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The Cytoarchitecture of the Inferior Colliculus Revisited:

A Common Organization of the Lateral Cortex in Rat and Cat

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Abstract

The inferior colliculus (IC) is the major component of the auditory midbrain and contains three major subdivisions: a central nucleus, a dorsal cortex, and a lateral cortex (LC). Discrepancies in the nomenclature and parcellation of the LC in the rat and cat seem to imply different, species-specific functions for this region. To establish a comparable parcellation of the LC for both rat and cat, we investigated the histochemistry and inputs of the LC. In both species, the deep lateral cortex is marked by a transition between the NADPH-d rich superficial cortex and a cytochrome oxidase rich central nucleus. In both species, focal injections of anterograde tracers in the cochlear nucleus at sites of known best frequency produced bands of labeled inputs in two different subdivisions of the IC. A medial band of axons terminated in the central nucleus, while shorter bands were located laterally and oriented nearly perpendicularly to the medial bands. In the rat, these lateral bands were located in the third, deepest layer of the lateral (external) cortex. In the cat, the bands were located in a region that was previously ascribed to the central nucleus, but now considered to belong to the third, deepest layer of the LC, the ventrolateral nucleus. In both species, the LC inputs had a tonotopic organization. In view of this parallel organization, we propose a common parcellation of the IC for rat and cat with a new nomenclature. The deep layer of the LC, previously referred to as layer 3 in the rat, is designated as the 'ventrolateral nucleus' of the LC, making it clear that this region is thought to be homologous with the ventrolateral nucleus in the cat. The similar organization of the LC implies that this subdivision of the IC has similar functions in cats and rats.

Keywords

auditory pathways; external cortex; external nucleus; pericentral nucleus; ventrolateral nucleus

INTRODUCTION

The lateral cortex (LC) is one of the three subdivisions of the inferior colliculus (IC), that also includes the central nucleus and dorsal cortex, but it is the least understood. Interspecies differences in the cytoarchitecture in the lateral region of the IC (see, for example Morest and Oliver, 1984, Faye-Lund and Osen, 1985, Malmierca et al., 1993) have limited our understanding of the functional role of the lateral IC. Nevertheless, it is clear that the lateral IC has both auditory and somatosensory inputs, and some parts may be involved in multisensory integration (Aitkin et al., 1978, Aitkin et al., 1981, Jain and Shore, 2005, Zhou

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and Shore, 2006). Auditory inputs to the deeper parts of the lateral IC arise from the cochlear nucleus and superior olive (Adams, 1979, Brunso-Bechtold et al., 1981, Shneiderman and Henkel, 1987, Shneiderman et al., 1988, Schofield and Cant, 1992, Oliver et al., 1995, Schofield and Cant, 1996, Oliver et al., 1997, Oliver et al., 1999, Cant and Benson, 2003, Loftus et al., 2004a, Cant and Benson, 2006). These same auditory inputs also target the central nucleus and dorsal cortex of the IC. Somatosensory afferents arise from spinal cord, dorsal column nuclei, and trigeminal nucleus (Aitkin et al., 1978, Robards, 1979, Feldman and Kruger, 1980, Aitkin et al., 1981, Morest and Oliver, 1984, Coleman and Clerici, 1987, Wiberg et al., 1987, Jain and Shore, 2005, Zhou and Shore, 2006). Recent studies of the lateral IC suggest that it may play a unique role in the descending auditory system (Groff and Liberman, 2003, Ota et al., 2004). Despite the potential significance of the LC for both ascending and descending auditory processing, results obtained in different species have been difficult to compare because of perceived differences in its architecture and connections.

Here, we studied the architecture and auditory connections of the lateral IC in both the rat and cat. Architecture was addressed by analyzing the distribution of two chemical markers, cytochrome oxidase (CO) and nicotinamide adenine dinucleotide phosphate-diaphorase (NADPH-d) in the IC. CO is a mitochondrial enzyme associated with oxidative metabolism. NADPH-d is colocalized with nitric oxide synthase that catalyzes the production of the retrograde messenger, nitric oxide. These markers have previously been used to distinguish IC subdivisions (NADPH-d: Druga and Syka, 1993, CO: Cant and Benson, 2005).

Electrophysiological and anatomical approaches were combined in order to identify frequency-specific inputs to the IC. Deposits of anterograde tracers in the cochlear nucleus labeled the terminations of auditory inputs to the IC. Recordings of tone-evoked responses at the injected sites revealed the frequency selectivity of labeled inputs, and allowed us to determine if LC afferents are organized tonotopically.

In both species, we found that: 1) the deep LC was characterized as a transition zone between the CO rich central nucleus and a NADPH-d rich perimeter; 2) auditory inputs target the deep LC and had a consistent spatial relationship to the inputs to the central nucleus, and 3) auditory inputs to the LC had a tonotopic organization within the LC, separate from that of the central nucleus. These commonalities suggest a homologous structure and function for the lateral IC in the cat and rat. To emphasize these commonalities, we propose a new nomenclature for the lateral cortex of the IC that can be applied to both species.

EXPERIMENTAL PROCEDURES

Anatomical tracer experiments were performed on 6 cats and 6 rats using procedures and some animals reported earlier (cat: Oliver et al., 1997, rat: Malmierca et al., 2002). In addition, three cats and two rats were used for CO and NADPH-de assays in the IC. All experiments were done in accordance with institutional guidelines at the University of Salamanca, University of Connecticut Health Center, and NIH guidelines for the care and use of laboratory animals.

Procedures for the anatomical tracer experiments are as follows. Anesthesia was induced in rats with ketamine (57 mg/kg i.m.) and xylazine (8.6 mg/kg i.m) and the animals were maintained in an areflexive state with the same compounds during the surgery and recording. Anesthesia was induced in cats with ketamine (33 mg/kg i.m.) and xylazine (1 mg/kg i.m.). Cats were then intubated and maintained in an areflexive state with isoflurane mixed with oxygen for the duration of the surgery and recording.

All of the procedures described henceforth were the same for both cats and rats. Animals were put into a stereotaxic frame which incorporated hollow ear bars to deliver sound stimuli, appropriately sized for the species. Surgery and sound recording was done in a double walled

sound attenuating chamber (IAC, Bronx, NY). Cochlear nuclei on the right side were exposed by a craniotomy and aspiration of parts of the lateral and floccular cerebellum.

Extracellular recordings and tracer injections were done with glass micropipettes filled with anatomical tracers dissolved in saline. These were advanced into the dorsal cochlear nucleus or anteroventral cochlear nucleus while calibrated tonal stimuli were delivered by speakers coupled to the hollow ear bars of the stereotaxic frame. Stimuli were sequences of pure tone bursts swept through a range of frequencies and delivered at the same, moderate intensity (60-70 dB SPL). For a given intensity, the frequency that elicited the largest single- or multi-unit response was deemed the best frequency (BF) for that recording site. At a selected site, tracer was iontophoresed through the same pipette used for recording. Two types of tracers were used for anterograde transport: i) 10% tetramethylrhodamine dextran (TMR), dissolved in 0.9% saline, and ii) a mixture of 10% biotinylated dextran amine (BDA) and 10% fluorescein dextran (FD), dissolved in 0.9% saline. Iontophoresis parameters varied between 2-6 μA for durations of 5-24 min, with a 50% duty cycle (7s on / 7s off).

After the survival period of 7-10 days for anterograde transport, animals were deeply anesthetized and then perfused transcardially with 4% paraformaldehyde. Tissue was prepared for light microscopy according to previously described procedures (Oliver et al., 2003, Loftus et al., 2004a, Malmierca et al., 2005). Brains were blocked in the Horsley-Clark plane and transverse sections were cut at a 50 μm thickness. Histology included Avidin biotin complex histochemistry for visualization and stabilization of BDA-labeled afferents using cobalt and nickel to make a black reaction and immunohistochemistry with antisera for TMR, followed by ABC histochemistry with Nova Red or DAB without cobalt and nickel to visualize the TMR labeled afferents. Every sixth section was Nissl stained and used to outline the cytoarchitectural subdivisions of the IC.

Tissue was analyzed with epifluorescence (for FD and TMR) and light microscopy (for stabilized BDA and TMR). In the latter material, BDA-labeled axons and boutons appear black and TMR-labeled axons and boutons appear red. Data analysis consisted of plotting the axons and boutons in transverse sections of the IC using Neurolucida software (Microbrightfield, Colchester, VT). Closed contours were used to outline the fields of boutons. Comparison of the photographs of the raw data with outlines indicated that contours accurately captured the afferent organization. Digital images of injection sites in the cochlear nucleus and labeled afferents in the IC were acquired with a SPOT camera (Diagnostic Instruments, Inc., Sterling Heights, MI) and contrast, brightness, and color were adjusted with Photoshop software (Adobe Systems, Inc., San Jose, CA).

Methods for the CO and NADPH-d histochemistry were the same for both species. Briefly, animals were perfused transcardially with 4% paraformaldehyde. Brains were blocked in the Horsley-Clark plane, cryoprotected overnight in 10% sucrose, and then cut into 50 μm thick sections in the transverse plane. Two of every six sections were sampled for CO and NADPH histochemistry. For CO staining, free floating sections were incubated in a reaction mixture of 0.025% cytochrome C (Sigma C-7752) in 0.12 M phosphate buffer for ~ 21 h at 37°C. For NADPH-d staining, sections were incubated in a solution of 0.05% b-NADPH (QBiogene ALX-480-004-M250) in 0.12M phosphate buffer for 44 h at 4°C followed by 4 h at 37°C.

The images of the CO and NADPH-d stained tissue presented here were processed in Photoshop software in the following manner. Digitized color images were converted to gray scale, the grey level histograms were equalized, and the grey level range was inverted so that areas of more intense staining appear brighter. Images of a CO section and nearest NADPH-d section were aligned using the IC outline and blood vessels as a guide. A pseudo-color image

was formed by assigning the CO image to the green channel and the NADPH-d image to the red channel.

RESULTS

Architecture of the Lateral Cortex (LC)

The LC can be subdivided into superficial and deep parts in both rats and cats. Figure 1 shows these regions in Nissl-stained sections along with the names used in previous studies of these species and new names that we propose. In cats (Fig. 1A), the LC has a superficial portion named the lateral nucleus (LN) with two layers (Fig. 1A, *1*, *2*), a fibrous layer 1 that includes the fibers of the brachium of the IC and a cellular layer 2. The deep portion of the LC is the ventrolateral nucleus (*VLN*) and contains a mixture of neurons of different sizes including larger ones than in layers 1 and 2. Dorsally, the LN borders the dorsolateral, low frequency part of the central nucleus (Fig. 1A, *CNIC*). Ventrally, the VLN is intercalated between the LN and the lateral margin of the central nucleus.

In rats (Fig. 1B), the LC is better known as the external cortex of the IC (Fig. 1B, *ECIC*). As in the cat, the superficial portion of the rat's LC can be divided into two layers: an outer fibrous layer 1 and a small cell middle layer 2 (Fig. 1B, *1*, *2*). The deeper layer 3 contains larger neurons (Fig. 1B, *3*), and is adjacent to the entire lateral border of the central nucleus (Fig. 1B, *CNIC*). We propose that this layer 3 corresponds to the VLN of the cat.

The basic architecture is seen in histochemical stains to reveal NADPH-d or CO. In both species, the LC stains most heavily for NADPH-d (Fig. 2A,2D, *LC*) as does the dorsal cortex (Fig. 2A, 2D, *DC*). This staining is mostly in the neuropil, although some heavily NADPH-d -stained neurons are found in the central nucleus. In contrast, the central nucleus stains most heavily for CO (Fig. 2B, *CNIC*). The deeper part of the LC, the VLN, is the only part of the LC that contains both CO and NADPH-d as seen in the merged images from the adjacent sections seen in Fig. 2C and 2F. This type of transition is also characteristic of the deeper part of the dorsal cortex where both CO and NADPH-d are found (Fig. 2C, 2F, *DC*).

Although this basic pattern is seen in both cat and rat, there are some differences. The VLN in both is completely filled with CO-stained neurons and processes, but the staining is more intense in the cat than the rat (compare Fig. 2B to 2E). In contrast, the NADPH-d staining in VLN is more complete and intense in the rat than in the cat, and the NADPH-d labeling extends medially to the border of the central nucleus in the rat. Consequently, the region of mixed CO and NADPH-d labeling in the cat appears to be thinner.

A similar difference appears in layer 2 of the superficial LC. There are small patches of CO staining in layer 2 of the rat (cf. Chernock et al., 2004) that intermix with the more extensive NADPH-d-stained regions. Thus, both layer 2 of LC and VLN in the rat exhibit a more mixed CO and NADPH-d expression than do the corresponding regions in the cat.

Comparison of Cochlear Nucleus Inputs to the LC

In both species, single, small injections in the cochlear nucleus labeled two laminar plexuses in the IC: a 'medial' principal band, or bands, in the central nucleus and a shorter 'lateral' band. (Rat-Fig. 3; Cat- Fig. 4). In all experiments, the main central nucleus plexus exhibited a size and orientation that has been thoroughly described in earlier reports (e.g. Oliver and Morest, 1984,Shneiderman and Henkel, 1987,Schofield and Cant, 1996,Oliver et al., 1999,Malmierca et al., 2005) and will not be discussed further in this report.

In the example of the lateral band in the rat, TMR was deposited at the dorsal cochlear nucleus site where neurons had a BF of 30 kHz (Fig. 3A). BDA was deposited in the anteroventral

cochlear nucleus of the same rat at a site with a similar BF (31 kHz, Fig. 3B). Labeled axons and boutons arising from both injections are shown in the photomicrographs (Fig. 3C-D); labeled synaptic boutons are shown in the inset in Figure 3D. Contour plots of bouton fields in transverse sections of the IC are shown in Figure 3E. In Figure 3C and 3E, the arrow indicates a lateral band and the asterisk indicates a central nucleus band. The lateral bands were either oblique or perpendicular to the central nucleus bands (Fig 3E) and projected into the deep layer of the LC/ECIC.

In an example of the lateral band in the cat, TMR was deposited at a site in the dorsal cochlear nucleus with a BF of 4.5 kHz (Fig 4A,B). In some of the transverse sections through the IC (i.e. Fig. 4C, D, sections 198-216), afferents showed the same pattern as in the rat: a lateral band (arrow) oriented obliquely to the central nucleus bands (asterisk). The lateral band entered the LC. In some sections (198, 204), the lateral bands branch off from the central nucleus band at a ventral 'vertex' in other sections (210, 216), the bands are interrupted by the lemniscal afferents entering ventrally. As in the rat, terminal boutons are seen in both lateral and medial bands (Fig. 4C), although in the cat, the lateral bands are confined to the VLN and do not enter the more superficial layers of the LC.

Tonotopic Organization of Inputs to the LC

The preceding data show that, in both species, points in the cochlear nucleus target at least two areas of the IC: i) the central nucleus and ii) the deep lateral cortex, i.e. layer 3 of rat LC and the VLN of the cat LC. We now ask the question if the lateral afferent bands also maintain a tonotopic order in the LC.

Figure 5 shows the results of two different tracer injections in the dorsal cochlear nucleus of rat 00-231, with each deposit at a site with a different BF. BDA and TMR deposits were centered at sites with BFs of 6 kHz and 29 kHz, respectively. Focusing on the lateral bands, the 6 kHz band is located dorsomedially to the higher frequency 29 kHz band, which has a longer dorsal-ventral extent.

For comparison to the cat, we addressed the issue of tonotopy by combining data from previous experiments with injections at different BFs. Figure 6 presents data from tracer deposits made at dorsal cochlear nucleus sites with BFs of 5, 13, and 25 kHz in three different cats (Fig. 6A-C). The contours of the bouton fields in all three representative cases were superimposed onto sections at the same anatomical level (Fig. 6D). As in the rat, the higher BF bands were at a more ventral position in the LC than the lower frequency bands. Cytoarchitectonic analysis in adjacent Nissl-stained sections (not shown) indicated that the bulk of these inputs target the VLN, in the deep part of the LC.

DISCUSSION

In the present report, we compared the cytoarchitecture of the LC of the IC and its inputs from the cochlear nuclei in both rats and cats. In both species, LC has a superficial region rich with NADPH-d and a deeper region that contains both CO and NADPH-d. Distinct laminar inputs to the LC from the cochlear nuclei are arranged in a low- to high frequency progression from dorsal to ventral, and this organization is nearly perpendicular to the laminae of the central nucleus. In view of these similarities, we suggest the terms 'lateral cortex' and 'ventrolateral nucleus' be used with reference to the lateral IC in both species. The LC refers to the entire three-layered structure which borders the central nucleus laterally. The VLN refers to the third, deepest layer of the LC, which receives the second set of lemniscal inputs. We recommend that these terms supplant the terms external nucleus and external cortex of the IC, which are not as anatomically specific.

Basis for Homology

The homology of the VLN may be obscured by species differences in the gross morphology of the IC between cat and rat. Figure 7 is an attempt to clarify this homology diagrammatically. Here, we show a canonical transverse section of the rat IC (top) transformed into a canonical section of the cat IC (bottom). Since the low frequency (< 2 kHz) representation of the central nucleus is enlarged in the cat (Fig. 7, white line shows location of 2 kHz lamina), the dorsolateral part of the central nucleus of the cat is also enlarged (middle). This enlargement displaces the dorsal half of the VLN that is compressed ventrally. As a result, the cat VLN is proportionately smaller than that of the rat. Relatedly, the rat VLN borders the entire lateral margin of the central nucleus while the cat VLN borders only the ventrolateral margin. These differences, combined with a global rotation of the entire IC, accounts for the differing appearance of the VLN in the cat and rat IC. The broader implication is that the IC maintains the same general plan across species, but with variations in the relative proportions of its subdivisions. This is supported by recent studies of connectivity in the gerbil and guinea pig IC, which also identify a ventrolateral region with inputs from the cochlear nucleus (gerbil: Cant and Benson, 2006, guinea pig: Zhou and Shore, 2006).

Comparison to Earlier Studies

Table 1 contrasts the new terminology, proposed here, with earlier nomenclature. In the cat, the lateral nucleus corresponds to layers 1 and 2 of the LC. The present VLN includes the ‘ventrolateral’ nucleus in the Golgi-based parcellation of Morest and Oliver (1984,Oliver and Morest, 1984) and also overlaps a region previously described as the lateral part of the central nucleus, i.e. ‘pars lateralis’. Unlike VLN, pars lateralis extends to the border of the dorsal cortex; therefore only the ventral 2/3 of pars lateralis is considered to be part of VLN. The LC also likely corresponds to the ‘ICX’ in the Nissl-based scheme of Berman (1968).

In the rat, the external cortex of the IC (Faye-Lund and Osen, 1985, Malmierca et al., 1993) includes the LC, plus the rostral shell of the rat IC. Thus, the term LC is more specific as it refers to the lateral aspect only (Malmierca, 1991, Oliver et al., 1999). The rostral part of the external cortex (Faye-Lund and Osen, 1985) in both the rat and the cat may be described more precisely as the intercollicular tegmentum (Morest and Oliver, 1984) or rostral cortex (Malmierca, 1991) that fills the area between the rostral IC and the superior colliculus. The third, deepest layer of the LC/ECIC corresponds to the VLN. It is noteworthy that Faye-Lund and Osen (1985) suspected that their delineation of the rat ‘external cortex’ included ‘pars lateralis’ and the ‘ventrolateral nucleus’ in the earlier cat parcellation (Morest and Oliver, 1984, Oliver and Morest, 1984). The present parcellation, for the most part, confirms this suspicion with the caveat that the dorsal part of ‘pars lateralis’ belongs to the low frequency region of the cat central nucleus.

The tonotopic organization of VLN afferents described here may underlie some aspects of frequency sensitivity in the lateral IC found in earlier studies. Schreiner and Langner (1988) reconstructed isofrequency contours in the IC of the cat, which had a shorter lateral limb oriented nearly orthogonally to the longer medial limb. The lateral limb extended into pars lateralis, which we believe corresponds to the area here called the VLN, and exhibited a similar low to high frequency gradient along the dorsal-ventral axis. This pattern is also consistent with a reversal in BF near the border of VLN and central nucleus, found by Roth et al. (1978) in a microelectrode mapping study of cat IC. Similar frequency reversals have been found in rodents by mapping the stimulus-induced expression of c-fos mRNA (Saint Marie et al., 1999).

The intrinsic connections of the IC in both rat and cat are consistent with our proposed parcellation. In the rat, single injections of the anterograde tracer PHA-L in the CNIC creates

two bands of labeled fibers in the injected IC: a main band in the CNIC and a lateral band in the LC (Saldañntilde;a and Merchaán, 1992). The spatial relationship of these intrinsic connections is similar to the medial and lateral bands of afferents described here. Moreover, the intrinsic connections in the LC mirror the afferent pattern of tonotopy observed here, i.e. injections at progressively higher frequency locations in the CNIC label bands at progressively more ventrolateral locations in the LC (compare present Fig. 5 with Fig. 7E in Saldañ and Merchaán, 1992). In the cat, BDA injections in the CNIC also label two sets of intrinsic connections which appear consistent with the input pattern shown here (Fig. 3 in Malmierca et al., 1998, Fig. 4 in Bajo et al., 1999).

The present results shed some light on the broader frequency tuning in the LC, in comparison to the central nucleus of the IC (Aitkin et al., 1975, Ota et al., 2004). The packing of afferents of different BF is tighter in the lateral cortex than in the central nucleus. For example, in Figure 5, the width between the centers of the 5 and 13 kHz afferent bands is about 60% smaller in the cat VLN than in the central nucleus. A similar ratio was found for the rat (Fig. 5). Thus, postsynaptic neurons in the LC might be more likely to receive convergent input from axons arising from adjacent laminae (Morest and Oliver, 1984). In addition, the dendritic branches of VLN neurons are less oriented than those in the central nucleus (Malmierca, 1991, Oliver et al., 1991), which would also facilitate integration across laminae, i.e. across frequency integration.

Functional Implications

Although the functions of the VLN and LC are not known, they likely play a role in multisensory integration, distinct from the ‘classical’ auditory role of the central nucleus. The VLN receives somatosensory input from spinal cord, dorsal column nuclei, and spinal trigeminal nuclei in the cat (Aitkin et al., 1978, Aitkin et al., 1981, Morest and Oliver, 1984), rat (Coleman and Clerici, 1987), opossum (Robards, 1979), monkey (Wiberg et al., 1987), and guinea pig (Jain and Shore, 2005, Zhou and Shore, 2006). Neurons in the LC appear to have relatively broad somatosensory receptive fields in addition to auditory responses, which are also broadly tuned (Aitkin et al., 1978). The somatosensory inputs may suppress responses to sound, rather than providing excitatory drive (Aitkin et al., 1978, Jain and Shore, 2005). The multisensory integration in the LC mirrors similar types of function at higher levels of the ‘extralemniscal’ auditory pathway. The LC projects to the medial division of the medial geniculate body (Calford and Aitkin, 1983), which also receives direct projections from the cochlear nucleus and inputs from the spinal cord and superior colliculus (Malmierca et al., 2002, Anderson et al., 2006). The medial division of the medial geniculate body is implicated as a modulatory input to auditory and somatosensory cortex and as a part of the network for auditory fear conditioning (LeDoux et al., 1985, Edeline and Weinberger, 1992).

A second role of the LC may be to provide auditory input to visual-motor areas that direct head and eye movements involved in gaze initiation. The VLN receives binaural inputs from the superior olivary complex (Shneiderman and Henkel, 1987, Loftus et al., 2004a) that convey information about the location of a sound source in space. Azimuthal sound location appears to be represented in the LC along the rostral-caudal axis in guinea pig (Binns et al., 1992). Both the LC and the nucleus of the brachium of the IC, the rostrally adjacent structure, project to the deep layers of the superior colliculus (Schnupp and King, 1997, King et al., 1998), which contains a map of auditory and visual space (Palmer and King, 1982). Thus, the LC may be a major source of binaural cues for gaze control in the superior colliculus.

Finally, the LC may have a unique influence on the olivocochlear system. Recent studies show that electrical stimulation of LC has a broadly tuned effect on cochlear responses, in contrast to central nucleus stimulation which has sharply tuned effects (Ota et al., 2004). LC stimulation also has long lasting enhancements or suppression of cochlear neural responses to sound stimuli

(Groff and Liberman, 2003) without changes in cochlear responses dominated by outer hair cells. These effects are likely due to activation of the lateral olivocochlear bundle. Thus, the medial and lateral olivocochlear bundles may be differentially activated by central nucleus and LC, respectively.

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LIST OF ABBREVIATIONS

BDA, biotinylated dextran amine
BF, best frequency
cic, commissure of the IC
CNIC, central nucleus of the IC
CO, cytochrome oxidase
DC, dorsal cortex of the IC
dnll, dorsal nucleus of the lateral lemniscus
ECIC, external cortex of the IC
FD, fluorescein dextran
IC, inferior colliculus
ICX, external cortex of the IC
LC, lateral cortex of the IC
LN, lateral nucleus
NADPH-d, nicotinamide adenine dinucleotide phosphate-diaphorase
pag, periaqueductal grey
TMR, tetramethylrhodamine dextran
VLN, ventrolateral nucleus

REFERENCES

Adams JC. Ascending projections to the inferior colliculus. J Comp Neurol 1979;183:519–538. [PubMed: 759446]

Aitkin LM, Dickhaus H, Schult W, Zimmermann M. External nucleus of inferior colliculus: auditory and spinal somatosensory afferents and their interactions. J Neurophysiol 1978;41:837–847. [PubMed: 681989]

Aitkin LM, Kenyon CE, Philpott P. The representation of the auditory and somatosensory systems in the external nucleus of the cat inferior colliculus. J Comp Neurol 1981;196:25–40. [PubMed: 7204665]

Aitkin LM, Webster WR, Veale JL, Crosby DC. Inferior colliculus. I. Comparison of response properties of neurons in central, pericentral, and external nuclei of adult cat. J Neurophysiol 1975;38:1196–1207. [PubMed: 1177012]

Anderson LA, Malmierca MS, Wallace MN, Palmer AR. Evidence for a direct, short latency projection from the dorsal cochlear nucleus to the auditory thalamus in the guinea pig. Eur J Neurosci 2006;24:491–498. [PubMed: 16836634]

Bajo VM, Merchan MA, Malmierca MS, Nodal FR, Bjaalie JG. Topographic organization of the dorsal nucleus of the lateral lemniscus in the cat. J Comp Neurol 1999;407:349–366. [PubMed: 10320216]

Berman, AL. The brain stem of the cat: A cytoarchitectonic atlas with stereotaxic coordinates. Univ. Wisconsin Press; Madison, Milwaukee, and London: 1968.

Binns KE, Grant S, Withington DJ, Keating MJ. A topographic representation of auditory space in the external nucleus of the inferior colliculus of the guinea-pig. Brain Res 1992;589:231–242. [PubMed: 1393591]

Brunso-Bechtold JK, Thompson GC, Masterton RB. HRP study of the organization of auditory afferents ascending to central nucleus of inferior colliculus in cat. J Comp Neurol 1981;197:705–722. [PubMed: 7229134]

Calford MB, Aitkin LM. Ascending projections to the medial geniculate body of the cat: evidence for multiple, parallel auditory pathways through thalamus. J Neurosci 1983;3:2365–2380. [PubMed: 6313877]

Cant NB, Benson CG. Parallel auditory pathways: projection patterns of the different neuronal populations in the dorsal and ventral cochlear nuclei. Brain Res Bull 2003;60:457–474. [PubMed: 12787867]

Cant NB, Benson CG. An atlas of the inferior colliculus of the gerbil in three dimensions. Hear Res 2005;206:12–27. [PubMed: 16080995]

Cant NB, Benson CG. Organization of the inferior colliculus of the gerbil (Meriones unguiculatus): differences in distribution of projections from the cochlear nuclei and the superior olivary complex. J Comp Neurol 2006;495:511–528. [PubMed: 16498677]

Chernock ML, Larue DT, Winer JA. A periodic network of neurochemical modules in the inferior colliculus. Hear Res 2004;188:12–20. [PubMed: 14759566]

Coleman JR, Clerici WJ. Sources of projections to subdivisions of the inferior colliculus in the rat. J Comp Neurol 1987;262:215–226. [PubMed: 3624552]

Druga R, Syka J. NADPH-diaphorase activity in the central auditory structures of the rat. Neuroreport 1993;4:999–1002. [PubMed: 8241467]

Edeline JM, Weinberger NM. Associative retuning in the thalamic source of input to the amygdala and auditory cortex: receptive field plasticity in the medial division of the medial geniculate body. Behav Neurosci 1992;106:81–105. [PubMed: 1554440]

Faye-Lund H, Osen KK. Anatomy of the inferior colliculus in rat. Anat Embryol 1985;171:1–20. [PubMed: 3985354]

Feldman SG, Kruger L. An axonal transport study of the ascending projection of medial lemniscal neurons in the rat. J Comp Neurol 1980;192:427–454. [PubMed: 6158530]

Groff JA, Liberman MC. Modulation of cochlear afferent response by the lateral olivocochlear system: activation via electrical stimulation of the inferior colliculus. J Neurophysiol 2003;90:3178–3200. [PubMed: 14615429]

Jain R, Shore S. External inferior colliculus integrates trigeminal and acoustic information: Unit responses to trigeminal nucleus and acoustic stimulation in the guinea pig. Neurosci Lett. 2005

King AJ, Jiang ZD, Moore DR. Auditory brainstem projections to the ferret superior colliculus: anatomical contribution to the neural coding of sound azimuth. J Comp Neurol 390:342–365. [PubMed: 9455897]

LeDoux JE, Ruggiero DA, Reis DJ. Projections to the subcortical forebrain from anatomically defined regions of the medial geniculate body in the rat. J Comp Neurol 1985;242:182–213. [PubMed: 4086664]

Loftus WC, Bishop DC, Saint Marie RL, Oliver DL. Organization of binaural excitatory and inhibitory inputs to the inferior colliculus from the superior olive. J Comp Neurol 2004a;472:330–344. [PubMed: 15065128]

Loftus WC, Malmierca MS, Bishop DC, Oliver DL. Ascending Inputs to the Lateral Cortex of the Inferior Colliculus (IC) in Rat and Cat. ARO Abstracts Abstract 2004b:1115.

Malmierca, MS. Computer-Assisted 3-D Reconstructions of Golgi Impregnated Cells in the Rat Inferior Colliculus (Doctoral Thesis). Anatomical Institute, University of Oslo; Oslo: 1991.

Malmierca MS, Blackstad TW, Osen KK, Karagulle T, Molowny RL. The central nucleus of the inferior colliculus in rat: a Golgi and computer reconstruction study of neuronal and laminar structure. J Comp Neurol 1993;333:1–27. [PubMed: 7688006]

Malmierca MS, Leergaard TB, Bajo VM, Bjaalie JG, Merchan MA. Anatomic evidence of a three-dimensional mosaic pattern of tonotopic organization in the ventral complex of the lateral lemniscus in cat. J Neurosci 1998;18:10603–10618. [PubMed: 9852596]

Malmierca MS, Merchan MA, Henkel CK, Oliver DL. Direct projections from cochlear nuclear complex to auditory thalamus in the rat. J Neurosci 2002;22:10891–10897. [PubMed: 12486183]

Malmierca MS, Saint Marie RL, Merchan MA, Oliver DL. Laminar inputs from dorsal cochlear nucleus and ventral cochlear nucleus to the central nucleus of the inferior colliculus: Two patterns of convergence. Neuroscience 2005;136:883–894. [PubMed: 16344158]

Morest DK, Oliver DL. The neuronal architecture of the inferior colliculus in the cat: Defining the functional anatomy of the auditory midbrain. J Comp Neurol 1984;222:209–236. [PubMed: 6699208]

Oliver DL, Beckius GE, Bishop DC, Kuwada S. Simultaneous anterograde labeling of axonal layers from lateral superior olive and dorsal cochlear nucleus in the inferior colliculus of cat. J Comp Neurol 1997;382:215–229. [PubMed: 9183690]

Oliver DL, Beckius GE, Bishop DC, Loftus WC, Batra R. Topography of interaural temporal disparity coding in projections of medial superior olive to inferior colliculus. J Neurosci 2003;23:7438–7449. [PubMed: 12917380]

Oliver DL, Beckius GE, Shneiderman A. Axonal projections from the lateral and medial superior olive to the inferior colliculus of the cat: a study using electron microscopic autoradiography. J Comp Neurol 1995;360:17–32. [PubMed: 7499562]

Oliver DL, Kuwada S, Yin TC, Haberly LB, Henkel CK. Dendritic and axonal morphology of HRP-injected neurons in the inferior colliculus of the cat. J Comp Neurol 1991;303:75–100. [PubMed: 2005240]

Oliver DL, Morest DK. The central nucleus of the inferior colliculus in the cat. J Comp Neurol 1984;222:237–264. [PubMed: 6699209]

Oliver DL, Ostapoff EM, Beckius GE. Direct innervation of identified tectothalamic neurons in the inferior colliculus by axons from the cochlear nucleus. Neuroscience 1999;93:643–658. [PubMed: 10465448]

Ota Y, Oliver DL, Dolan DF. Frequency-specific effects on cochlear responses during activation of the inferior colliculus in the Guinea pig. J Neurophysiol 2004;91:2185–2193. [PubMed: 14702337]

Palmer AR, King AJ. The representation of auditory space in the mammalian superior colliculus. Nature 1982;299:248–249. [PubMed: 7110344]

Paxinos, G.; Watson, C. The rat brain in stereotaxic coordinates. Academic Press; San Diego and London: 1998.

Robards MJ. Somatic neurons in the brainstem and neocortex projecting to the external nucleus of the inferior colliculus: an anatomical study in the opossum. J Comp Neurol 1979;184:547–565. [PubMed: 422756]

Roth GL, Aitkin LM, Andersen RA, Merzenich MM. Some features of the spatial organization of the central nucleus of the inferior colliculus of the cat. J Comp Neurol 1978;182:661–680. [PubMed: 721973]

Saint Marie RL, Luo L, Ryan AF. Effects of stimulus frequency and intensity on c-fos mRNA expression in the adult rat auditory brainstem. J Comp Neurol 1999;404:258–270. [PubMed: 9934998]

Saldañ E, Merchán MA. Intrinsic and commissural connections of the rat inferior colliculus. J Comp Neurol 1992;319:417–437. [PubMed: 1376335]

Schnupp JW, King AJ. Coding for auditory space in the nucleus of the brachium of the inferior colliculus in the ferret. J Neurophysiol 1997;78:2717–2731. [PubMed: 9356421]

Schofield BR, Cant NB. Organization of the superior olivary complex in the guinea pig: II. Patterns of projection from the periolivary nuclei to the inferior colliculus. J Comp Neurol 1992;317:438–455. [PubMed: 1578006]

Schofield BR, Cant NB. Projections from the ventral cochlear nucleus to the inferior colliculus and the contralateral cochlear nucleus in guinea pigs. Hear Res 1996;102:1–14. [PubMed: 8951445]

Schreiner CE, Langner G. Periodicity coding in the inferior colliculus of the cat. II. Topographical organization. J Neurophysiol 1988;60:1823–1840. [PubMed: 3236053]

Shneiderman A, Henkel CK. Banding of lateral superior olivary nucleus afferents in the inferior colliculus: a possible substrate for sensory integration. J Comp Neurol 1987;266:519–534. [PubMed: 2449472]

Shneiderman A, Oliver DL, Henkel CK. Connections of the dorsal nucleus of the lateral lemniscus: an inhibitory parallel pathway in the ascending auditory system? J Comp Neurol 1988;276:188–208. [PubMed: 3220980]

Wiberg M, Westman J, Blomqvist A. Somatosensory projection to the mesencephalon: an anatomical study in the monkey. J Comp Neurol 1987;264:92–117. [PubMed: 2445793]

Zhou J, Shore S. Convergence of spinal trigeminal and cochlear nucleus projections in the inferior colliculus of the guinea pig. J Comp Neurol 2006;495:100–112. [PubMed: 16432905]

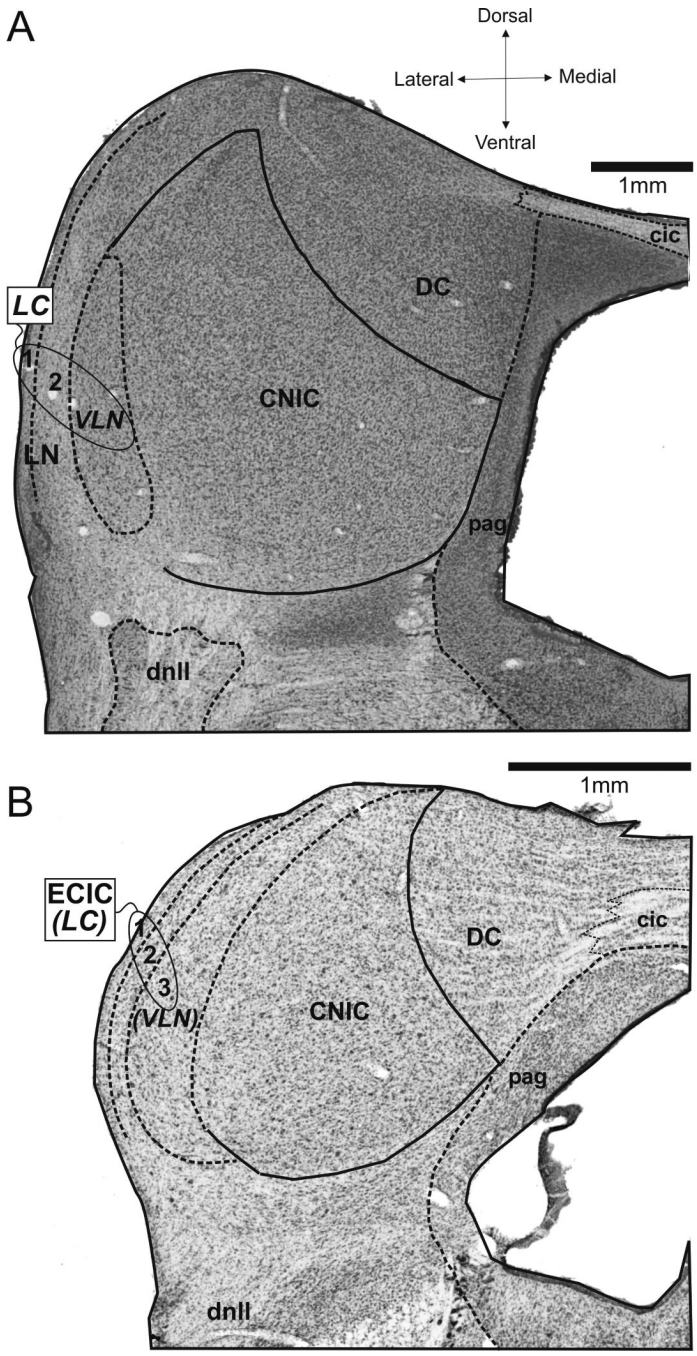

Figure 1.

Nissl-stained transverse sections through the IC of cat (*A*) and rat (*B*) with the major subdivisions labeled. Italicized labels (*LC* and *VLN*) indicate the new terminology introduced in this manuscript. The cat LC contains the two layers of the lateral nucleus (LN) plus the deeper ventrolateral nucleus (*VLN*). In rats, the LC corresponds to the lateral portion of external cortex (ECIC) in the classic parcellation (Faye-Lund and Osen, 1985, modified by Saldañ and Merchaán, 1992).

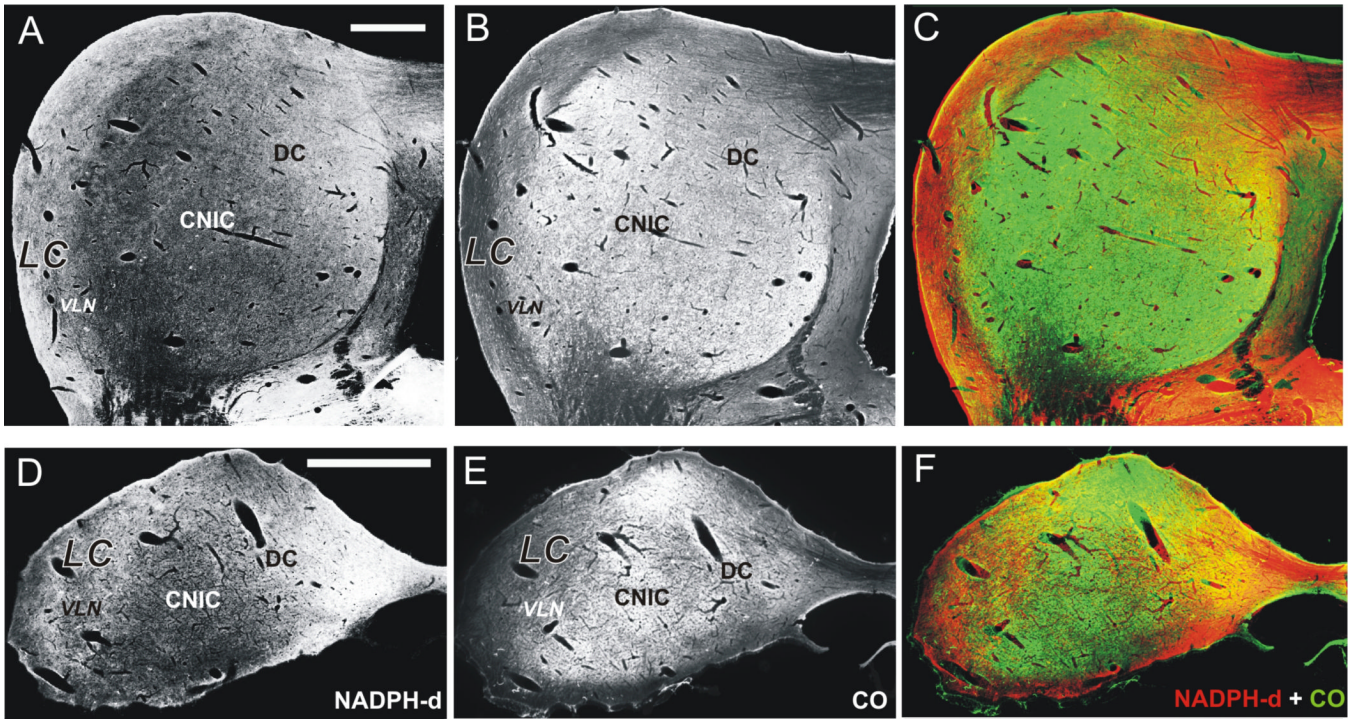

Figure 2.

NADPH-d and cytochrome oxidase (CO) staining in the IC of cat (*A-C*) and rat (*D-F*). A&D: NADPH-d stained transverse section through the IC. B&E: CO stained section through the same IC in each species. The gray scales have been inverted so that areas with more intense staining appear lighter. C&F: Pseudo- color image formed by merging the NADPH-d (*red*) and CO (*green*) images.

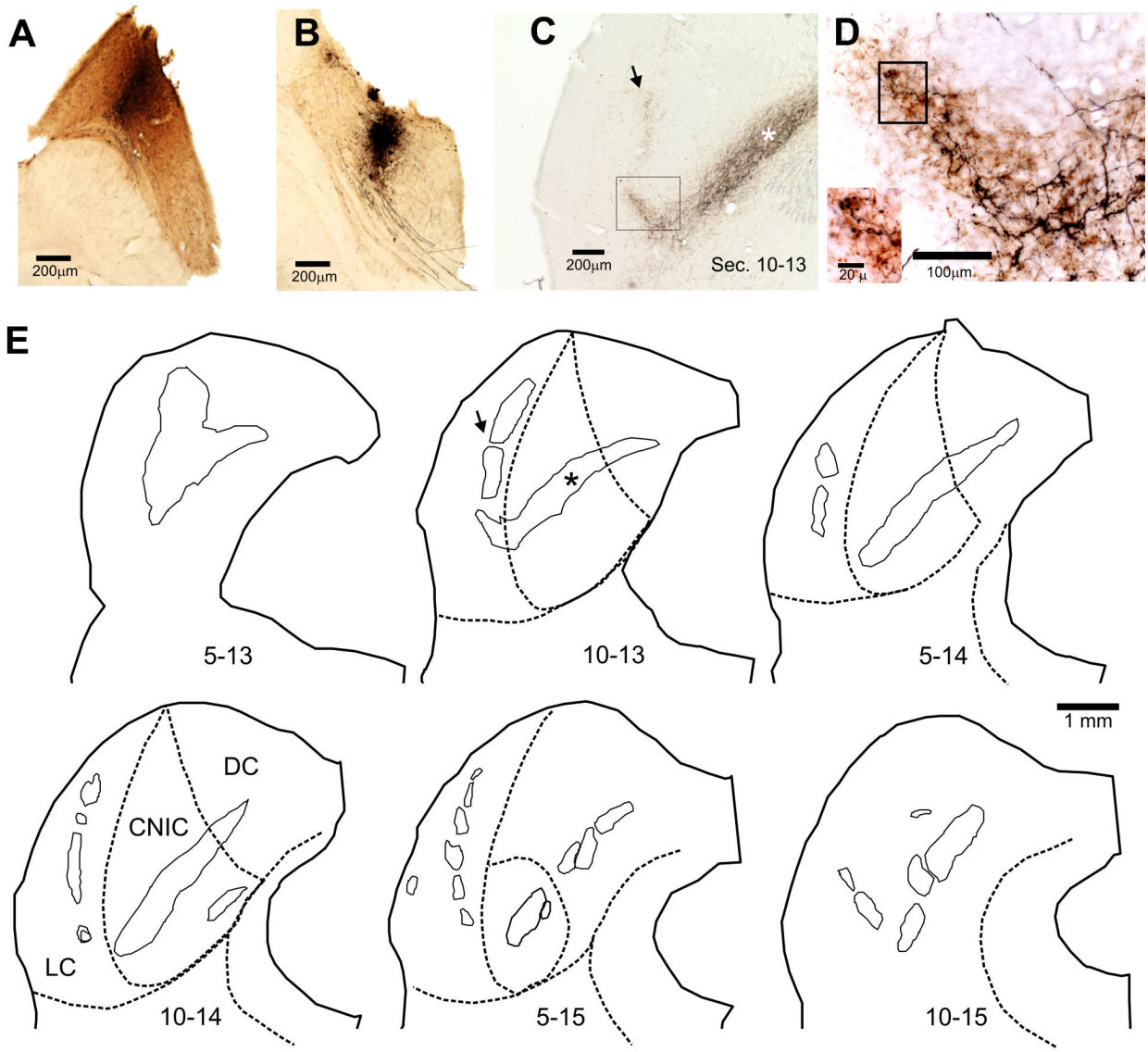

Figure 3.

Cochlear nucleus projection to the Lateral Cortex in Rat.

A: Photomicrograph of TMR injection in the right dorsal cochlear nucleus of rat # 00-122. The BF at the center of the injection site was 30 kHz. B: BDA injection in the right anteroventral cochlear nucleus of the same animal. The BF at the injection site was 31 kHz. C: Transverse section through the left IC of the same animal, showing bands of labeled afferent fibers in the CNIC and the deep LC. The *arrow* and *asterisk* indicate lateral and central nucleus bands of afferents, respectively. The boxed area over the LC is shown at higher magnification in D: TMR- and BDA-labeled fibers appear as red and black. The boxed area is shown at higher magnification in the lower left, revealing labeled boutons. E: Contour plots of bouton fields in transverse sections of the left IC of the same animal, from caudal (upper left) to rostral (lower right). Section 10-13 corresponds to the section illustrated in C and D.

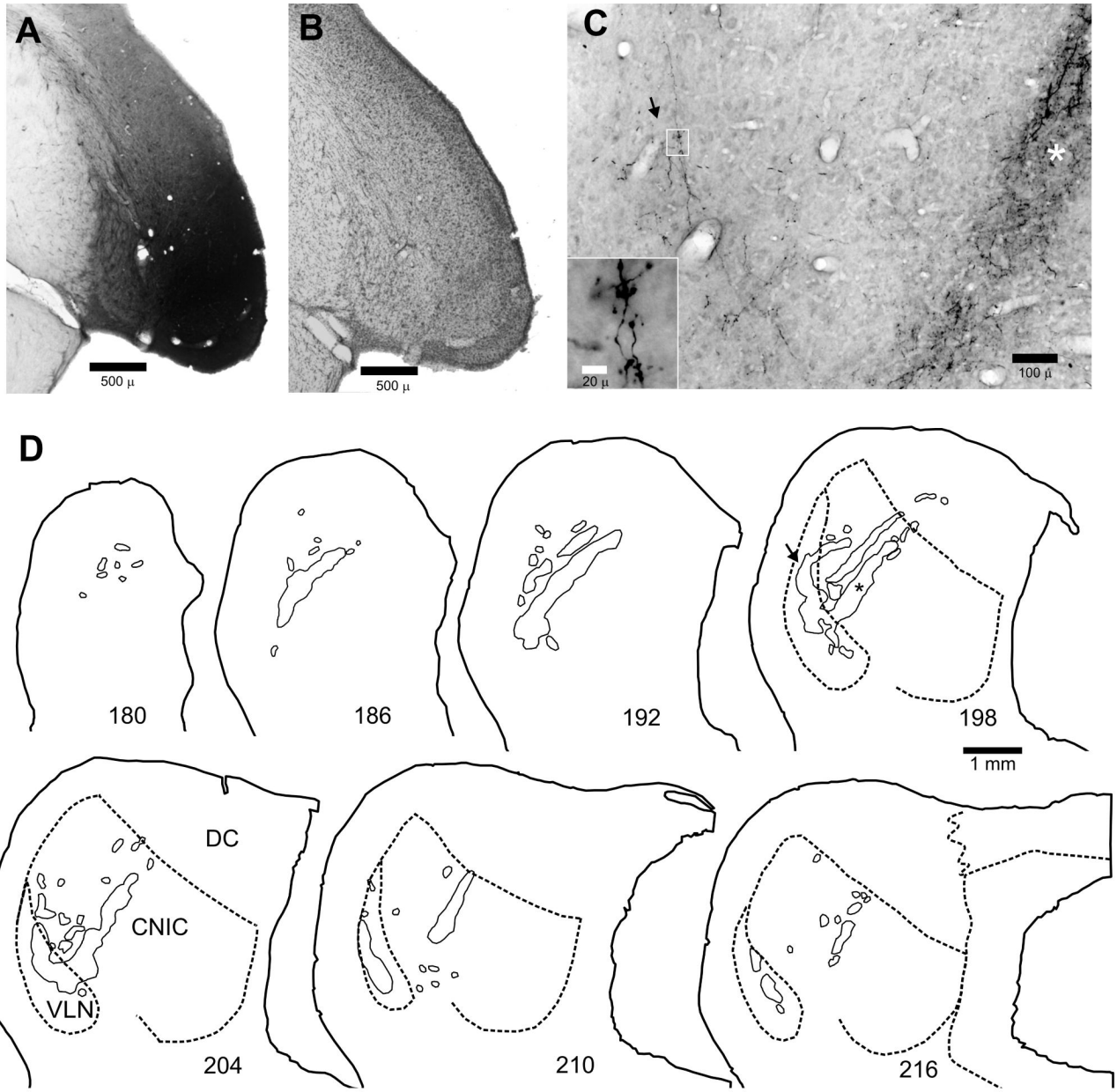

Figure 4.

Dorsal cochlear nucleus projection to the Lateral Cortex in Cat.

A: Photomicrograph of TMR injection in the right dorsal cochlear nucleus of cat # 99-19. B: The adjacent Nissl-stained section. C: Transverse section through the left IC of the same animal, showing bands of labeled afferent fibers in the CNIC and the VLN in the deep lateral cortex. The boxed area is shown at higher magnification in the lower left. D. Contour plots of bouton fields in the IC of the same animal. Conventions are as in figure 2E. Section 198 corresponds to the section illustrated in C.

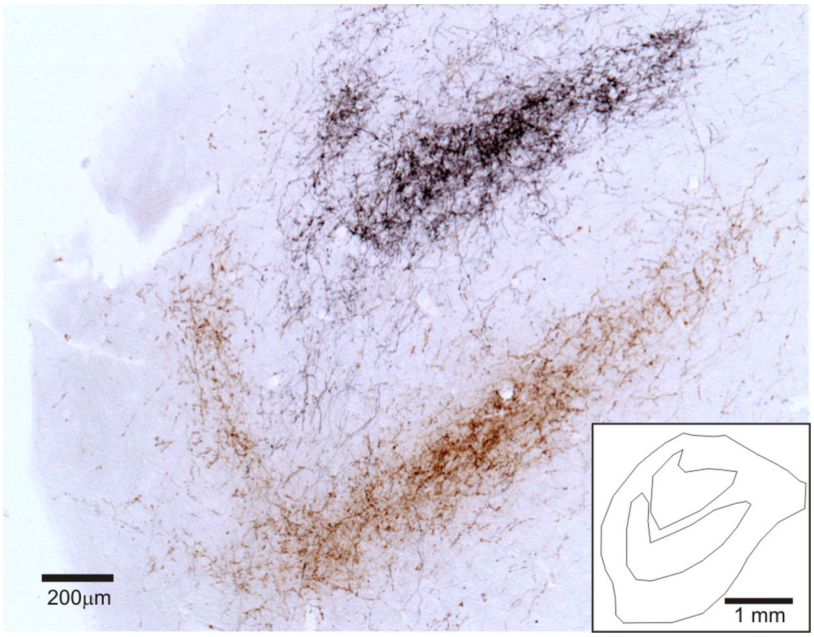

Figure 5.

Tonotopic organization of inputs to the Lateral Cortex in Rat.

Photomicrograph of a transverse section through the left IC of the same animal, showing bands of BDA labeled (*black*) and TMR labeled (*red*) fibers. The TMR was deposited at a site with a BF of 29 kHz; the BDA was deposited at a site with a BF of 6 kHz. *Inset*: Contour plots of the terminal bouton fields from the same section.

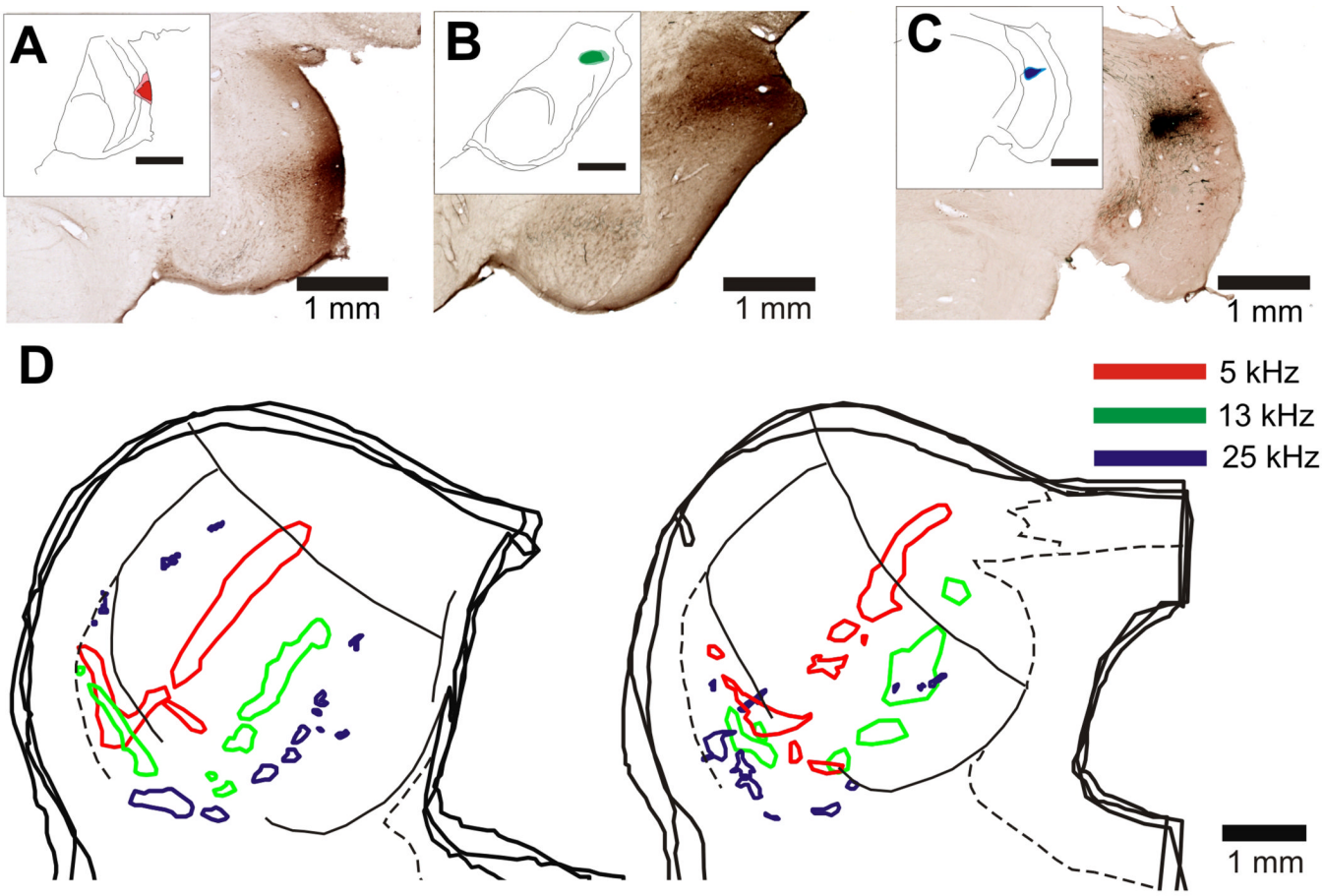

Figure 6.
Tonotopic organization of inputs to the Lateral Cortex in Cat.
Top: Photomicrographs and plots of injections in the right dorsal cochlear nucleus of three different cats, at sites with BFs of 5 kHz (A), 13 kHz (B), and 25 kHz (C). D: Contour plots of bouton fields in the IC of the same three cat, at similar rostrocaudal levels, shown superimposed on the same transverse section (left: rostral; right: caudal). Colors of the contour plots indicate the BF of the injection site, as indicated by the legend. Note that the injection in the 25 kHz case (*blue*) also labeled a sparser band in the more dorsoventral, lower frequency area of the central nucleus.

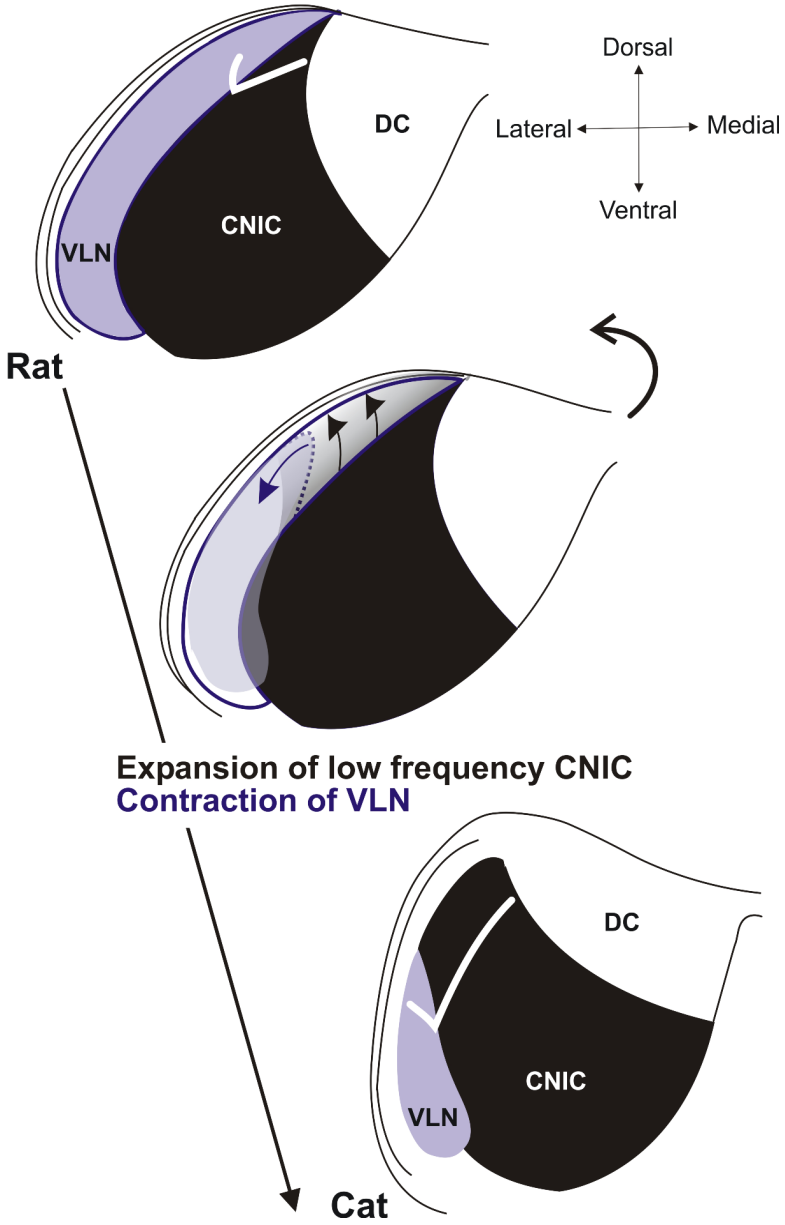

Figure 7.

The homology of the VLN in cat and rat, illustrated as a transformation of the rat IC (top) into the cat IC (bottom). The white contours in the CNIC and VLN indicate a frequency-specific laminated projection. The middle diagram shows the addition of lower frequency sensitivity to the dorsolateral aspect of the CNIC. This enlargement encroaches on the space occupied by the dorsal VLN, pushing it ventrally. Drawings are not to scale.

Table 1

Correspondence of the terms ‘VLN’ and ‘LC’ with earlier parcellations of the IC in rat and cat.

	Cat (Morest and Oliver, 1984)	***Rat (Faye-Lund and Osen, 1985, Paxinos and Watson, 1998)***
VLN	Ventral ~2/3 of pars lateralis + ‘ventrolateral’ nucleus	Third, deepest layer of the external cortex (lateral aspect)
LC	Lateral Nucleus + ventral ~2/3 of pars lateralis + ‘ventrolateral’ nucleus	External cortex (lateral aspect)