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The Inferior Colliculus: A Center for Convergence of Ascending and Descending Auditory Information

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Key Words
Auditory midbrain · Hearing · Inferior colliculus · Laminar organization · Tonotopic organization

Abstract
A major goal in auditory research is to understand completely how we hear, the physiology of the human auditory system and to identify the causes and treatments for hearing impairment. By understanding all the elements of the 'auditory scaffold' we will begin to achieve these important goals. The inferior colliculus (IC) occupies a strategic position in the central auditory system and may be considered a central hub or an interface between the lower auditory pathway, the auditory cortex and motor systems. The IC is the site for termination of the ascending fibers of the lateral lemniscus and also receives a heavy innervation from the auditory cortex. Furthermore, the IC receives crossed projections from its counterpart and possesses a dense network of local connections. Thus, the IC is the main site of auditory integration at the midbrain level. Anatomical and physiological experiments demonstrate that the IC is involved in a great diversity of functional roles in the auditory system, and that most of the interesting auditory features might already be extracted from incoming sounds by this midbrain nucleus.

Introduction

A basic role of the auditory system in all mammals is to identify sounds, selectively activate neural systems that focus attention to sounds, and generate suitable motor responses. In the first auditory relay center in the brain, the cochlear nuclear complex, information carried by the fibers of the cochlear nerve is conveyed to a number of different neuronal populations that, in turn, give rise to a number of parallel ascending pathways that project to a variety of brainstem targets. Projections from these targets as well as direct projections from the cochlear nuclei ultimately converge on the auditory midbrain, the inferior colliculus (IC) [1–6]. In contrast to the role of the superior colliculus within the visual system, the IC is the principal source of input to the auditory thalamus [7]. The IC probably also represents a major output to premotor pathways that initiate or regulate sound-evoked motor behavior [2].

Whereas most sensory systems have only two relay stations between the periphery and cerebral cortex, there is a minimum of three relays in the auditory system with several stages of convergence and divergence and at least seven levels of crossings from one side to the other [7]. Thus, the auditory system is unique among sensory systems with its highly complex network of pathways in the

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lower brainstem and a significant amount of processing accomplished in the IC, prior to the level of the thalamus. An important question is why an obligatory relay exists in the auditory midbrain. One intriguing explanation is that divergence at the early stages of auditory processing results in several distinct acoustic maps in the brainstem. The midbrain relay is required to enable their fusion into a single, integrated map at the level of the IC prior to relay to higher centers and for descending modulation from the neocortex.

The IC is not only the main site of termination of the ascending fibers of the lateral lemniscus but also receives a heavy innervation from the auditory cortex (AC) [8]. Furthermore, the IC receives crossed projections from the contralateral IC [9] and possesses a dense network of intrinsic connections [9–12]. Thus, the IC occupies a strategic position in the central auditory system and may be considered an interface between the lower auditory pathway and the AC and motor systems [2]. In this review, our current understanding of the structure and function of the mammalian IC will be discussed.

A General View of the Anatomy of the IC

The IC is visible on the dorsal surface of the midbrain immediately caudal to the superior colliculus. In the cat, it is nearly spherical while it is ellipsoid in the rat. The IC was originally subdivided using classical neuroanatomical methods. Ramón y Cajal [13, 14] identified three main subdivisions in Golgi-impregnated material in a variety of mammals: *the nucleus, the internuclear cortex and the lateral cortex*. This simple parcellation (fig. 1) has been preserved in studies for the past 25 years with some minor modifications [9, 10, 15–18]. Thus, the IC is made of a central nucleus (CNIC), a laterally and rostrally placed external cortex (ECIC) and a dorsal cortex (DCIC) that covers the CNIC dorsally and caudally. The lateral and rostral parts of the ECIC contain several distinct cell types and, for this reason, Malmierca [10] defined them as two separate cortices, the lateral cortex of the IC (LCIC, cf. [3, 19]) and the rostral cortex of the IC (RCIC, also referred to as the intercollicular zone, cf. [20]). Molecular mapping techniques based on calcium-binding proteins also distinguish the CNIC from the cortices. Thus, parvalbumin has a higher concentration in the CNIC while calbindin and calretinin show a higher concentration in the DCIC [reviewed in ref. 21]. The metabolic marker cytochrome oxidase also delineates the CNIC [reviewed in ref. 18, 21].

In the rat, the ECIC appears to occupy a relatively larger proportion of the IC than in the cat [16, 17, 19]. In the mustache bat, the 'dorsoposterior division' of the CNIC has an expanded representation for the high tonal frequencies used for echolocation [22].

The CNIC is defined by the presence of *laminae* (fig. 2), distinguishable in Golgi material as a parallel orientation of afferent lemniscal fibers and neurons with flattened dendritic arbors, usually referred to as 'fibrodendritic laminae' [23]. The characteristic laminar organization of the CNIC has been observed in all species studied so far [21]. The laminar organization of the CNIC constitutes the structural basis for its tonotopic map [24–26].

Neuron Types of the IC Subdivisions

The Central Nucleus

The CNIC possesses two main types of neurons that were first defined in the cat as disk-shaped and stellate neurons, which have flattened dendritic arbors and dendritic arbors that often transverse the laminae, respectively [12, 27]. In the rat, corresponding types have been referred to as flat (F) and less flat (LF) neurons using computer-assisted 3D reconstructions of Golgi-impregnated material [17] (fig. 1, 2). The F neurons clearly conform to the definition of disk-shaped neurons described in the cat [27], but the correspondence between the LF and stellate is less clear.

F and LF neurons (fig. 2) differ in dendritic arbor thickness, dendritic branching pattern, location and orientation with regard to the laminae. The thickness of the dendritic arbor of the F neurons is 50 μm while that of LF neurons is 100 μm, with the latter being less dense and branched than the former. The dendritic arbors of most F and LF neurons are elongated and located in parallel with the ventrolaterally to dorsomedially oriented long axis of the laminae. The F neurons are strictly parallel and form laminae mostly one cell thick (~40–70 μm) [16]. The LF neurons lie roughly parallel to the F neurons [17] and populate interlaminar compartments that separate the laminae defined by the F neurons. The orientation of the F neurons (i.e. laminae) is almost horizontal in the dorsolateral part of the nucleus, but a gradual shift takes place so that they become more vertical in the medial part [17]. Similarly, a gradient in cell size and packing density of cell bodies as seen in Nissl-stained sections also prevails with the smallest cell bodies and highest packing density in the dorsolateral (low frequency) area (fig. 3G from Faye-Lund and Osen [16]).

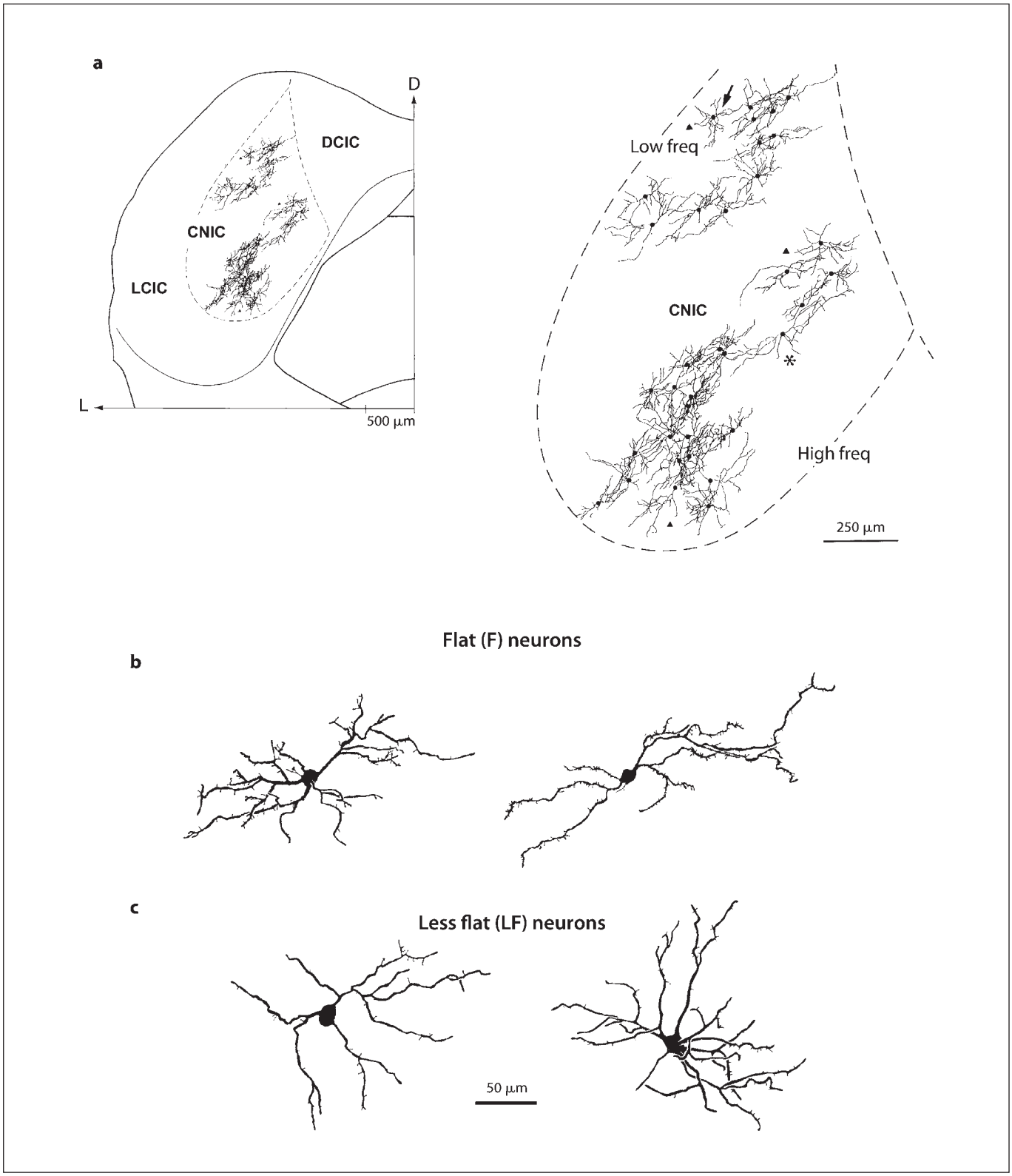

Fig. 1. a Computer-assisted 3D reconstruction of 35 neurons from the low- and high-frequency regions of the CNIC maintaining their mutual relationship. Camera lucida drawings of two F (**b**) and LF neurons (**c**). Redrawn from Malmierca et al. [65].

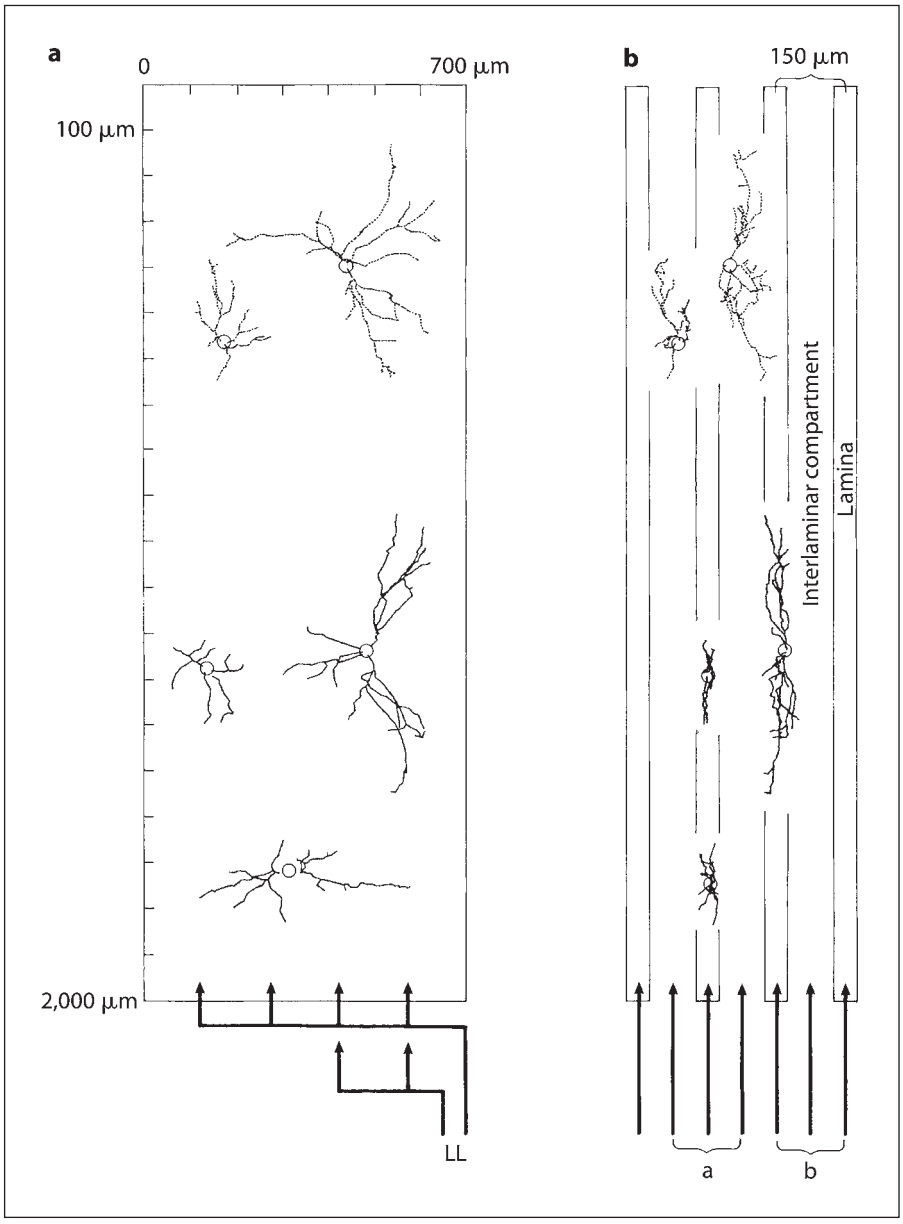

Fig. 2. Diagram of the laminar and interlaminar compartments of the CNIC seen *en face* (**a**) and *on edge* (**b**). Redrawn from Malmierca et al. [65].

Thus far, I have described the neuronal types in the IC based primarily on their dendritic morphology, as F and LF. However, this dual classification does not correlate entirely with some of the functional properties observed [21]. IC neurons also vary in their neurochemistry, projections and their electrophysiological properties. The neurochemistry of the F and LF neurons has been studied in the rat [28] and cat [29]. In the cat, about 20% of the cells are γ-aminobutyric acid (GABA)ergic while in rat the proportion may be slightly larger (up to 25%) according to Merchán et al. [28]. It seems that GABAergic cells may have either F or LF morphology [28]. In a recent study using whole-cell patch-clamp techniques in CNIC neurons in brain slices of rats, Sivaramakrishnan and Oliver [30] have characterized the potassium currents present and correlated them with the firing patterns observed by Peruzzi et al. [31]. Their study demonstrated the presence of six distinct physiological cell types: sustained regular, onset, pause build, rebound regular, rebound adapting and rebound transient. Each of these six

types possesses a firing pattern caused by unique potassium currents and a set of other parameters (fig. 3). Because of differences in ionic currents, some neurons in the CNIC are likely to integrate their temporal and intensity inputs while others may act as simple relays. There is apparently no simple correlation between the anatomy and physiology of the F and LF cells [31]. Thus, while the F and LF morphology is clearly related to the maintenance of tonotopic organization, there may be several types of F and LF cells with complex functional roles.

The Lateral Cortex

The definition of the LCIC varies among species and the homology in rat and cat is just beginning to be clear [19]. Three layers are defined in the lateral part [10, 16]. Layer 1 is a continuation of the fibrodendritic capsule of the DCIC. Layer 2 is composed of small and medium-sized neurons, partly aggregated in dense clusters in myelin-rich neuropil. The aggregates are also rich in parvalbumin, cytochrome oxidase, nicotinamide adenine dinucleotide phosphate-diaphorase, and acetylcholinesterase, but they are immunonegative for glycine, calbindin, serotonin and choline acetyltransferase [32, 33]. Ascending auditory input to layer 2 is sparse, but the dorsal column nuclei and spinal trigeminal nucleus provide it with primary ascending sensory input. Therefore, the external cortex could participate in spatial orientation and somatic motor control through its intrinsic and extrinsic projections [33]. Layer 3 constitutes the largest part of the ECIC and appears to continue into the non-stratified rostral part (rostral cortex), which is topographically related to the fascicles of the commissural fibers. In addition to small and medium-sized cells, layer 3 contains large multipolar cells, especially ventromedially and rostrally. The border of the ECIC with the CNIC is indicated by a distinct shift in dendritic orientation, particularly conspicuous dorsolaterally as seen in caudal transverse sections [10, 16] where three morphologically distinct neuron types (bitufted, pyramidal-like and chandelier neurons) have been described [10]. Similar neurons have been described in the mouse. Willard and Ryugo [34] described large stellate cells with elongated dendritic arbors whose main axis is aligned perpendicular to the pial surface. Furthermore, computer-assisted 3D reconstructions of neurons in this region demonstrated that their dendritic arbors are different from those of the F neurons in the CNIC in several respects, including their thickness and orientation [10]. Because of this, some authors have hypothesized that the LCIC is compatible with a cortical-like architecture (i.e. a laminar architecture with distinct input-output strata) in conformity with the original description made by Ramón y Cajal [13, 14]. This notion is supported by McCown and Breese [35] in neonatal rats, who proposed that the modulation of sensorimotor function may be modulated by the IC cortices prior to the maturation of the cerebral cortex.

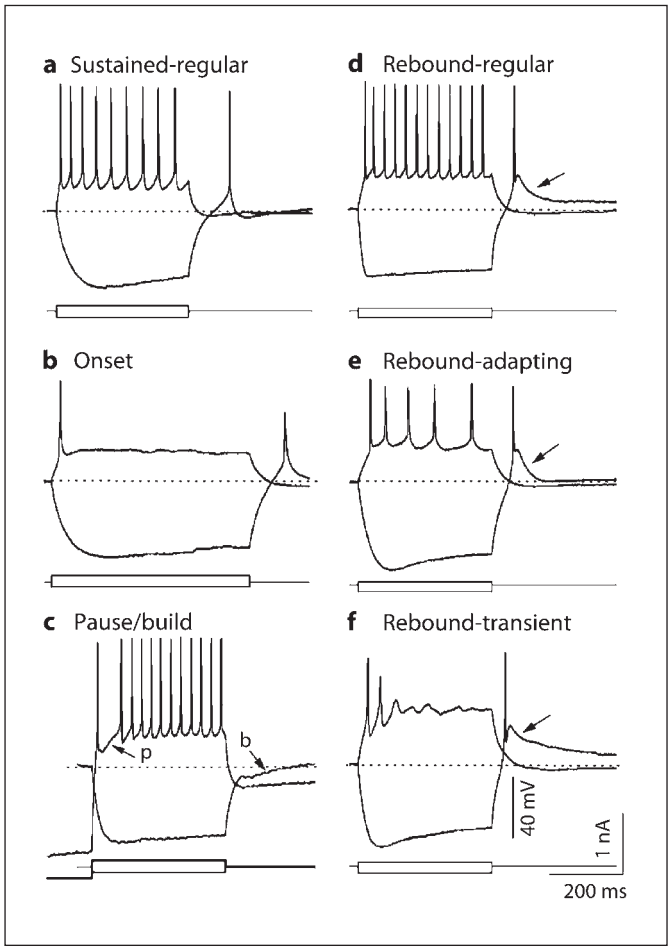

Fig. 3. The six firing patterns found in the IC after depolarizing and hyperpolarizing current pulses. **a–f** The top two traces are the voltage response to each current pulse (bottom traces). Redrawn from Sivaramakrishnan and Oliver [30] .

The Dorsal Cortex

The DCIC covers the dorsomedial and caudal aspects of the CNIC. In the cat, the dorsomedial part consists of four layers and the thinner caudal part is unlayered [15]. The rat possesses only three layers [16]. The superficial-most layer (layer 1) is a thin fibrocellular capsule that continues with that over the LCIC. It contains scattered, small, flattened neurons. The deeper, slightly thicker lay-

er 2 consists of small and medium-sized, mostly multipolar neurons. These two layers together constitute about one third the maximum thickness of the DCIC. Layer 3 contains small and medium-sized cells. There are large multipolar neurons at the border with the CNIC that differ in several respects from the F and LF neurons of the CNIC as demonstrated with computer-assisted 3D reconstructions of Golgi-impregnated neurons [10]. Layer 3 also contains elongated neurons located at the border between the CNIC and the DCIC whose dendritic arbors parallel the orientation of the laminae [10]; these may represent modified disk-shaped cells and have been referred to as transitional neurons [10].

The Rostal Cortex

The neurons in the RCIC also differ from those in the CNIC and LCIC as they are very large multipolar cells [10, 16, 17]. In addition, small and medium-sized multipolar neurons are present in the rostral cortex.

Connections of the IC Subdivisions

Ascending afferent inputs to the IC arise from lower auditory centers and tend to terminate more densely in the ventral portions of the IC, whereas the afferent input from the AC and commissural input from the contralateral IC terminate more densely in the dorsal portions [2]. Therefore, the ventral portion of the CNIC appears to be functionally connected with lower auditory centers, while neurons in the DCIC may be more influenced by descending pathways from the AC. However, there is an area of overlap between regions receiving the ascending and descending inputs at the border of the CNIC and DCIC [36, 37], so neurons located in this region may receive a combination of ascending, descending, intrinsic and commissural inputs. Altogether, the neuroanatomical studies suggest the presence of complementary gradients of innervation by the ascending and descending pathways to the IC. These gradients may serve to produce functional gradients within a given lamina and such overlapping gradients of ascending and descending inputs may differ from species to species [2].

In the following, first a review of the afferent ascending connections to the different IC subdivisions is given, subsequently focusing on its descending connections. Finally, the functional organization of the efferent connections (both ascending and descending) as well as that of the local and commissural connections within and between the two colliculi is shown in detail.

Afferent (Ascending) Projections (fig. 4)

The CNIC receives ascending input from more than 10 brainstem auditory centers [reviewed in ref. 2, 18], each of which is unique in structure and function. The main pathways arise from the cochlear nuclear complex, superior olivary complex (SOC) and nuclei of the lateral lemniscus, as demonstrated by retrograde axonal transport of tracers injected into the IC. The projections originate in the ventral cochlear nucleus (VCN) and dorsal cochlear nucleus (DCN) contralaterally, ventral nucleus of the lateral lemniscus and medial superior olive (MSO) ipsilaterally and the dorsal nucleus of the lateral lemniscus (DNLL) and lateral superior olive (LSO) bilaterally [1–5, 38–41]. In addition to these main projections, some species also have a projection from the ipsilateral cochlear nucleus to the low frequency part of the CNIC and a bilateral projection from the highest frequency parts of the MSO [38, 39]. Experiments using small injections of retrograde tracers injected into the IC demonstrate that the afferents are topographically (tonotopically) organized. Complementary experiments using anterograde tracers such as wheat germ agglutinin-conjugated horseradish peroxidase or ^{3}H-leucine injected into the lower centers have shown that besides being tonotopically organized, many of the ascending systems show a non-uniform distribution in the CNIC, exhibiting a 'banded' pattern, with dense axonal bands about 200 μm thick separated by bands of less dense labeling [21]. Bands formed by the projections from the ipsilateral and contralateral LSOs are intercalated, rather than overlapping. The banded pattern of bilateral projections to the CNIC from nuclei like the LSO and the DNLL may be more distinct on one side than on the other side, and the terminal fields of the various ascending projections may also vary in extent along the main axis of the IC. The terminal fibers from the SOC are confined to the ventral part of the laminae in the CNIC, whereas those from the VCN, DCN and the DNLL extend more dorsally in the laminae, extending into the deep region of the DCIC. Comparisons of the distribution of afferent axons from the DCN and the LSO to the contralateral IC in the same animal [39] show that layered axons from the DCN and LSO are superimposed only in the ventral part of the contralateral central nucleus. In the dorsal part of the central nucleus, the layer of axons from the DCN does not terminate with afferents from the LSO. Similar experiments in the rat, combining the injection of two different tracers in the VCN and DCN [40], suggest that some parts of these projections remain segregated within the CNIC laminae. Furthermore, two main components in the IC laminae have been reported:

a major lamina that included the largest fibers and largest boutons, and a broader lamina, composed of thin fibers and only small boutons, which flank the major lamina. The major laminae originate from larger cell types in the cochlear nucleus, while the paralaminar zone may represent an input from small cells. Thus, two types of IC laminar structures may originate from the cochlear nucleus, and the small boutons in the paralaminar zone may provide an important modulatory input to the neurons of the IC. Very recently, Cant and Benson [18] demonstrated that the CNIC of the gerbil is made of two parts based on the inputs they receive from the brainstem. Lateral and rostral zones of the CNIC receive input from both the cochlear nuclei and SOC, whereas the medial and caudal zones of the CNIC receive inputs from the cochlear nucleus but not from the SOC. These and previous data have led to the hypothesis that specific functional zones may be created within the laminae of the CNIC [21].

The DCIC receives ascending input from the sagulum [41]. The LCIC and RCIC also receive fibers from many non-auditory structures, including the cuneate and trigeminal nuclei, the lateral nucleus of the substantia nigra, the parabrachial region, the midbrain central gray, the periventricular nucleus and the globus pallidus [42].

Afferent (Descending) Projections (fig. 4)

Neurons in the collicular cortices may be more influenced by the AC than by ascending connections because of their bias toward descending projections [6, 20, 37, 42]. The descending input to the rat DCIC may originate largely from the primary AC bilaterally, with a small component to layer 1 from the area ventrocaudal to the primary cortex. Like the ascending projections to the CNIC, the neocortical terminals terminate in a topographic, banded pattern in parallel with the isofrequency contours of the CNIC [37]. The external cortex receives descending input from the cerebral cortex originating immediately rostral to the primary AC [20, 36, 43]. This projection is ipsilateral and terminates in layer 3.

Secondary regions of the AC also project to the IC [20]. Cortical area Te2 projects primarily to the superficial layers of the DCIC and LCIC, while Te3 primarily innervates the RCIC. These projections originate in the pyramidal cells of layer V [44]. In addition, the AC has been shown to project not only to the cortical regions of the IC but also to the CNIC in the rat. Ultrastructural studies have demonstrated that the corticocollicular fibers terminate on thin dendritic shafts and spines, forming small boutons with round synaptic vesicles and asymmetric glutamatergic synapses [36, 45]. However, electrical stimulation of the cat AC elicits not only excitatory effects but also inhibitory and complex interactions in IC neurons [46]. Thus, the AC may modulate the processing of sounds in the IC both directly and also through the activation of local inhibitory connections within the IC.

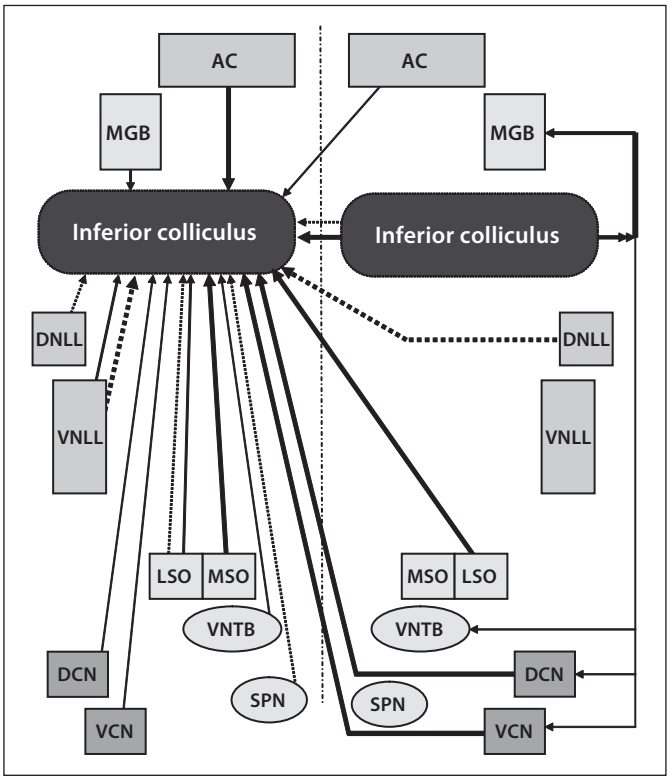

Fig. 4. Schematic wiring diagram of the afferent connections to the left IC and efferent connections of the right IC. Thicker lines show heavier projections than thinner lines. Solid lines indicate excitatory projections and discontinuous lines inhibitory connections. VNLL = Ventral nucleus of the lateral lemniscus; VNTB = ventral nucleus of the trapezoid body; SPN = superior paraolivary nucleus.

A direct descending pathway from the medial geniculate to the ECIC was recently demonstrated in the rat [47], a finding also reported in other species. In addition, Marsh et al. [48] recently established a direct, widespread projection from the basal amygdala to the IC in the mustache bat. They suggest the presence of a rapid thalamo-amygdalo-collicular feedback circuit that may impose emotional content onto processing of sensory stimuli at a relatively low level of an ascending sensory pathway.

Efferent (Ascending) Projections (fig. 4)

Thus far, the general pattern of the inputs to the IC has been detailed. In turn, the IC projects to the medial ge-

niculate body (MGB) [49–51] and to lower auditory centers such as the SOC and the cochlear nuclear complex [52–54]. Furthermore, the IC also has projections to non-auditory nuclei such as the pontine nuclei, a route by which auditory information can reach the cerebellum for coordination of motor responses to sound [55].

The CNIC projects to the laminated ventral division of the MGB in a strictly tonotopic manner. This projection is largely to the ipsilateral side but there is also a small crossed component. The CNIC also has a weak projection to the medial and dorsal divisions. The ECIC projects mainly to the dorsal and medial divisions of the MGB. The DCIC projects to the dorsal division of the MGB. The projections from the three subdivisions of the IC overlap, especially in the medial division [1–6].

The CNIC projections originate from both the F and LF neurons [50, 56]. Although the majority of neurons that project from CNIC to the MGB are glutamatergic, recent studies have shown that a significant proportion of the projection is GABAergic [56, 57]. The GABAergic projection originates from CNIC, DCIC and ECIC neurons, although the proportion from the cortical regions is lower. This projection has been confirmed in in vitro studies in which short-latency, monosynaptic inhibitory postsynaptic potentials from thalamocortical inputs have been demonstrated in the MGB [revised in ref. 4, 5].

Efferent (Descending) Projections (fig. 4)

IC neurons also contribute to the descending auditory pathways, targeting the SOC (colliculo-olivary projections) and the cochlear nuclei (colliculo-cochlear projection). The rat IC also projects to the non-auditory pontine and mesencephalic reticular nuclei [53].

The *colliculo-olivary* projections form a band of terminals in the ventral nucleus of the trapezoid body [53, 54]. This projection is topographic and originates from the CNIC and ECIC. The terminals in the ventral nucleus of the trapezoid body overlap the site of origin of the medial olivocochlear system [54], although it remains to be demonstrated by electron microscopy whether these fibers from the IC make synaptic contact on the medial olivocochlear neurons. Physiological studies have shown that electrical stimulation of the IC produces an increase in the latency and a reduction in the amplitude of the auditory whole-nerve response and also reduces the temporal threshold shift that appears after the exposure to a loud noise [58]. These effects are similar to those elicited by electrical stimulation of the medial olivocochlear system. More recent studies have shown that selective electrical stimulation within the CNIC produces frequency-specific reductions in neural activity in the cochlea [59] that are spatially restricted and bilateral. These effects are greater in the contralateral ear [60].

The *colliculo-cochlear* projection originates in the CNIC and ECIC (fig. 4) and targets the DCN and granule cell domain of the VCN, but its functional role is currently unknown [53, 61].

Intrinsic and Commissural Connections (fig. 4)

In addition to the connections discussed above, the IC possesses well-developed fiber systems made up of intrinsic and commissural inputs. Fibers that interconnect the three subdivisions of the IC on one side are referred to as *local* or *intrinsic* while fibers that interconnect the two sides are referred to as *commissural*. [9, 11, 42, 62]. Both types of fibers may represent collaterals of axons with projections to the thalamus or lower brainstem or, alternatively, they may represent the sole projection of a neuron that is truly an interneuron restricted to the IC [11]. The terminal territories of the intrinsic fibers form 'sheets' that are parallel to the isofrequency contours of the CNIC [11, compare fig. 22 and 25]. The sheets extend into the DCIC, and, via a sharp bend, into the ECIC [9, 62]. Retrograde transport of horseradish peroxidase has also shown that the CNIC receives input from the DCIC bilaterally and from the ECIC ipsilaterally. The DCIC and ECIC on the same side are also mutually interconnected.

Recent studies are beginning to uncover the functional role for both local and commissural connections. Miller et al. [11] have demonstrated that within a given isofrequency contour, intrinsic connections ascend from the ventrolateral portion to more dorsomedial points along the contour, forming a cascaded system of intrinsic feedforward connections that seem ideally suited to provide the delay lines necessary to produce several forms of selectivity for temporal patterns in IC neurons (see below). Injections of *Phaseolus vulgaris* leukoagglutinin or biotinylated dextran amine in one IC show that labeled fibers extend over the midline forming a mirror-like sheet on the contralateral side, thus indicating connections between the lamina devoted to the same frequency on the two sides. The majority of cells that project to the ipsilateral MGB also send collaterals to the contralateral IC. In guinea pigs, the commissural projection may be glutamatergic [63]. Consistent with the presence of both excitatory and inhibitory transmitters, physiological studies in vitro have shown that the commissural inputs may have either an excitatory or inhibitory influence on the contralateral IC [64]. In further in vivo studies, Mal-

mierca et al. [65, 66] recorded sound-evoked responses of single neurons in one IC while injecting kynurenic acid into a corresponding region of the opposite IC. This procedure allowed the reversible blockage of excitation by commissural projections to the recorded IC. The changes observed in the neural responses when inputs from the opposite IC are blocked again confirmed that the commissural projection exerts both excitatory and inhibitory influences. The inhibition could be accounted for by monosynaptic or disynaptic connections, and the responses to both monaural and binaural stimulation are affected. Furthermore, the effects are proportionately greater at near-threshold sound levels. The results suggest that one function of the commissure of the IC may be to modulate the response gain of IC neurons to acoustic stimulation.

Neurochemistry

As already mentioned, the neurochemistry of the F and LF neurons has been studied in detail. Both F and LF may be GABAergic [28, 29], but the majority of neurons (75% or more) are not inhibitory. It is tempting to suggest that the excitatory neurotransmitter of the IC neurons is glutamatergic. The IC lacks glycinergic neurons [28].

IC neurons possess both N-methyl-D-aspartic acid (NMDA) and 2-amino-3-(3-hydroxy-5-methylisoxazol-4-yl)propionic acid (AMPA) receptors [67]. The different physiological roles of the NMDA and AMPA receptors have been studied using microiontophoretic application of NMDA and AMPA antagonists in vivo [67]. Both AMPA and NMDA receptors contribute to excitatory responses at all levels of acoustic stimulation that elicit action potentials, although there are more GluR2 and GluR3 receptors in the IC than GluR1 and GluR4 [68]. The NMDA and AMPA receptors have a selective influence on early and late components of tone-evoked responses [67]. Thus, the AMPA receptors are important at the onset of the neuronal responses in the IC while both AMPA and NMDA are involved in the maintenance of the response for the duration of the stimulus.

The NMDA receptors are more abundant in the cortices than in the CNIC [67]. Thus, their distribution pattern matches that of the denser projection of the descending projections from the AC (*v.s.*). The cortico-collicular projection has been shown to cause long-lasting changes (>2 h) in the neuronal responses of the IC [69], suggesting that the NMDA receptors play a significant role in neuronal plasticity. Further evidence of this role has been shown in in vitro studies demonstrating that some IC neurons exhibit long-term potentiation [70].

In addition to glutamatergic receptors, IC neurons also possess $GABA_A$, $GABA_B$ and glycine receptors [67]. In vivo studies using microiontophoresis have demonstrated that both GABA and glycine inhibit IC neurons in several species [67, 71, 72].

Other neurotransmitters are also present in the IC and appear to be distributed differently by region. Serotonin terminals and receptors as well as noradrenergic fibers have been reported in the rat [73]. They originate from the locus ceruleus and dorsal raphe nucleus and seem to be more abundant in the cortical regions. Their functional role is unclear but recent studies in the bat have shown that serotonin modulates responses to species-specific vocalizations in the IC [74].

Basic Functional Properties of IC Neurons

Space limitation precludes a detailed account of the functional properties of the IC neurons; therefore the major spectral, binaural and temporal functional properties of the IC neurons are highlighted.

Multi- and single-unit recording to pure tone stimulation and functional mapping studies with c-*fos* revealed that a fundamental physiological feature of the CNIC is its tonotopic organization (fig. 5). A narrow range of best frequencies is represented within each isofrequency lamina [25, 26]. In addition, the laminae have highly organized representations of acoustic signals based on both spectral and temporal properties [for review see ref. 25, 75].

Neurons in the IC exhibit several different types of peri-stimulus time histograms, including onset, on-sustained, pauser and sustained and regular responses [71]. The majority of neurons in the IC have V-shaped tuning curves similar to those seen in the auditory nerve, but frequency response areas in the IC may also include non-V-shaped maps, as described in many species [72, 76–79]. The non-V-shaped maps form a heterogeneous group that includes closed, narrow, low- and high-tilt, and multipeaked types (fig. 6).

Binaural processing is initiated at the level of the SOC where interaural time and intensity differences are first encoded, but there appears to be further binaural processing in the IC. Kelly et al. [80] classified the responses of neurons to interaural intensity differences in the rat as either suppression, summation or mixed. Binaural suppression responses were more numerous at high frequen-

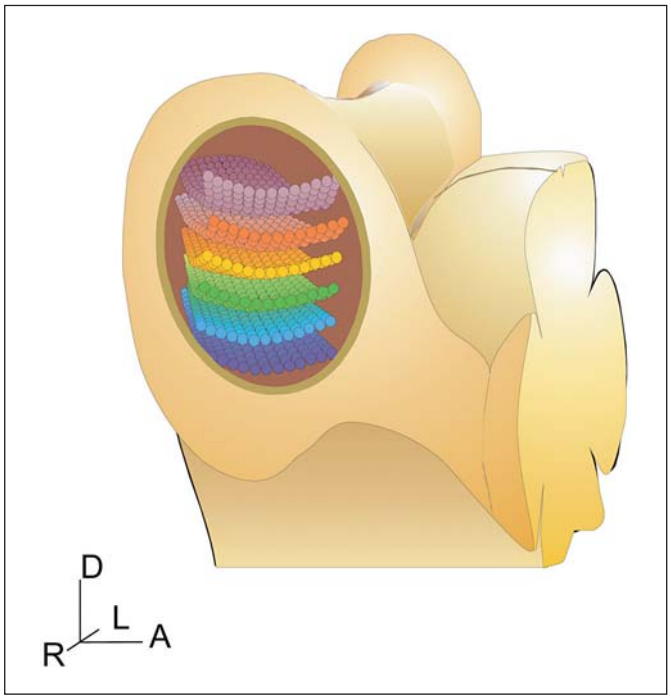

Fig. 5. Cartoon of the tonotopic and laminar organization of the IC. The cartoon shows a 3D schematic view of two ICs, and the anatomical laminae in the the right CNIC in different colors. D = Dorsal; A = anterior; L = left; R = right. The figure was kindly provided by Dr. G. Langner.

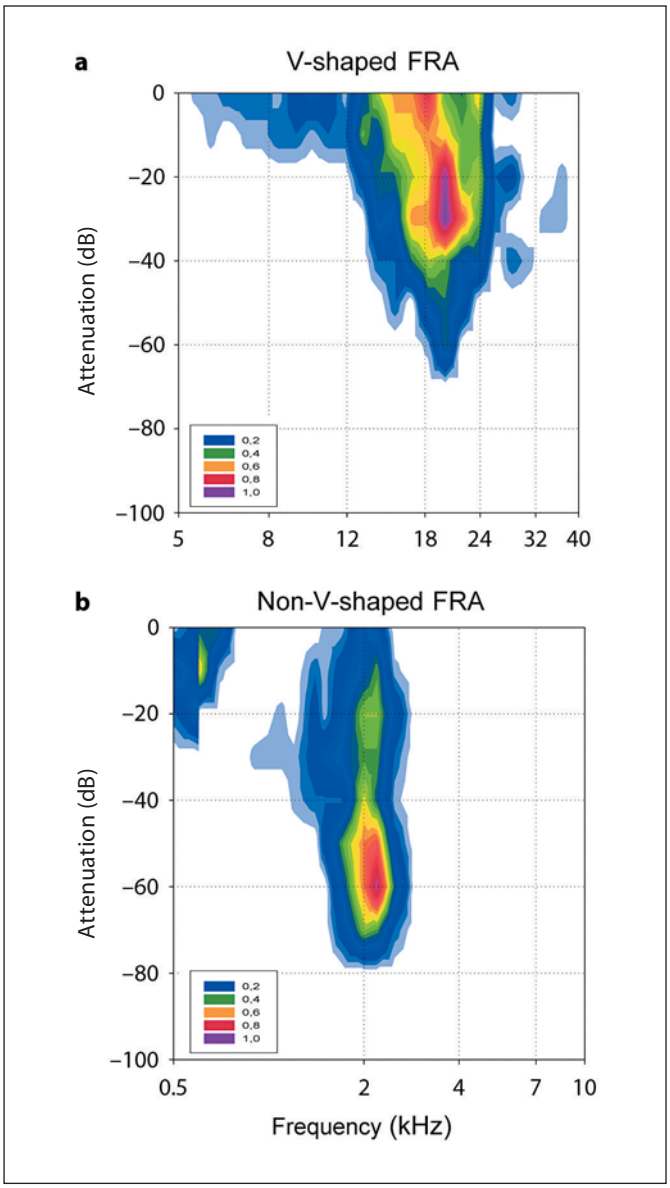

Fig. 6. Frequency response areas (FRA) from the IC. **a** V shaped. **b** Narrow (non-V shaped). Data from Hernández et al. [78].

cies and summation responses were more numerous at low frequencies. Studies based on the iontophoretic application of GABA and glycine antagonists have shown that neural inhibition contributes to the binaural response of neurons in the IC [81].

An important issue is the functional significance of binaural interaction at the level of the IC, given that the basic binaural comparisons occur at the level of the SOC. Kuwada et al. [81] have shown the emergence of interaural time difference (ITD) functions with an asymmetrical shape (sawtooth ITD functions) in the IC through the convergence of excitatory input from MSO and inhibitory input from DNLL. These sawtooth ITD functions are different from the classical peak or trough ITD functions seen in neurons in the SOC. Spitzer and Semple [82] have also suggested that the emergence of motion sensitivity in the IC might reflect the same pattern of convergence. Sound sources are not stationary in nature, and it may be that the binaural processing that takes place in the IC is related to the analysis of dynamic properties of sound source location. It may also be that the convergence of binaural pathways and spectral information at the IC could contribute to a map of auditory space, as it is the case in the barn owl's midbrain [83].

In the first part of this review, an idea of the complexity of the ascending auditory pathways was given. As detailed very elegantly by Casseday et al. [2], the ascending input to the IC may produce an array of delay lines and temporally redesigned response patterns that alter the ways in which the neuronal representation of any given stimulus is distributed in time. Temporally modified inputs from multiple pathways, combined with excitation

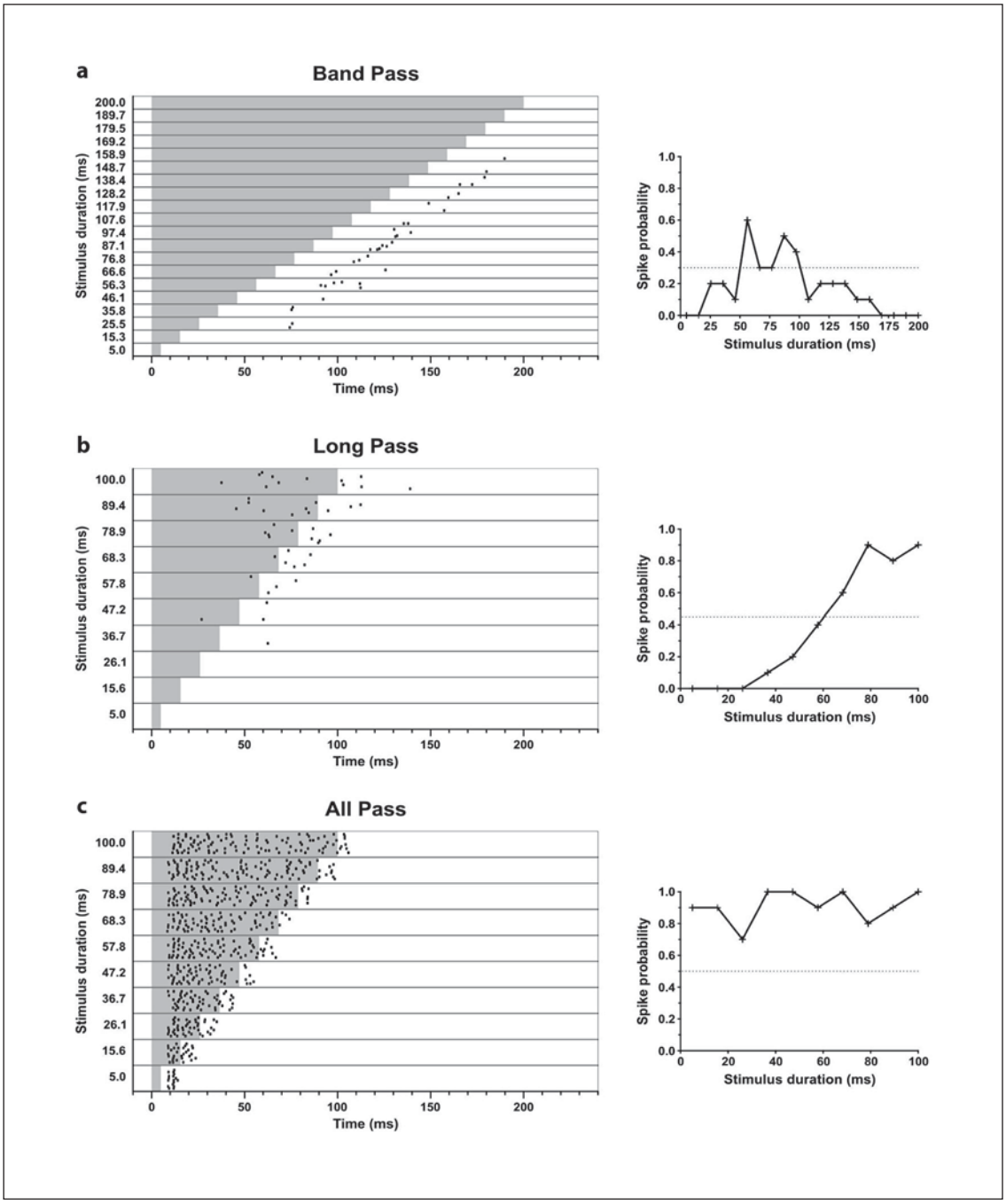

Fig. 7. Example of two (**a**, **b**) duration-tuned neurons from the IC and one non-duration-tuned neuron (**c**). Redrawn from Pérez-González et al. [88].

and inhibition, may be the basis for creating selectivity to temporal features of sounds in the IC. The first account suggesting that neural delay lines might be used to analyze auditory temporal patterns was presented by Jeffress in [84] in his now classical model for encoding ITDs. Licklider [85] also proposed a model for frequency discrimination based on coincidence detection and synaptic delays.

Ascending inputs provide the IC with different temporal response patterns that comprise onset, sustained

and offset responses with a wide range of latencies. They may be either excitatory or inhibitory (fig. 4). The results of the convergence onto single IC cells must result in a multifaceted temporal response of excitation and inhibition as demonstrated by intracellular recordings [81]. Temporal features that are generated de novo in the IC include tuning to rate and direction of frequency-modulated sweeps [86], tuning to sound duration [87, 88] (fig. 7) or delay of two sounds [89], and tuning to temporally sensitive facilitation in frequency combination neurons [90].

Thus far, the physiological features of the neurons of the central nucleus have been described. There are no detailed studies of the other subdivisions apart from the early studies from Aitkin et al. [91, 92], in which they demonstrated that ECIC neurons are multimodal, in agreement with their multisensory inputs. Only very recently, Pérez-Gonzalez et al. [93] have revealed that some neurons in the rat DCIC and ECIC show rapid and pronounced habituation to repeated presentations of identical stimuli but briefly recovered their responsiveness when some stimulus parameter was changed. Hence these neurons have been referred to as 'novelty detectors'. An important function of the auditory system is to differentiate behaviorally uninteresting patterns of sound, which are often repetitive, from sounds that may require attention or action, and thus novelty neurons may be important for this vital function. Furthermore, the properties of novelty neurons in the IC are consistent with stimulation paradigms that produce mismatch negativity in humans and animals, so novelty neurons might be the neuronal correlate of mismatch negativity. Similar neurons have been shown also to be present in the AC [94].

Finally, a few additional comments about plasticity in the IC are worth mentioning. As described above, the IC is equipped with neuronal machinery (NMDA, AMPA and GABA receptors as well as neuromodulators such as acetylcholine, serotonin and adrenaline) that has been shown to be the basis for plasticity in other brain areas. Nevertheless, it is somewhat puzzling that there is little evidence for plasticity in the adult IC after cochlear damage or spiral ganglion lesions. Despite the wide variety in techniques employed to produce cochlear trauma in order to alter the response properties of the IC neurons [95, 96], most of the changes seen can be explained as a postlesional expression of preexisting inputs [96, 97]. This is in contrast to the well-established plastic changes demonstrated at thalamic and cortical levels in the auditory system [97–99].

Concluding Remarks

The IC is not only the main site of termination for the ascending fibers of the lateral lemniscus, it is also heavily innervated by the AC. Furthermore, the IC receives crossed projections from its counterpart and possesses a dense network of local connections [1–5]. Thus, the IC occupies a strategic position in the central auditory system and may be considered as a central hub or an interface between the lower auditory pathway, the AC and motor systems [2]. Anatomical and physiological experiments demonstrate that the IC is involved in a great diversity of functional roles in the auditory system, and that most of the interesting auditory features might already be extracted from incoming sounds by this midbrain nucleus. It has even been suggested that the IC might be considered as the auditory analog of the primary visual cortex [100], leaving the AC to organize these features into auditory objects.

The ultimate goal of auditory science is to understand completely how we hear. The aim of this review was to outline the interaction between structure and function in the auditory midbrain. Elucidation of the elements of the 'auditory scaffold' will help to fit the pieces of the puzzle together and solve the mechanisms by which the auditory system processes acoustic stimuli, i.e. how we hear.

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