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REVIEW

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Multimodal inputs to the granule cell domain of the cochlear nucleus

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Abstract There is growing evidence that hearing involves the integration of many brain functions, including vision, balance, somatic sensation, learning and memory, and emotional state. Some of these integrative processes begin at the earliest stages of the central auditory system. In this review, we will discuss evidence that reveals multimodal projections into the granule cell domain of the cochlear nucleus.

Keywords Audition · Mossy fibers · Sensory integration · Synapses

Introduction

It is clear that "hearing" involves more than simply the transduction of vibrations in air. At a most basic level, we must *detect* sounds. Once a sound is detected, several processes are immediately initiated. There is a need to *localize* the sound source. This task requires the two ears and knowledge of head position. In the case of animals with mobile ears, pinna orientation becomes important. Proprioceptive, vestibular, and visual cues inform us whether we or the sound is moving. We must also *identify* the sound, a process involving learning and memory. That is, sounds made by a potential mate will be different from those made by a predator. Then there is the issue of "acoustic streams". The immediate acoustic history of a moving sound source allows anticipation of its trajectory and prediction of its future position. Likewise, the acoustic history of communication signals defines the topic of conversation and establishes boundary conditions for combinations of sounds uttered and sounds received. These boundary conditions will obviously be different for a discussion of sports than for that of cooking. As a corollary to this idea, mismatched expectation probably contributes to our difficulty in understanding speech with a foreign accent. Acoustic comprehension involves the integration of many brain functions. In this review, we will discuss data that demonstrate multimodal projections into the granule cell domain of the cochlear nucleus.

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The granule cell domain of the cochlear nucleus

The cochlear nucleus is the first central site of neural processing in the ascending auditory system. The mammalian cochlear nucleus is composed of cells that form a magnocellular core and a microneuronal shell. The magnocellular core is a heterogeneous aggregation of neuron classes exhibiting distinct dendritic characteristics (Osen 1969; Brawer et al. 1974; Hackney et al. 1990), physiological response features (Pfeiffer 1966; Evans and Nelson 1973; Young and Brownell 1976; Young et al. 1988; Blackburn and Sachs 1989), and projections to higher centers (Roth et al. 1978; Adams 1979; Glendenning et al. 1981; Warr 1982; Ryugo and Willard 1985; Schofield 1995; Schofield and Cant 1996a, 1996b; Alibardi 1998, 2000, 2001). This central core is primarily innervated by the axons of type I spiral ganglion neurons (Ramón y Cajal 1909; Lorente de Nó 1981; Fekete et al. 1984). By contrast, there is a thin shell of microneurons that is situated over the medial, dorsal, and lateral surface of the ventral cochlear nucleus and expands into layer II of the dorsal cochlear nucleus (Fig. 1; Mugnaini et al. 1980a, 1980b; Weedman et al. 1996). Contained in the shell there is a variety of different microneuronal types with distinctive morphology (Fig. 2). Unlike the magnocellular core, the microneurons participate in local circuit connections with the dorsal cochlear nucleus (DCN; Mugnaini et al. 1980a, 1980b; Weedman et al. 1996;

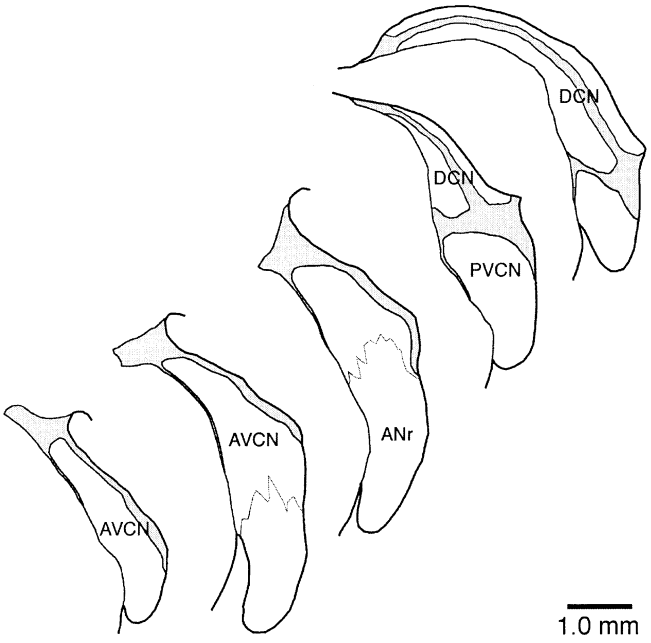

Fig. 1 Camera lucida drawings of coronal sections through the cochlear nucleus of a rat. Sections are spaced at 20% intervals, going from anterior (*lower left*) to posterior (*upper right*). The granule cell domain (GCD) is shaded in *gray*. In general, the GCD forms a thin shell lying over the dorsal, medial and lateral surface of the ventral cochlear nucleus. It thickens in the so-called lamina between the ventral (VCN) and dorsal cochlear nucleus (DCN), and forms a thin sheet that extends into layer II of the DCN. *ANr* auditory nerve root, *AVCN* anteroventral cochlear nucleus, *PVCN* posteroventral cochlear nucleus

Doucet and Ryugo 1997; Hurd et al. 1999). The microneuronal shell is referred to as the granule cell domain (GCD) because granule cells are the most numerous cell type (Mugnaini et al. 1980a). It does not receive inputs from the myelinated auditory nerve fibers (Fekete et al. 1984) but instead receives input from the unmyelinated type II fibers (Brown et al. 1988). Thus, the magnocellular and microneuronal regions differ in their cellular composition, projections, and inputs from the auditory nerve.

Inputs to the granule cell domain

Our interest concerns the synaptic inputs to the GCD. Not surprisingly, others have previously examined this issue. When the GCD was examined using electron microscopy, the region featured the presence of mossy fiber endings (McDonald and Rasmussen 1971; Mugnaini et al. 1980b). These mossy endings in the cochlear nucleus are provocative because they resemble those of cerebellar glomeruli (Palay and Chan-Palay 1974), characterized by relatively large but irregular profiles, tightly packed synaptic vesicles, moderate amounts of glycogen, and prominent postsynaptic densities. Mossy fibers provide a major source of cerebellar input and arise from many different neural systems. The prominence of mossy endings in the superficial GCD posed an important question because their origin was unknown. They did not arise from the auditory nerve because the type I fibers do not innervate the GCD and type II fibers do not give rise to large mossy-like endings.

Work in our laboratory sought to determine the origin of these mossy fiber endings. The basic strategy has been to place retrograde cell-markers into the GCD, and then to observe the distribution of cell bodies that are labeled throughout the brain stem. Injection sites, restricted to the cochlear nucleus, labeled cells in the following nonauditory structures (among others): cuneate nucleus, external cuneate nucleus, spinal trigeminal nucleus, Roller's nucleus, pontine nuclei, lateral reticular nucleus, and inferior olive (Fig. 3). Labeled cells were also found in auditory structures including the contralateral inferior colliculus, ventral nucleus of the lateral lemniscus and cochlear nucleus, and bilateral ventral and lateral nuclei of the trapezoid body. We then placed anterograde dyes into specific nuclei that contained retrogradely labeled cells in order to verify the axonal projections, to analyze terminal morphology, and to map the distribution of the synaptic endings. This method permitted the identification of the postsynaptic targets when using electron microscopy.

Nonauditory inputs to the DCN have been previously demonstrated for the cuneate nucleus (Itoh et al. 1987; Weinberg and Rustioni 1987). This cuneo-cochlear nucleus projection originates from the lateral part of the cuneate nucleus, particularly in the region mediating discriminative touch and proprioception for the neck (head position) and scalp (pinna position). The pathway terminates in the GCD (Fig. 4), primarily in the lamina between DCN and VCN and in layer 2 of the DCN (Wright and Ryugo 1996). We found that this projection terminated as mossy fibers, characterized as large, vesicle-filled endings surrounded by the terminal claw of granule cell dendrites (Fig. 5). Using double-labeling methods, cuneo-cochlear nucleus mossy fiber terminals in the GCD were immunostained for glutamate, but not for choline acetyltransferase or GABA (Wright and Ryugo 1996). Other mossy fibers have stained for acetylcholinesterase (McDonald and Rasmussen 1971) or glycine (L. Alibardi, personal communication). These data emphasize that mossy fibers represent a rich and varied population in the GCD.

Anterograde tracing methods have shown that the spinal trigeminal nucleus of the cat projected into the GCD (Itoh et al. 1987). Retrograde labeling studies have confirmed these observations (Haenggeli et al. 2002a, 2002b), and others have reported direct projections from the trigeminal ganglion into the auditory brain stem (Shore et al. 2000). It may be that cutaneous and proprioceptive afferents of the head and neck, which are processed through the cuneate, external cuneate, and trigeminal nuclei, convey information related to pinna and head position. The inputs to the GCD could mediate information arising from neck and pinna muscle afferents as well as from cutaneous stretch receptors around the

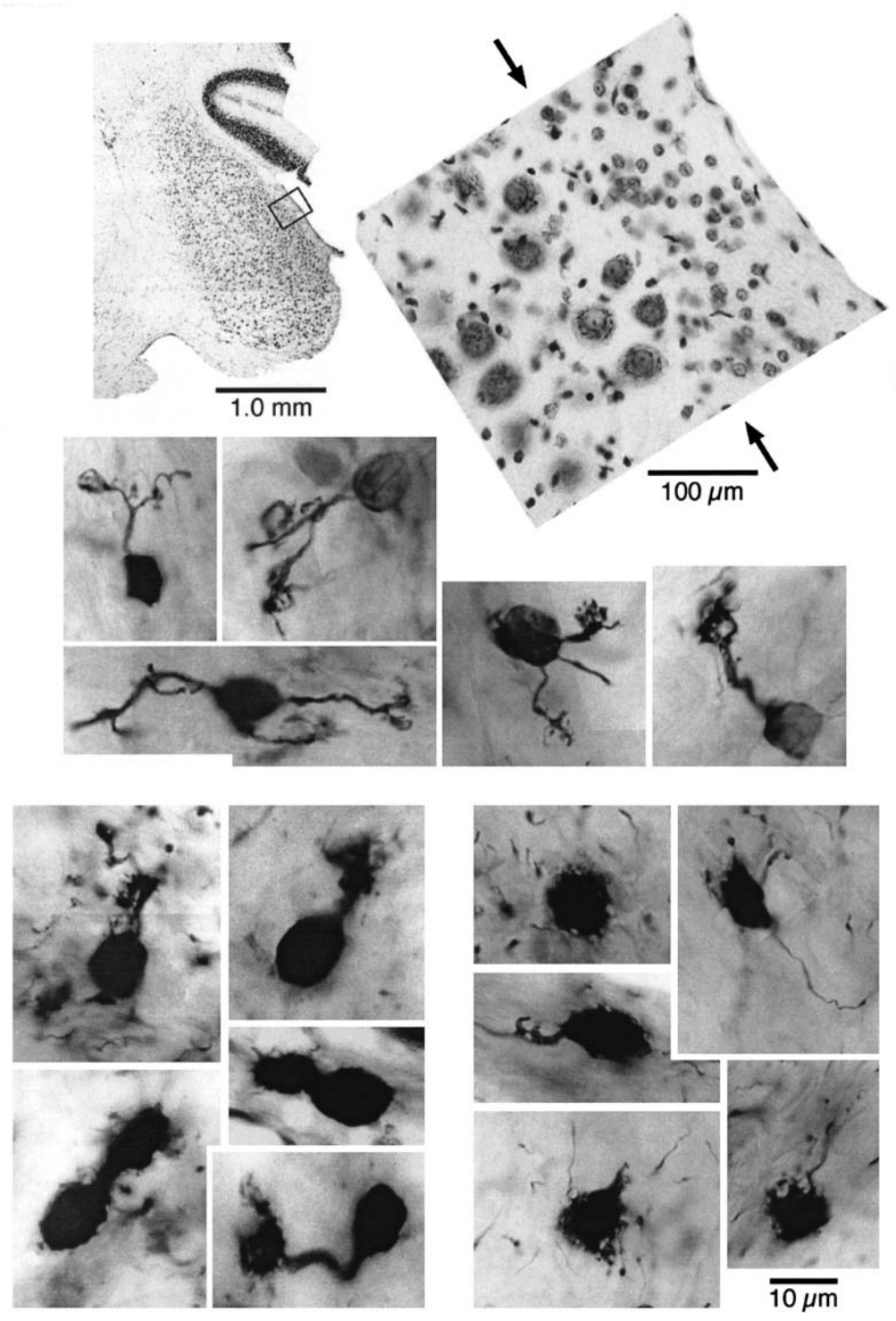

Fig. 2 Photomicrographs of some representatives of neuronal types in the granule cell domain (GCD). A coronal view through the anteroventral cochlear nucleus (AVCN) is shown (*top left*); the *box* indicates the area shown in the photomicrograph (*top right*), where *arrows* mark the border between the GCD (microneurons) and the spherical bushy cell region. Photomicrographs illustrate cells labeled by biotinylated dextran amine (BDA): granule cells (*middle row*), unipolar brush cells (*bottom left*) and chestnut cells (*bottom right*). Modified from Doucet and Ryugo (1997)

pinnae (Millar and Basbaum 1975; Maslany et al. 1991; Prihoda et al. 1991). Furthermore, direct projections from the C2 dorsal root ganglion have been shown to have a small terminal field in the medial edge of the GCD near the VCN (Pfaller and Arvidsson 1988), and C2 stimulation produces a large evoked response in the DCN (Kanold and Young 2001). Sensory input contained in C2 arises from the skin surrounding the pinna and presumably contributes to information about pinna position. We have reported that the nucleus of the spinal trigeminal tract sends projections to the ipsilateral GCD and the deep layers of the DCN (Haenggeli et al. 2002a, 2002b). Furthermore, these projections are in the form of mossy fiber endings, contacting the distal dendrites of granule cells, and closely resemble the mossy fiber endings from the cuneate nucleus. The large size of some of the labeled

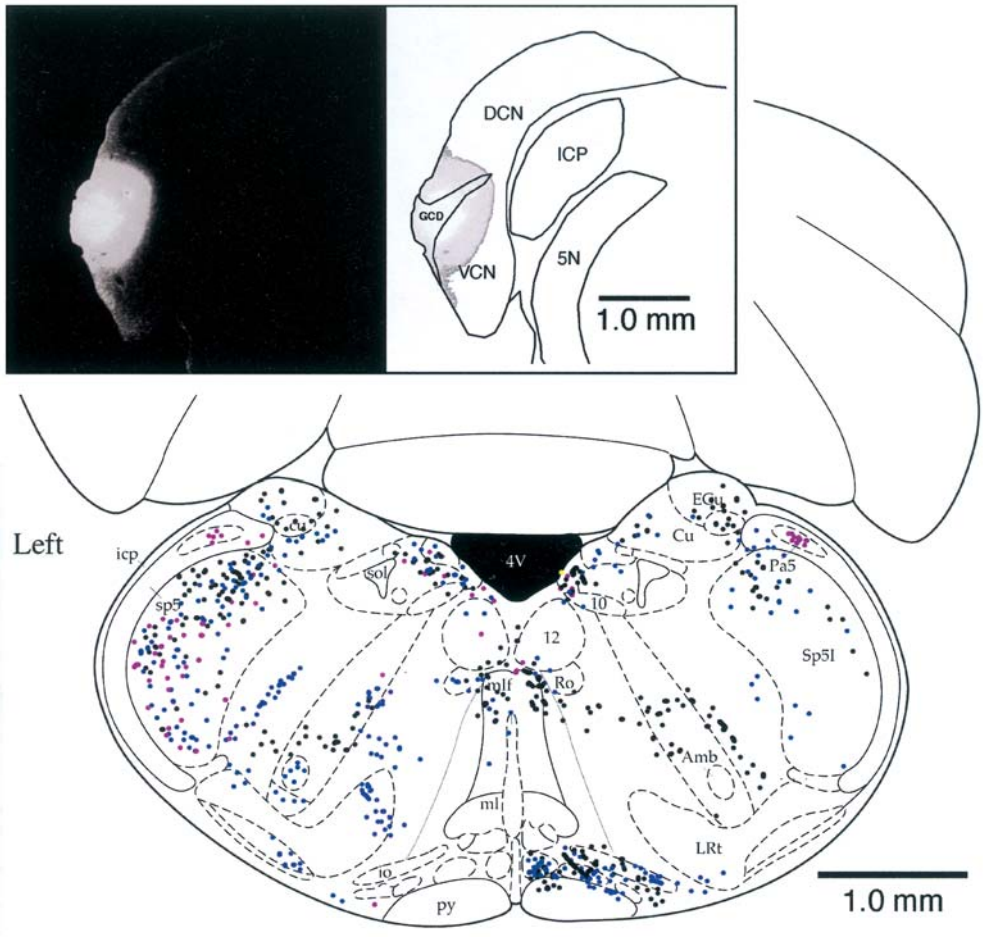

Fig. 3 Photomicrograph of a typical injection site of Fast Blue into the cochlear nucleus of a rat (*inset*). In this coronal view, note that the injection site is confined entirely within the cochlear nucleus and centered in the granule cell domain (*GCD*). Injections such as these produce retrogradely labeled cells (*black dots*) that have been plotted for four rats onto a standard section taken from a stereotaxic atlas of the rat (Swanson 1992). *4V* 4th Ventricle, *5N* nucleus of the spinal trigeminal, *10* vagus nucleus, *12* hypoglossal nucleus, *Amb* nucleus ambiguous, *Cu* cuneate nucleus, *DCN* dorsal cochlear nucleus, *ECu* external cuneate nucleus, *ICP* inferior cerebellar peduncle, *io* inferior olive, *LRt* lateral reticular nucleus, *ml* medial lemniscus, *mlf* medial longitudinal fasciculus, *Pa5* paratrigeminal nucleus, *py* pyramidal tract, *Ro* Roller's nucleus, *sol* solitary tract, *sp5* spinal trigeminal tract, *sp5I* spinal trigeminal nucleus (pars interpolaris), *VCN* ventral cochlear nucleus. Adapted from Haenggeli et al. (2002a)

mossy fibers, exceeding 20 μm in diameter, and the extent of the projections into the cochlear nucleus indicate that somatosensory cues are important to the earliest stages in the central auditory pathway. The type of somatosensory information carried by these projections, however, is not entirely clear, but current data imply that cues conveying head and pinna position are used for processing acoustic information, perhaps in terms of orienting to a sound source (Young et al. 1995; Davis et al. 1996; Kanold and Young 2001).

Along these lines, we have data on a range of other nonauditory inputs to the cochlear nucleus. For example, on the basis of retrograde labeling studies, we have shown that vestibular neurons residing in the medial vestibular nucleus and Scarpa's ganglion project into the cochlear nucleus. These observations are consistent with reports of primary and secondary vestibular afferents projecting into the cochlear nucleus (Burian and Gstoettner 1988; Kevetter and Perachio 1989; Bukowska 2002). The projection from Roller's nucleus, a structure involved in the control of eye gaze (McCrea et al. 1987), into the GCD suggests an integration of auditory and vestibular signals, perhaps involving the coordination of gaze and head position to a sound source.

We recently discovered that the pontine nuclei send a prominent bilateral projection to the GCD of the VCN but not to layer II of the DCN (Ohlrogge et al. 2001). The pontine nuclei therefore emerge as a potentially important crossroad for mediating ascending and descending fiber systems. They receive ascending projections from the cochlear nucleus (Faye-Lund 1986; Kandler and Herbert 1991) and the periolivary nuclei (Faye-Lund 1986), and descending projections from auditory cortex (Azizi et al. 1985; Knowlton et al. 1993) as well as other cortical fields (Potter et al. 1978; Glickstein 1997) and the inferior colliculus (Kawamura 1975; Aitkin and Boyd 1978). Sound stimulation has produced fos-like immunoreactivity in the pontine nuclei of the big brown bat (Qian and Jen 1994). The proto-oncogene c-fos is expressed throughout the central auditory pathway following acoustic stimulation and is interpreted as indicating sound-activated neuronal activity (Ehret and Fischer 1991; Rouiller et al. 1992; Brown and Liu 1995). Consistent with these data is the observation that single-unit activity can also be recorded in the pontine nuclei in response to sound stimulation (Aitkin and Boyd 1978; Azizi et al. 1985; Kamada et al. 1992). There are similarities in single-unit response properties between the pontine nuclei and the cerebellar vermis (Aitkin and Boyd 1975), two

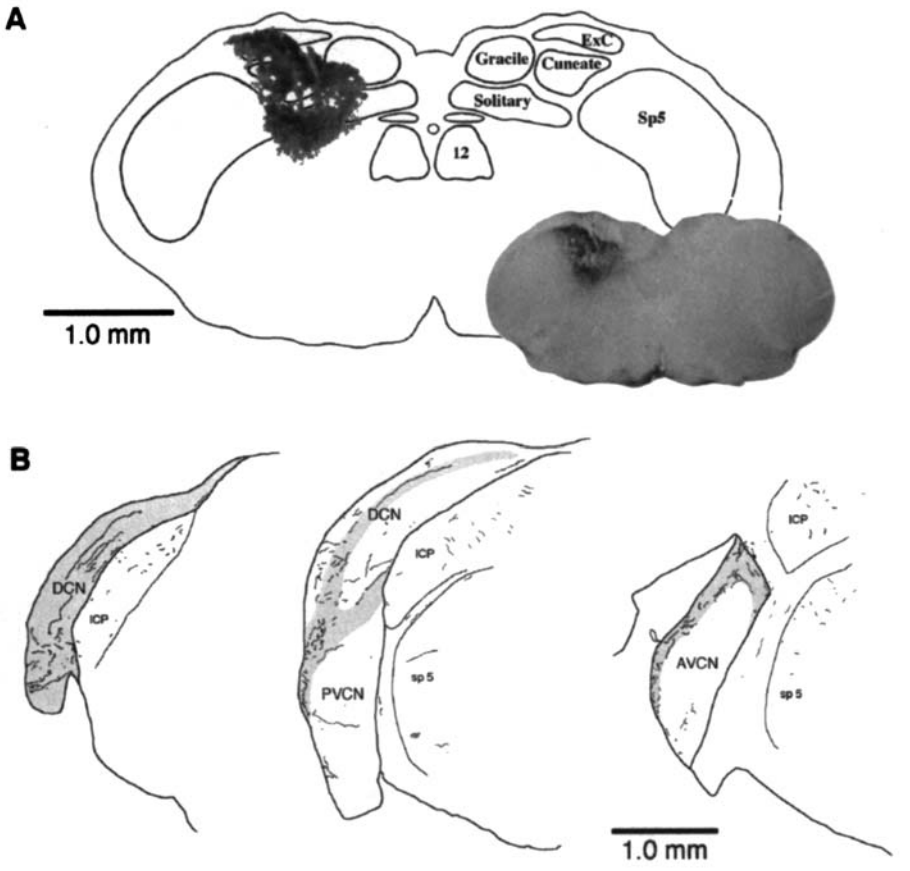

Fig. 4. A Plot and photomicrograph (*inset*) of neuronal marker PHA-L injection in the cuneate nucleus of a rat. *12* hypoglossal nucleus, *Cuneate* cuneate nucleus, *ExC* external cuneate nucleus, *Gracile* gracile nucleus, *Solitary* nucleus of the solitary tract, *Sp5* spinal trigeminal nucleus. **B** Plots of anterograde labeling of axons and terminals in the cochlear nucleus from the cuneate injection site in **A**. In these drawing tube reconstructions, three sections through the cochlear nucleus are illustrated. The granule cell domain (GCD) is shown in *gray*, whereas labeled axons and terminals are plotted in *black*. Note that the projections are primarily confined to the GCD. *AVCN* anteroventral cochlear nucleus, *DCN* dorsal cochlear nucleus, *ICP* inferior cerebellar peduncle, *PVCN* posteroventral cochlear nucleus, *sp5* spinal trigeminal nucleus. Adapted from Wright and Ryugo (1996)

interconnected regions. Does a separate class of pontine neurons project exclusively to the GCD, or do the projections arise from collaterals of axons headed to other regions?

With pontine nuclei involved in the auditory pathway, a system of sensory-motor circuits is evident in the processing of acoustic information. The pontine nuclei are well known for their projection into the cerebellar cortex as mossy fibers (Palay and Chan-Palay 1974). Not surprisingly, some pontine neurons project to the parafloccular lobule of the cerebellar cortex (Azizi and Woodward 1990; Huang et al. 1990) in the form of mossy fibers (Glickstein 1997). The most striking feature of the pontine projection to the GCD is that many of the endings are mossy fiber terminals. The extent to which these different pontine projection neurons are integrated with each other, however, is not known, and so a number of questions arise. Do different pontine cell groups (Mihailoff et al. 1981) receive convergent or segregated inputs from the separate input sources? Do separate groups of pontine neurons project in turn to different target structures? Do any of these cell groups project to more than one target (e.g., the cerebellum and the cochlear nucleus)? Do the signals to the GCD represent a duplication of descending motor commands as a kind of "efferent copy" or is there additional coding of signals?

Functional speculations

The observations that the GCD received nonauditory inputs, whereas the magnocellular core received auditory inputs, fit with a notion that sensory pathways are composed of (1) a pure sensory pathway (e.g., visual, auditory, somatic sensory) involved in faithfully conveying environmental stimuli, and (2) a polysensory pathway that integrates across modalities and modulates the activity in the "pure" pathway. Such an idea had its root in the "specific" and "unspecific" thalamic projections to primary sensory cortex (Lorente de Nó 1938), and was refined by the proposal concerning a "lemniscal" and a "nonlemniscal" pathway for sensory processing (Graybiel 1974). Surrounding the main sensory nuclei of the midbrain and thalamus were multimodal nuclei. For example, adjacent to the central nucleus of the inferior colliculus is the external nucleus upon which converge nonauditory projections (Schroeder and Jane 1971; Casseday et al. 1976; RoBards 1979). Likewise, the medial division of the medial geniculate nucleus receives nonauditory input (Lund and Webster 1967a, 1967b; Walsh and Ebner 1973) and exhibits polysensory response properties (Erickson et al. 1964; Wepsic 1966; Love and Scott 1969; Aitkin 1973; Ryugo and Weinberger 1978). Perhaps the initiation of the nonlemniscal pathway begins at the earliest level of the ascending auditory pathway in the GCD of the cochlear nucleus.

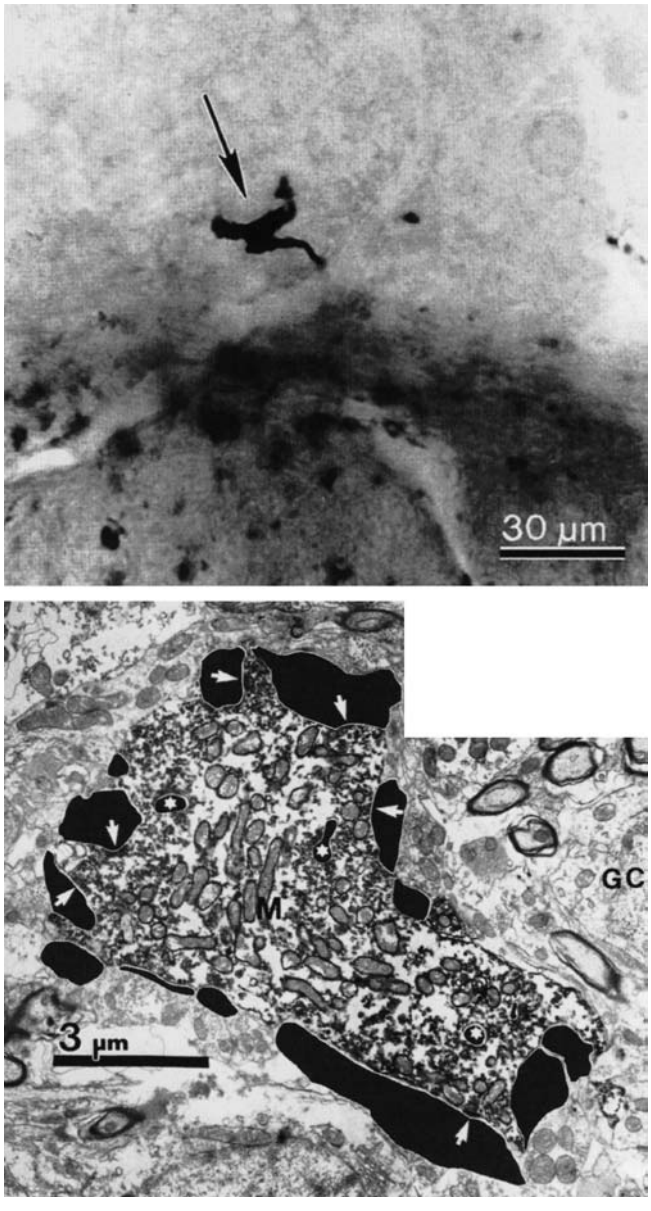

Fig. 5 Photomicrograph of a mossy fiber ending (*top*, *arrow*), labeled with neuronal marker PHA-L, in the granule cell domain (GCD) lamina situated between the dorsal and ventral cochlear nuclei. This particular mossy fiber is relatively large, and when examined with the electron microscope (*bottom*), was found to have features typical of cerebellar mossy fibers. The mossy fiber (*M*) resembled those mossy fibers previously described (McDonald and Rasmussen 1971; Mugnaini et al. 1980b). That is, it is irregular in shape, filled with round synaptic vesicles, and makes many synapses (*arrows*). It is surrounded by numerous dendritic profiles (*black with white outline*) of granule cells, some of which penetrate deep into the mossy fiber (*white asterisk*). *GC* granule cell. Adapted from Wright and Ryugo (1996)

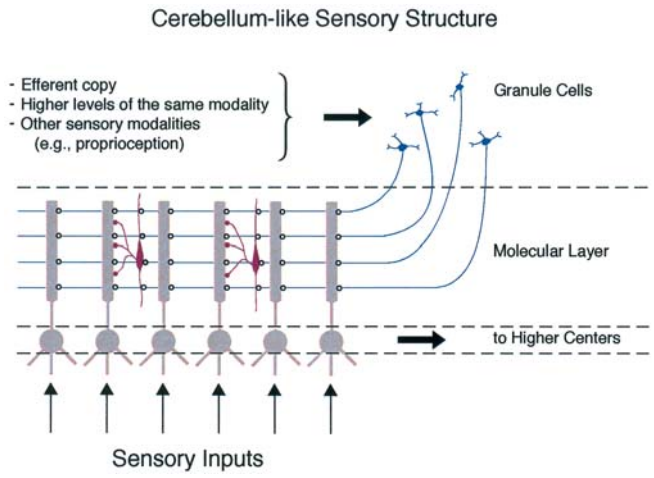

Fig. 6 Schematic illustration of cerebellum-like circuitry that resembles the mammalian dorsal cochlear nucleus. The main output cells (*gray*, pyramidal cells) receive two sources of excitatory inputs: primary sensory information (auditory nerve fibers) onto the basal dendrites and integrated information by way of granule cell parallel fibers. In this instance, "efferent copy" refers to descending motor commands that are replicated and sent via collaterals to granule cells. This projection is not to be confused with olivocochlear efferents, which project to the subjacent small cell cap of the cochlear nucleus, not the granule cell domain (GCD). Inhibitory interneurons (*dark*) reside within the molecular layer. The highly processed data are then sent to higher centers (e.g., inferior colliculus). Illustration modified from Bell et al. (1999)

The anatomical relationship of the GCD to the dorsal cochlear nucleus has long prompted the consideration of the DCN as resembling a cerebellar folium (Mugnaini et al. 1980a, 1980b; Lorente de Nó 1981; Mugnaini and Morgan 1987; Wright and Ryugo 1996; Devor 2000). This neural circuit (Fig. 6) has been functionally studied in the electrosensory lobe of mormyrid electric fish where the cerebellum-like structure has been shown to provide "sensory subtraction" of predictable features of the sensory environment (Bell et al. 1997, 1999). Can this kind of comparative approach provide insight into GCD function? It is known that the external ear (pinna) modifies the frequency spectrum of sounds in a way that depends on the location of the sound source (Shaw 1982; Middlebrooks et al. 1989; Musicant et al. 1990; Rice et al. 1992). Animals with mobile pinnae present additional cues for sound localization (Populin and Yin 1995). It seems that certain types of predictive information could be "subtracted" from the acoustic inflow, including self-generated noise (e.g., vocalizations, chewing), motion, and context.

In summary, the processing of sound is not only defined by the circuits traditionally viewed as auditory (e.g., pathways directly or indirectly connected to the cochlea) but also by nonauditory variables such as neck muscle position and tension (somatic proprioception), head position (vestibular afferents), affective state (arousal level), and memory. As we learn more about the kinds of inputs to the GCD (Fig. 7), the data can guide studies on functional circuits that lead to a greater understanding of the integrative nature of acoustic processing.

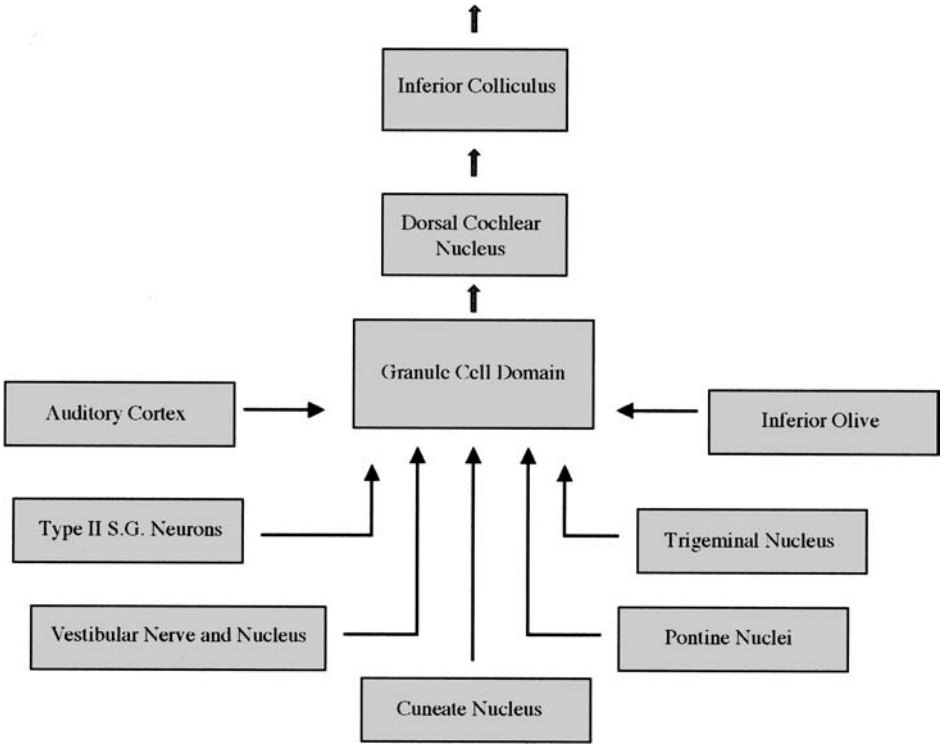

Fig. 7 Block diagram that summarizes the inputs to the granule cell domain (GCD). The available data emphasize the complex convergence of inputs into this region

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References

Adams JC (1979) Ascending projections to the inferior colliculus. J Comp Neurol 183:519–538

Aitkin LM (1973) Medial geniculate body of the cat: Responses to tonal stimuli of neurons in medial division. J Neurophysiol 36:275–283

Aitkin LM, Boyd J (1975) Responses of single units in cerebellar vermis of the cat to monaural and binaural stimuli. J Neurophysiol 38:418–429

Aitkin LM, Boyd J (1978) Acoustic input to the lateral pontine nuclei. Hear Res 1:67–77

Alibardi L (1998) Ultrastructural and immunocytochemical characterization of neurons in the rat ventral cochlear nucleus projecting to the inferior colliculus. Ann Anat 180:415–426

Alibardi L (2000) Cytology, synaptology and immunocytochemistry of commissural neurons and their putative axonal terminals in the dorsal cochlear nucleus of the rat. Ann Anat 182:207–220

Alibardi L (2001) Fine structure and neurotransmitter cytochemistry of neurons in the rat ventral cochlear nucleus projecting to the ipsilateral dorsal cochlear nucleus. Ann Anat 183:459–469

Azizi SA, Woodward DJ (1990) Interactions of visual and auditory mossy fiber inputs in the paraflocculus of the rat: a gating action of multimodal inputs. Hear Res 533:255–262

Azizi SA, Burne RA, Woodward DJ (1985) The auditory corticopontocerebellar projection in the rat: inputs to the paraflocculus and midvermis. An anatomical and physiological study. Exp Brain Res 59:36–49

Bell CC, Bodznick D, Montgomery J, Bastian J (1997) The generation and subtraction of sensory expectations within cerebellum-like structures. Brain Behav Evol 50:17–31

Bell CC, Han VZ, Sugawara Y, Grant K (1999) Synaptic plasticity in the mormyrid electrosensory lobe. J Exp Biol 202:1339–1347

Blackburn CC, Sachs MB (1989) Classification of unit types in the anteroventral cochlear nucleus: PST histograms and regularity analysis. J Neurophysiol 62:1303–1329

Brawer JR, Morest DK, Kane EC (1974) The neuronal architecture of the cochlear nucleus of the cat. J Comp Neurol 155:251–300

Brown MC, Liu TS (1995) Fos-like immunoreactivity in central auditory neurons of the mouse. J Comp Neurol 357:85–97

Brown MC, Berglund AM, Kiang NYS, Ryugo DK (1988) Central trajectories of type II spiral ganglion neurons. J Comp Neurol 278:581–590

Bukowska D (2002) Morphological evidence for secondary vestibular afferent connections to the dorsal cochlear nucleus in the rabbit. Cells Tissues Organs 170:61–68

Burian M, Gstoettner W (1988) Projection of primary vestibular afferent fibers to the cochlear nucleus in the guinea pig. Neurosci Lett 84:13–17

Casseday HJ, Diamond IT, Harting JK (1976) Auditory pathways to the cortex in *Tupaia glis*. J Comp Neurol 166:303–340

Davis KA, Miller RL, Young ED (1996) Effects of somatosensory and parallel-fiber stimulation on neurons in dorsal cochlear nucleus. J Neurophysiol 76:3012–3024

Devor A (2000) Is the cerebellum like cerebellar-like structures? Brain Res Rev 34:149–156

Doucet JR, Ryugo DK (1997) Projections from the ventral cochlear nucleus to the dorsal cochlear nucleus in rats. J Comp Neurol 385:245–264

Ehret G, Fischer R (1991) Neuronal activity and tonotopy in the auditory system visualized by *c-fos* gene expression. Brain Res 567:350–354

Erickson RP, Jane JA, Waite R, Diamond IT (1964) Single neuron investigation of sensory thalamus of the opossum. J Neurophysiol 27:1026–1047

Evans EF, Nelson PG (1973) The responses of single neurones in the cochlear nucleus of the cat as a function of their location and anesthetic state. Exp Brain Res 17:402–427

Faye-Lund H (1986) Projection from the inferior colliculus to the superior olivary complex in the albino rat. Anat Embryol 175:35–52

Fekete DM, Rouiller EM, Liberman MC, Ryugo DK (1984) The central projections of intracellularly labeled auditory nerve fibers in cats. J Comp Neurol 229:432–450

Glendenning KK, Brunso-Bechtold JK, Thompson GC, Masterton RB (1981) Ascending auditory afferents to the nuclei of the lateral lemniscus. J Comp Neurol 197:673–703

Glickstein M (1997) Mossy-fibre sensory input to the cerebellum. Prog Brain Res 114:251–259

Graybiel AM (1974) Studies on the anatomical organization of the posterior association cortex. In: Schmitt FO, Worden FG (eds) The Neurosciences Third Study Program. MIT Press, Cambridge, pp 205–214

Hackney CM, Osen KK, Kolston J (1990) Anatomy of the cochlear nuclear complex of guinea pig. Anat Embryol 182:123–149

Haenggeli C-A, Doucet JR, Ryugo DK (2002a) Trigeminal projections to the cochlear nucleus in rats. ARO Abstr 25:7

Haenggeli C-A, Doucet JR, Ryugo DK (2002b) Projections of the spinal trigeminal nucleus to the cochlear nucleus. Proceedings of the Scientific Program, "Central auditory processing—integration with other systems", Monte-Verità, Switzerland, P36

Huang C-M, Liu L, Pettavel P, Huang RH (1990) Target areas of presumed auditory projections from lateral and dorsolateral pontine nuclei to posterior cerebellar vermis in rat. Brain Res 536:327–330

Hurd LB, Hutson KA, Morest DK (1999) Cochlear nerve projections to the small cell shell of the cochlear nucleus: the neuroanatomy of extremely thin sensory axons. Synapse 33:83–117

Itoh K, Kamiya H, Mitani A, Yasui Y, Takada M, Mizuno N (1987) Direct projections from the dorsal column nuclei and the spinal trigeminal nuclei to the cochlear nuclei in the cat. Brain Res 400:145–150

Kamada T, Wu M, Jen H-S (1992) Auditory response properties and spatial response areas of single neurons in the pontine nuclei of the big brown bat. Brain Res 575:187–198

Kandler K, Herbert H (1991) Auditory projections from the cochlear nucleus to pontine and mesencephalic reticular nuclei in the rat. Brain Res 562:230–242

Kanold PO, Young ED (2001) Proprioceptive information from the pinna provides somatosensory input to cat dorsal cochlear nucleus. J Neurosci 21:7848–7858

Kawamura K (1975) The pontine projection from the inferior colliculus in the cat. An experimental anatomical study. Brain Res 95:309–322

Kevetter GA, Perachio AA (1989) Projections from the sacculus to the cochlear nuclei in the Mongolian gerbil. Brain Behav Evol 34:193–200

Knowlton BJ, Thompson JK, Thompson RF (1993) Projections from the auditory cortex to the pontine nuclei in the rabbit. Behav Brain Res 56:23–30

Lorente de Nó R (1938) The cerebral cortex: architecture, intracortical connections, motor projections. In: Fulton JF (ed) Physiology of the nervous system. Oxford University Press, New York, pp 291–340

Lorente de Nó R (1981) The primary acoustic nuclei. Raven Press, New York

Love JA, Scott JW (1969) Some response characteristics of cells of the magnocellular division of the medial geniculate body of the cat. Can J Physiol Pharm 47:881–888

Lund RD, Webster KE (1967a) Thalamic afferents from the dorsal column nuclei. An experimental anatomical study in the rat. J Comp Neurol 130:301–312

Lund RD, Webster KE (1967b) Thalamic afferents from the spinal cord and trigeminal nuclei. An experimental anatomical study in the rat. J Comp Neurol 130:313–328

Maslany S, Crockett DP, Egger MD (1991) Somatotopic organization of the dorsal column nuclei in the rat: transganglionic labelling with B-HRP and WGA-HRP. Brain Res 564:56–65

McCrea RA, Strassman A, May E, Highstein SM (1987) Anatomical and physiological characteristics of vestibular neurons mediating the horizontal vestibulo-ocular reflex of the squirrel monkey. J Comp Neurol 264:547–570

McDonald DM, Rasmussen GL (1971) Ultrastructural characteristics of synaptic endings in the cochlear nucleus having acetylcholinesterase activity. Brain Res 28:1–18

Middlebrooks JC, Makous JC, Green DM (1989) Directional sensitivity of sound-pressure levels in the human ear canal. J Acoust Soc Am 59:89–108

Mihailoff GA, McArdle CB, Adams CE (1981) The cytoarchitecture, cytology, and synaptic organization of the basilar pontine nuclei in the rat. I. Nissl and Golgi studies. J Comp Neurol 195:181–201

Millar J, Basbaum AI (1975) Topography of the projection of the body surface of the cat to cuneate and gracile nuclei. Exp Neurol 49:281–290

Mugnaini E, Morgan JI (1987) The neuropeptide cerebellin is a marker for two similar neuronal circuits in rat brain. Proc Natl Acad Sci 84:8692–8696

Mugnaini E, Osen KK, Dahl AL, Friedrich Jr. VL, Korte G (1980a) Fine structure of granule cells and related interneurons (termed Golgi cells) in the cochlear nuclear complex of cat, rat, and mouse. J Neurocytol 9:537–570

Mugnaini E, Warr WB, Osen KK (1980b) Distribution and light microscopic features of granule cells in the cochlear nuclei of cat, rat, and mouse. J Comp Neurol 191:581–606

Musicant AD, Chan JCK, Hind JE (1990) Direction-dependent spectral properties of cat external ear: New data and cross-species comparisons. J Acoust Soc Am 87:757–781

Ohlrogge M, Doucet JR, Ryugo DK (2001) Projections of the pontine nuclei to the cochlear nucleus in rats. J Comp Neurol 436:290–303

Osen KK (1969) Cytoarchitecture of the cochlear nuclei in the cat. J Comp Neurol 136:453–482

Palay SL, Chan-Palay V (1974) Cerebellar cortex, cytology and organization. Springer-Verlag, New York

Pfaller K, Arvidsson J (1988) Central distribution of trigeminal and upper cervical primary afferents in the rat studied by anterograde transport of horseradish peroxidase conjugated to wheat germ agglutinin. J Comp Neurol 268:91–108

Pfeiffer RR (1966) Classification of response patterns of spike discharges for units in the cochlear nucleus: tone burst stimulation. Exp Brain Res 1:220–235

Populin LC, Yin TCT (1995) Topographical organization of the motoneuron pools that innervate the muscles of the pinna of the cat. J Comp Neurol 363:600–614

Potter RF, Rüegg DG, Wiesendanger M (1978) Responses of neurons of the pontine nuclei to stimulation of the sensorimotor, visual and auditory cortex of rats. Brain Res Bull 3:15–19

Prihoda M, Hiller M-S, Mayr R (1991) Central projections of cervical primary afferent fibers in the guinea pig: an HRP and WGA/HRP tracer study. J Comp Neurol 308:418–431

Qian Y, Jen H-S (1994) Fos-like immunoreactivity elicited by sound stimulation in the auditory neurons of the big brown bat *Eptesicus fuscus*. Brain Res 664:241–246

Ramón y Cajal R (1909) Histologie du Système Nerveux de l'Homme et des Vertébrés. Instituto Ramón y Cajal, Madrid

Rice JJ, May BJ, Spirou GA, Young ED (1992) Pinna-based spectral cues for sound localization in cat. Hear Res 58:132–152

RoBards MJ (1979) Somatic neurons in the brainstem and neocortex projecting to the external nucleus of the inferior colliculus: anatomical study in the opossum. J Comp Neurol 184:547–566

Roth GL, Aitken LM, Anderson RA, Merzenich MM (1978) Some features of the spatial organization of the central nucleus of the inferior colliculus of the cat. J Comp Neurol 182:661–680

Rouiller EM, Wan XST, Moret V, Liang F (1992) Mapping of c-fos expression elicited by pure tone stimulation in the auditory pathways of the rat, with emphasis on the cochlear nucleus. Neurosci Lett 144:19–24

Ryugo DK, Weinberger NM (1978) Differential plasticity of morphologically distinct neuron populations in the medical geniculate body of the cat during classical conditioning. Behav Biol 22:275–301

Ryugo DK, Willard FH (1985) The dorsal cochlear nucleus of the mouse: A light microscopic analysis of neurons that project to the inferior colliculus. J Comp Neurol 242:381–396

Schofield BR (1995) Projections from the cochlear nucleus to the superior paraolivary nucleus in guinea pigs. J Comp Neurol 360:135–149

Schofield BR, Cant NB (1996a) Origins and targets of commissural connections between the cochlear nuclei in guinea pigs. J Comp Neurol 375:128–146

Schofield BR, Cant NB (1996b) Projections from the ventral cochlear nucleus to the inferior colliculus and the contralateral cochlear nucleus in guinea pigs. Hear Res 102:1–14

Schroeder DM, Jane JA (1971) Projections of the dorsal column nuclei and spinal cord to brain stem and thalamus in the tree shrew (*Tupaia glis*). J Comp Neurol 142:309–350

Shaw EAG (1982) External ear response and sound localization. In: Gatehouse RW (ed) Localization of sound: theory and applications. Amphora, Groton, pp 30–42

Shore SE, Vass Z, Wys NL, Altschuler RA (2000) Trigeminal ganglion innervates the auditory brainstem. J Comp Neurol 419:271–285

Swanson LW (1992) Brain maps: structure of the rat brain. Elsevier, Amsterdam

Walsh TM, Ebner F (1973) Distribution of the cerebellar and somatic lemniscal projections in the ventral nucleus complex of the Virginia opossum. J Comp Neurol 147:427–446

Warr WB (1982) Parallel ascending pathways from the cochlear nucleus: Neuroanatomical evidence of functional specialization. In: Neff WD (ed) Contributions to sensory physiology, vol 7. Academic Press, New York, pp 1–38

Weedman DL, Pongstaporn T, Ryugo DK (1996) Ultrastructural study of the granule cell domain of the cochlear nucleus in rats: Mossy fiber endings and their targets. J Comp Neurol 369:345–360

Weinberg RJ, Rustioni A (1987) A cuneocochlear pathway in the rat. Neuroscience 20:209–219

Wepsic JG (1966) Multimodal sensory activation of cells in the magnocellular medial geniculate nucleus. Exp Neurol 15:299–318

Wright DD, Ryugo DK (1996) Mossy fiber projections from the cuneate nucleus to the cochlear nucleus in the rat. J Comp Neurol 365:159–172

Young ED, Brownell WE (1976) Responses to tones and noise of single cells in dorsal cochlear nucleus of unanesthetized cats. J Neurophysiol 39:282–300

Young ED, Shofner WP, White JA, Robert J-M, Voigt HF (1988) Response properties of cochlear nucleus neurons in relationship to physiological mechanisms. In: Edelman GM, Gall WE, Cowan WM (eds) Auditory function: neurobiological bases of hearing. Wiley, New York, pp 277–312

Young ED, Nelken I, Conley RA (1995) Somatosensory effects on neurons in dorsal cochlear nucleus. J Neurophysiol 73:743–765