooks, J.C. and Green, D.M. (1991) Sound localization by human listeners. *Annu. Rev. Psychol.* 42, 135–159
- 4 Blauert, J. (1996) *Spatial Hearing: The Psychophysics of Human Sound Localization*, MIT Press
- 5 May, B.J. (2000) Role of the dorsal cochlear nucleus in the sound localization behavior of cats. *Hear. Res.* 148, 74–87
- 6 Sutherland, D.P. et al. (1998) Role of acoustic striae in hearing: reflexive responses to elevated sound-sources. *Behav. Brain Res.* 97, 1–12
- 7 Osen, K.K. (1970) Course and termination of the primary afferents in the cochlear nuclei of the cat. *Arch. Ital. Biol.* 108, 21–51
- 8 Mugnaini, E. et al. (1980) Distribution and light microscopic features of granule cells in the cochlear nuclei of cat, rat, and mouse. *J. Comp. Neurol.* 191, 581–606
- 9 Weinberg, R.J. and Rustioni, A. (1987) A cuneocochlear pathway in the rat. *Neuroscience* 20, 209–219
- 10 Burian, M. and Gstoettner, W. (1988) Projection of primary vestibular afferent fibres to the cochlear nucleus in the guinea pig. *Neurosci. Lett.* 84, 13–17
- 11 Ohlrogge, M. et al. (2001) Projections of the pontine nuclei to the cochlear nucleus in rats. *J. Comp. Neurol.* 436, 290–303
- 12 Brown, M.C. et al. (1988) Central trajectories of type II spiral ganglion neurons. *J. Comp. Neurol.* 278, 581–590
- 13 Golding, N.L. et al. (1995) Recordings from slices indicate that octopus cells of the cochlear nucleus detect coincident firing of auditory nerve fibers with temporal precision. *J. Neurosci.* 15, 3138–3153
- 14 Caicedo, A. and Herbert, H. (1993) Topography of descending projections from the inferior colliculus to auditory brainstem nuclei in the rat. *J. Comp. Neurol.* 328, 377–392
- 15 Feliciano, M. et al. (1995) Direct projections from the rat primary auditory neocortex to nucleus sagulum, paralemniscal regions, superior olivary complex, and cochlear nuclei. *Aud. Neurosci.* 1, 287–308
- 16 Funschilling, U. and Reichardt, L.F. (2002) Cre-mediated recombination in rhombic lip derivatives. *Genesis* 33, 160–169
- 17 Mugnaini, E. et al. (1997) The unipolar brush cells of the mammalian cerebellum and cochlear nucleus: cytology and microcircuitry. *Prog. Brain Res.* 114, 131–150
- 18 Ferragamo, M. et al. (1998) Golgi cells in the superficial granule cell domain overlying the ventral cochlear nucleus: Morphology and electrophysiology in slices. *J. Comp. Neurol.* 400, 519–528
- 19 Zhang, S. and Oertel, D. (1993) Cartwheel and superficial stellate cells of the dorsal cochlear nucleus of mice: intracellular recordings in slices. *J. Neurophysiol.* 69, 1384–1397
- 20 Wouterlood, F.G. and Mugnaini, E. (1984) Cartwheel neurons of the dorsal cochlear nucleus: a Golgi-electron microscopic study in rat. *J. Comp. Neurol.* 227, 136–157
- 21 Berrebi, A.S. and Mugnaini, E. (1988) Effects of the murine mutation 'nervous' on neurons in cerebellum and dorsal cochlear nucleus. *J. Neurocytol.* 17, 465–484
- 22 Manis, P.B. et al. (1994) Physiology and morphology of complex spiking neurons in the guinea pig dorsal cochlear nucleus. *J. Comp. Neurol.* 348, 261–276
- 23 Golding, N.L. and Oertel, D. (1997) Physiological identification of the targets of cartwheel cells in the dorsal cochlear nucleus. *J. Neurophysiol.* 78, 248–260
- 24 Montgomery, J.C. et al. (1995) Hindbrain sensory processing in lateral line, electrosensory, and auditory systems: a comparative overview of anatomical and functional similarities. *Aud. Neurosci.* 1, 207–231
- 25 Devor, A. (2000) Is the cerebellum like cerebellar-like structures? *Brain Res. Rev.* 34, 149–156
- 26 Fujino, K. and Oertel, D. (2003) Bidirectional synaptic plasticity in the cerebellum-like mammalian dorsal cochlear nucleus. *Proc. Natl. Acad. Sci. U. S. A.* 100, 265–270
- 27 Manis, P.B. and Molitor, S.C. (1996) *N*-methyl-D-aspartate receptors at parallel fiber synapses in the dorsal cochlear nucleus. *J. Neurophysiol.* 76, 1639–1656
- 28 Gardner, S.M. et al. (2001) Correlation of AMPA receptor subunit composition with synaptic input in the mammalian cochlear nuclei. *J. Neurosci.* 21, 7428–7437
- 29 Molitor, S.C. and Manis, P.B. (2003) Dendritic Ca²⁺ transients evoked by action potentials in rat dorsal cochlear nucleus pyramidal and cartwheel neurons. *J. Neurophysiol.* 89, 2225–2237

- 30 Petralia, R.S. *et al.* (1996) The metabotropic glutamate receptors, mGluR2 and mGluR3, show unique postsynaptic, presynaptic and glial localizations. *Neuroscience* 71, 949–976
- 31 Wright, D.D. *et al.* (1996) Immunocytochemical localization of the mGluR1 α metabotropic glutamate receptor in the dorsal cochlear nucleus. *J. Comp. Neurol.* 364, 729–745
- 32 Molitor, S.C. and Manis, P.B. (1997) Evidence for functional metabotropic glutamate receptors in the dorsal cochlear nucleus. *J. Neurophysiol.* 77, 1889–1905
- 33 Balschun, D. *et al.* (1999) Deletion of the ryanodine receptor type 3 (RyR3) impairs forms of synaptic plasticity and spatial learning. *EMBO J.* 18, 5264–5273
- 34 Nishiyama, M. *et al.* (2000) Calcium stores regulate the polarity and input specificity of synaptic modification. *Nature* 408, 584–588
- 35 Ryugo, D.K. *et al.* (1995) Inositol 1,4,5-trisphosphate receptors: immunocytochemical localization in the dorsal cochlear nucleus. *J. Comp. Neurol.* 358, 102–118
- 36 Mugnaini, E. (1985) GABA neurons in the superficial layers of the rat dorsal cochlear nucleus: light and electron microscopic immunocytochemistry. *J. Comp. Neurol.* 235, 61–81
- 37 Young, E.D. and Davis, K.A. (2002) Circuitry and function of the dorsal cochlear nucleus. In *Integrative Functions in the Mammalian Auditory Pathway* (Oertel, D. *et al.*, eds), pp. 160–206, Springer
- 38 Parham, K. and Kim, D.O. (1995) Spontaneous and sound-evoked discharge characteristics of complex-spiking neurons in the dorsal cochlear nucleus of the unanesthetized decerebrate cat. *J. Neurophysiol.* 73, 550–561
- 39 Parham, K. *et al.* (2000) Purkinje cell degeneration and control mice: responses of single units in the dorsal cochlear nucleus and the acoustic startle response. *Hear. Res.* 148, 137–152
- 40 Spirou, G.A. *et al.* (1999) Spectral integration by type II interneurons in dorsal cochlear nucleus. *J. Neurophysiol.* 82, 648–663
- 41 Rhode, W.S. (1999) Vertical cell responses to sound in cat dorsal cochlear nucleus. *J. Neurophysiol.* 82, 1019–1032
- 42 Voigt, H.F. and Young, E.D. (1990) Cross-correlation analysis of inhibitory interactions in dorsal cochlear nucleus. *J. Neurophysiol.* 64, 1590–1610
- 43 Winter, I.M. and Palmer, A.R. (1995) Level dependence of cochlear nucleus onset unit responses and facilitation by second tones or broadband noise. *J. Neurophysiol.* 73, 141–159
- 44 Palmer, A.R. *et al.* (1996) Responses of ventral cochlear nucleus onset and chopper units as a function of signal bandwidth. *J. Neurophysiol.* 75, 780–794
- 45 Zhang, S. and Oertel, D. (1993) Tuberculoventral cells of the dorsal cochlear nucleus of mice: intracellular recordings in slices. *J. Neurophysiol.* 69, 1409–1421
- 46 Nelken, I. and Young, E.D. (1994) Two separate inhibitory mechanisms shape the responses of dorsal cochlear nucleus type IV units to narrowband and wideband stimuli. *J. Neurophysiol.* 71, 2446–2462
- 47 Yu, J.J. and Young, E.D. (2000) Linear and nonlinear pathways of spectral information transmission in the cochlear nucleus. *Proc. Natl. Acad. Sci. U. S. A.* 97, 11780–11786
- 48 Davis, K.A. *et al.* (2003) Auditory processing of spectral cues for sound localization in the inferior colliculus. *J. Assoc. Res. Otolaryngol.* 4, 148–163
- 49 Middlebrooks, J.C. (1992) Narrow-band sound localization related to external ear acoustics. *J. Acoust. Soc. Am.* 92, 2607–2624
- 50 Sutherland, D.P. *et al.* (1998) Role of acoustic striae in hearing: discrimination of sound-source elevation. *Hear. Res.* 120, 86–108
- 51 Davis, K.A. *et al.* (1996) Effects of somatosensory and parallel-fiber stimulation on neurons in dorsal cochlear nucleus. *J. Neurophysiol.* 76, 3012–3024
- 52 Kanold, P.O. and Young, E.D. (2001) Proprioceptive information from the pinna provides somatosensory input to cat dorsal cochlear nucleus. *J. Neurosci.* 21, 7848–7858
- 53 Nixon, P.D. (2003) The role of the cerebellum in preparing responses to predictable sensory events. *Cerebellum* 2, 114–122
- 54 Lisberger, S.G. (1998) Physiologic basis for motor learning in the vestibulo-ocular reflex. *Otolaryngol. Head Neck Surg.* 119, 43–48
- 55 Ohyama, T. *et al.* (2003) What the cerebellum computes. *Trends Neurosci.* 26, 222–227
- 56 Bell, C. *et al.* (1997) The generation and subtraction of sensory expectations within cerebellum-like structures. *Brain Behav. Evol.* 50 (Suppl. 1), 17–31
- 57 Bell, C.C. *et al.* (1993) Storage of a sensory pattern by anti-Hebbian synaptic plasticity in an electric fish. *Proc. Natl. Acad. Sci. U. S. A.* 90, 4650–4654
- 58 Bell, C.C. *et al.* (1999) Synaptic plasticity in the mormyrid electro-sensory lobe. *J. Exp. Biol.* 202, 1339–1347
- 59 Roberts, P.D. and Bell, C.C. (2000) Computational consequences of temporally asymmetric learning rules: II. Sensory image cancellation. *J. Comput. Neurosci.* 9, 67–83
- 60 Young, E.D. *et al.* (1996) Effects of pinna position on head-related transfer functions in the cat. *J. Acoust. Soc. Am.* 99, 3064–3076
- 61 Rice, J.J. *et al.* (1992) Pinna-based spectral cues for sound localization in cat. *Hear. Res.* 58, 132–152
- 62 Huang, A.Y. and May, B.J. (1996) Sound orientation behavior in cats. II. Mid-frequency spectral cues for sound localization. *J. Acoust. Soc. Am.* 100, 1070–1080
- 63 Xu, L. and Middlebrooks, J.C. (2000) Individual differences in external-ear transfer functions of cats. *J. Acoust. Soc. Am.* 107, 1451–1459
- 64 Golding, N.L. and Oertel, D. (1996) Context-dependent synaptic action of glycinergic and GABAergic inputs in the dorsal cochlear nucleus. *J. Neurosci.* 16, 2208–2219
- 65 Petralia, R.S. *et al.* (1996) Ionotropic and metabotropic glutamate receptors show unique postsynaptic, presynaptic, and glial localizations in the dorsal cochlear nucleus. *J. Comp. Neurol.* 372, 356–383
- 66 Rubio, M.E. and Wenthold, R. (1997) Glutamate receptors are selectively targeted to postsynaptic sites in neurons. *Neuron* 18, 939–950
- 67 Petralia, R.S. *et al.* (2000) Differential distribution of glutamate receptors in the cochlear nuclei. *Hear. Res.* 147, 59–69
- 68 Manis, P.B. and Molitor, S.C. (1996) *N*-methyl-D-aspartate receptors at parallel fiber synapses in the dorsal cochlear nucleus. *J. Neurophysiol.* 76, 1639–1656

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