For The Auditory Brainstem

Editor Karl Kandler

Unifying the midbrain: the commissure of the inferior colliculus

Adrian Rees and Llwyd D Orton

Correspondence:

Adrian Rees
Institute of Neuroscience
Newcastle University
Newcastle upon Tyne
NE2 4HH, UK

adrian.rees@ncl.ac.uk

Llwyd David Orton
School of Healthcare Science
Manchester Metropolitan University
M1 5GD, UK

l.orton@mmu.ac.uk

1. Introduction

The auditory system is unique amongst mammalian sensory systems in having *pre-cortical* commissural connections that interconnect homologous structures on either side of the brain. In the somatosensory and visual systems, crossing fibres occur at the spinal cord and optic chiasm respectively, but these are decussations, where fibres travel obliquely to terminate in structures at a level above their origin. True commissural interactions in most sensory and motor systems are found within the cerebral cortex, where the two hemispheres are interconnected by the corpus callosum and the other major commissures. However, as in several aspects of its functional organisation, the auditory system proves to be the maverick amongst sensory systems, operating according to its own distinct requirements.

The first commissural connections in the auditory pathway occur between the cochlear nuclei, the direct recipients of input from the cochlea. There are two systems: one glycinergic that originates mainly in the core of the ventral cochlear nucleus (VCN) and another, excitatory, which arises from neurons in the small cell cap of the VCN (Cant and Gaston 1982; Shore et al. 1992; Schofield and Cant 1996a; Alibardi 1998; Arnott et al. 2004; Doucet et al. 2009; Brown et al. 2013). Given their different organisation, these two systems likely serve several functions, including balancing binaural interactions between the cochlear nuclei (Needham and Paolini 2006; Doucet et al. 2009).

Commissural projections are absent between the nuclei of the superior olivary complex, and next occur near the head of the brainstem where the commissure of Probst, a primarily GABAergic pathway, interconnects the binaurally responsive neurons of the dorsal nucleus of the lateral lemniscus (Adams and Mugnaini 1984; Shneiderman et al. 1988; Chen et al. 1999; van Adel et al. 1999). Interestingly, the mainly monaural neurons in the ventral nucleus of the lateral lemniscus, which receive inputs predominantly from the contralateral cochlear nucleus, are not commissurally interconnected - an observation again consistent with the idea that commissural connections are important in binaural processing.

Of all the subcortical auditory commissures, the most substantial interconnects the inferior colliculi. The significance of this reciprocal innervation is evidenced by the fact that the commissure of the inferior colliculus (CoIC) is likely the largest single external source of input received by the IC (Moore 1988). This chapter explores what is currently known about the organisation and function of the CoIC, and speculates as to its role in sound analysis.

1.1 Structure of the review

The chapter begins by considering the anatomy of the CoIC, including the sources and connections of its fibre. These sections are followed by a discussion of experiments that have investigated the function of the CoIC, and we conclude with a consideration of the putative role of the CoIC, and identify the major gaps in our knowledge. The aim is not to be historically exhaustive, but rather to highlight the major principles of CoIC organisation.

2. Anatomical organisation of the CoIC

2.1 Gross structure of the commissure

The CoIC principally interconnects neurons in the two ICs, although, as discussed later, some of its fibres originate in, or target, other centres in the auditory pathway. In appearance, the CoIC is a curvilinear tract comprised of heavily myelinated fibres that interconnect the ICs dorsal to the cerebral aqueduct (Figure. 1A) (Faye Lund and Osen 1985; Saldaña and Merchán 2005). The number of CoIC fibres increases dorsally, medially and rostrally as they coalesce to cross the midline, forming the

caudal part of the tectal commissure, a fibre bundle that also contains the commissural fibres of the superior colliculus (Faye Lund and Osen 1985). The CoIC courses symmetrically about the midline, forming a direct projection from neurons in one IC to those opposite. Intermingled between the commissural fibres are neurons that form a commissural nucleus, located between the dorsal cortex of the IC (ICD) and the periaquaductal grey in cat (Morest and Oliver 1984) and rat (Faye Lund and Osen 1985). This structure is now considered to be the caudal portion of a more extensive, tectal longitudinal column that receives collaterals of commissural fibres (Saldaña et al. 2007; Aparicio et al. 2010). Lateral to the commissural nuclei, CoIC fibres splay across the entirety of the IC and their fascicles decrease in density as they project toward their targets.

Figure 1 near here

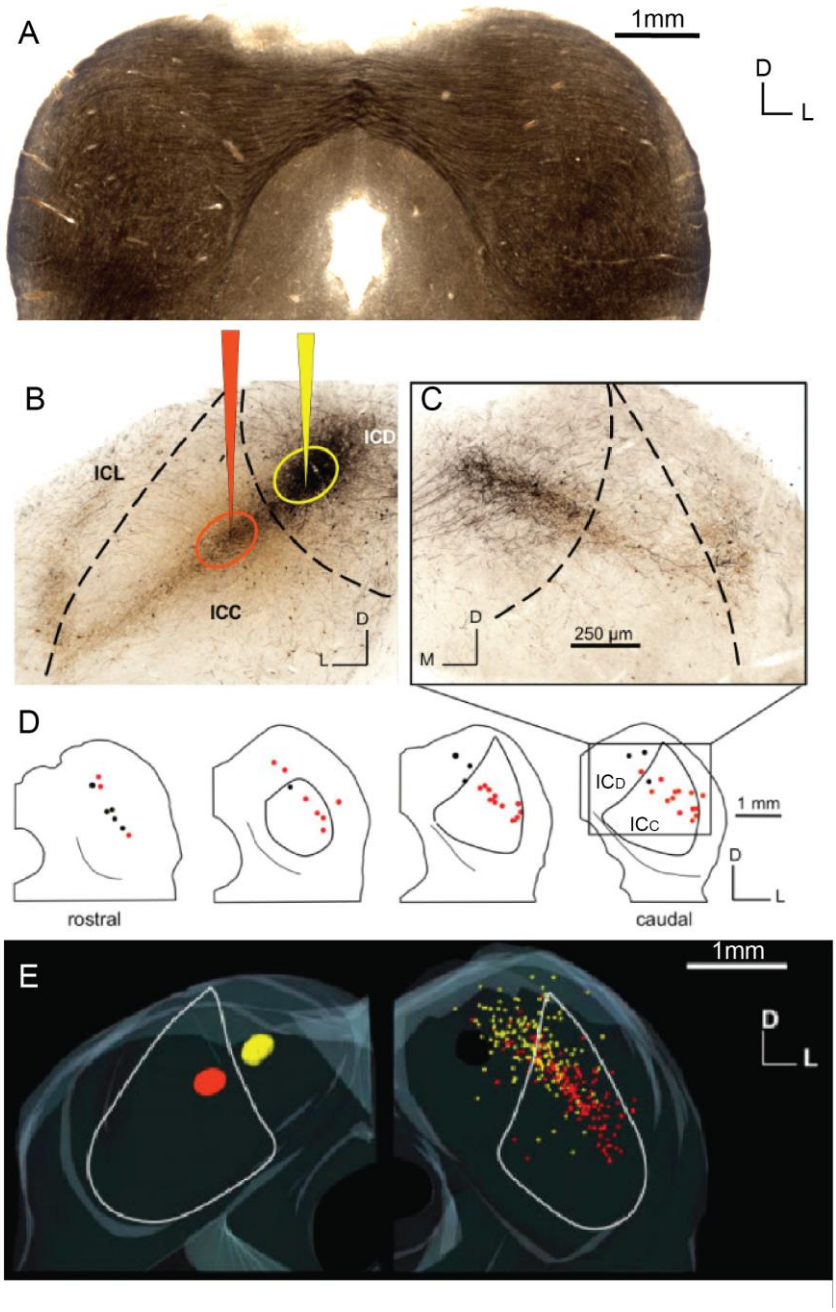

Figure 1

A*. Coronal section (50-µm thick) of the tectal midbrain in guinea pig stained for myelin with osmium tetroxide to show the commissure of the inferior colliculus (CoIC). Commissural fibres can be seen*

crossing the midline and fanning out into each IC. Fibres of the lateral lemniscus can be seen entering the ICs from below. ***B****. Photomicrograph showing injections of two different tracers into the same frequency band lamina in the IC of rat. The best frequency at the injection sites was determined by electrophysiological recording to sound to be 10-10.5 kHz. The injection of tetramethyl-rhodamine dextran (TRD) in the dorsal cortex (IC*$_D$*, yellow circle) and biotinylated dextran amine (BDA) into the central nucleus (IC*$_C$*, red circle). A V-shaped plexus of intrinsic axons is labelled ipsilateral to the injections with a central wing in IC*$_C$ *that extends into IC*$_D$*, and a lateral wing that turns into the lateral cortex (IC*$_L$*).* ***C****. In the contralateral IC, commissural fibres are labelled in mirror image distribution to those ipsilateral, with retrogradely labelled neuronal somata scattered amongst them.* ***D****. Camera lucida drawings from sections at different locations along the rostro-caudal axis, showing the locations of somata labelled by the injection in the central nucleus (red dots) and the dorsal cortex (black dots) respectively.* ***E.*** *Three dimensional reconstructions in the coronal plane of the locations of the injection sites (left) and of retrogradely labelled somata (right) for the case shown in* ***B-D.*** *The injection in the IC*$_C$ *labels somata (red points) in the contralateral IC*$_C$ *and IC*$_D$*. Somata labelled following an injection in the IC*$_D$ *(yellow points) are restricted to the cortical regions. (Some of the latter appear in this view to be in the IC*$_C$*, but viewing from other orientations shows them to be in the cortex rostral and caudal to the IC*$_C$*.) Neurons in the IC*$_L$ *do not give rise to commissural projections. D, dorsal; L, lateral. (B-E adapted from Malmierca et al., 2009).*

2.2 Connectivity of commissural fibres between the ICs

The overall of schema of intercollicular connectivity is highly conserved across mammalian species. The patterns of connections formed by the intercollicular fibres were first demonstrated in a variety of species using degeneration techniques (Woollard and Harpman 1940; Moore and Goldberg 1966; Powell and Hatton 1969; van Noort 1969). More recent studies using anterograde and retrograde tracers have added detail and clarity to those earlier findings, demonstrating that there are commissural neurons in IC that project contralaterally to all its subdivisions (Adams 1980; Gonzalez Hernandez et al. 1986; Coleman and Clerici 1987; Saldana and Merchan 1992; Malmierca et al. 1995; Malmierca et al. 2009).

The first detailed study of commissural projections, using the anterograde tracer Phaseolus vulgaris-leucoagglutinin (PHA-L), was conducted in rat (Saldana and Merchan 1992). Tracer deposits in ICc labelled, in the coronal plane, two bands of fibres that coursed through rostral part of the ipsilateral IC; one through the dorsal cortex (IC$_D$) and central nucleus (ICc), the other through the lateral cortex (IC$_L$) (save for the most superficial layer). Caudally, the two bands converged to form one continuous laminar plexus. A mirror symmetric, though less extensive, distribution of axon terminal fibres was revealed in the contralateral IC. Intercollicular connections therefore follow a reciprocal topographic pattern, with terminals distributed throughout the contralateral fibrodendritic lamina in all subdivisions (Saldana and Merchan 1992; Saldaña and Merchán 2005).

A similar distribution of intercollicular projections was demonstrated in guinea pig using biocytin injections combined with electrophysiological recording (Malmierca et al. 1995). This approach allowed the injection sites and the resulting labelled laminae to be characterised with respect to the frequency organisation of the IC. In the IC contralateral to the tracer injection, electrolytic lesions placed at sites with the same best frequency as the tracer injection confirmed the precise symmetry of these intercollicular connections.

Thus, the consistent finding from studies using anterograde tracers is a mirror symmetric pattern of labelling in each IC defining the arc of the fibrodendritic laminae (Figure. 1B and C) (Saldana and Merchan 1992; Malmierca et al. 1995; Malmierca et al. 2009). These laminae are the underlying

structural substrate for the tonotopic representation of sound frequency in the IC (Rose et al. 1963; Merzenich and Reid 1974)

Although these studies show the general organisation of commissural connections between the ICs, they do not address the intricacies of the circuitry involved. Particularly pertinent is whether the ipsilateral and contralateral laminae are connected in a point-to-point fashion, or whether neurons at a single location on a lamina send divergent connections across the lamina surface? A partial answer to this question was obtained using retrograde labelling from small injections of two dextran tracers. Malmierca et al. (2009) placed tracers at different frequency locations and subdivisions in rat IC and reconstructed in 3D the locations of retrograde labelled neurons on the contralateral side. Labelled somata were distributed throughout the contralateral lamina from an injection in ICc, but the number of labelled somata in the contralateral IC was maximal at a point mirror symmetric to the injection site (Figure 1B-E).

The caveats of tracer studies notwithstanding, the observed pattern of labelling suggests that commissural neurons make divergent connections. Thus a single point on a lamina receives convergent connections from neurons distributed over the surface of the homologous lamina in the contralateral side, but the greater weight of connections occurs between homotopic points (Figure 2A). Such an organisation may provide the basis for complex convergent and divergent information processing between the ICs. However, we do not know whether different classes of neurons contribute to these different projection patterns. The answer to this question awaits the detailed connectivity mapping of individual commissural neurons.

In addition to interconnecting neurons in the contralateral ICc, neurons in the ICc also receive projections from the contralateral ICd. An injection in ICc retrogradely labelled neurons in contralateral ICd whose distribution followed the axis of the lamina in ICc. In contrast, an injection in ICd resulted in a diffuse pattern of labelled somata in contralateral ICd (Malmierca et al. 2009). These distributions suggest there are two distinct populations of neurons within ICd giving rise to commissural connections: neurons in the ventral part of ICd, a region into which the frequency band laminae extend, project to the contralateral ICc and ventral ICd, whereas neurons in the dorsal part of ICd connect more widely throughout the contralateral ICd (Figure 2B). Neurons in ICl were rarely labelled following injections in ICc or ICd, indicating that although commissural projections terminate in this subdivision, it is not a source of commissural connections.

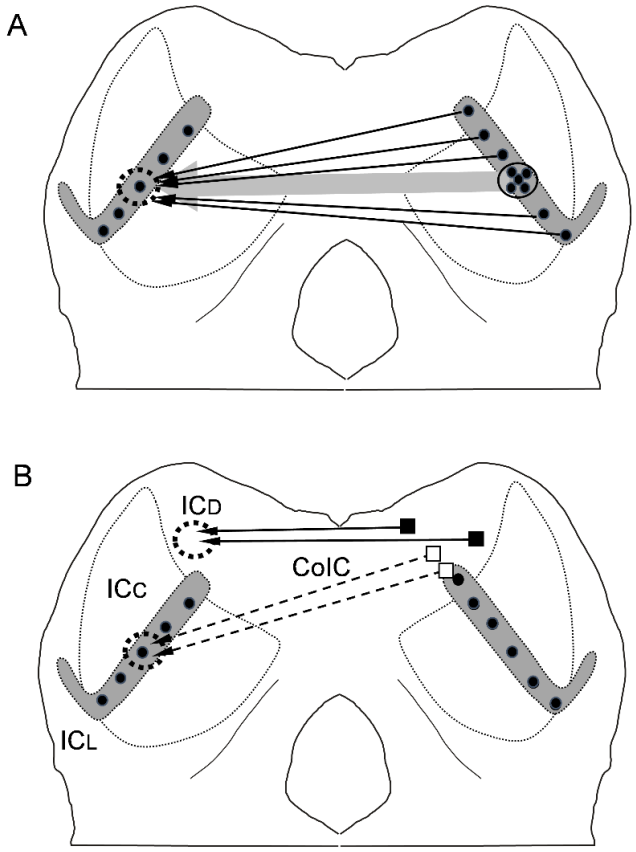

Figure 2

Schematic diagrams to illustrate the patterns of commissural connections between the different subdivisions of the inferior colliculus (IC) based on retrograde labelling following tracer injections like those in Fig 1.

A. *An injection (dotted circle) into the central nucleus (ICC) results in fibro-dendritic labelling of a V-shaped axonal plexus (grey) in both ICs (see Fig 1B). Retrogradely labelled somata (filled dots) are observed over the length of the lamina in the contralateral (right) IC, consistent with each of these neurons making divergent commissural projections (thin arrows) to the injection site and sites along the lamina. Cell counts show the projection is weighted (broad arrow) to a point on the lamina (solid circle) corresponding to that of injection site.* ***B.*** *Neurons in the dorsal cortex make two types of projection: an injection in ICC retrogradely labels neurons in the deeper layers of the dorsal cortex (open squares) in line with the lamina, while an injection in ICD labels neurons distributed more diffusely in the dorsal cortex (solid squares).*

Figure 2 near here

Together, these findings suggest that different populations of commissural neurons interconnect the two ICs in distinct ways, perhaps in a manner analogous to the functional zones identified for the multiple sources of afferent input to the IC (Cant and Benson 2006; Loftus et al. 2010; Cant 2013). The search for the organising principles of interactions within and between the fibrodendritic laminae of the IC remains an important, but unanswered, challenge.

2.3 Commissural fibres arising outside the ICs

Not all fibres passing through the commissure originate in the IC. A subset of ascending lemniscal fibres cross via the commissure to the contralateral IC (Barnes et al. 1943; Hutson et al. 1991). These originate from the ventral (Whitley and Henkel 1984), intermediate (Hutson et al. 1991), and dorsal nuclei of the lateral lemniscus (Bajo et al. 1993), as well as the sagulum (Henkel and Shneiderman 1988). Some neurons in the paraolivary nucleus of the superior olivary complex similarly send collaterals to dorsal cortex of the contralateral colliculus via the commissure (Saldaña et al. 2009). A recent report finds even fibres originating from a location as peripheral as the DCN may reach the ipsilateral IC by traversing the brainstem to the contralateral IC before crossing back through the CoIC to terminate in ipsilateral ICD (Milinkeviciute et al. 2015). Cells in the fusiform layer of the DCN can project to both ICs (Schofield and Cant 1996b) and this finding suggests a possible route via the CoIC.

The CoIC also likely contains an ascending projection from IC to the ventral nucleus of the *contralateral* MGB (Kudo and Niimi 1978; Oliver 1984; González-Hernández et al. 1991; Coomes and Schofield 2004). Double labelling experiments suggest that as many as 30% of IC neurons projecting to the ipsilateral MGB also project to the contralateral MGB (González-Hernández et al. 1991). Such projections may provide a means for further bilateral integration within MGB.

In addition to conveying ascending and laterally directed fibres, the CoIC also mediates descending connections. While cortico-collicular, and thalamo-collicular connections are predominantly ipsilateral, a small proportion reach the contralateral IC directly via the commissure. Most terminals of such cortico-collicular fibres are found medially and dorsally, and in contrast to their ipsilateral equivalents, labelling in ICc only extends into its most dorsal part, and is absent in ICL (Rockel and Jones 1973; Adams and Wenthold 1979; Saldana et al. 1996). After tracer injections in both ICs, around 5% of cortico-collicular neurons were found to be double labelled in guinea pig and opossum (Willard and Martin 1984; Coomes et al. 2005). In contrast, Bajo and Moore (2005) failed to find any double-labelled cells in auditory cortex after large tracer injections in both left and right IC in gerbil. Nevertheless, it seems that, at least in some species, cortical neurons may send collateralised inputs to both ICs.
We do not know the exact proportion of commissural fibres that originate outside the IC, but they are likely a small proportion of the total. It is also interesting, that, in contrast to the weight of intercollicular connections between the ICcs, commissural connections to the IC from extra-collicular sources are predominantly restricted to ICD.

There are a few reports of non-auditory projections *to* IC which first project through the CoIC. Aside from the projection from auditory cortex, higher order areas such as insula (Winer et al. 2002) and orbitofrontal cortex (Mizuno et al. 1968) innervate IC via CoIC. Subcortical sources include the substantia nigra pars lateralis, a tonically firing GABAergic output of the basal ganglia (Afifi and Kaelber 1965; Olazabal and Moore 1989), the cholinergic basolateral amygdala (Marsh et al. 2002), and bilateral projections from the hypothalamus (Adams 1980). These little considered sources of input suggest processing in the IC goes beyond the analysis of sound per se.

2.4 The neurochemistry of commissural fibres

Studies concur that the CoIC comprises both excitatory and inhibitory fibres. Saint Marie (1996) demonstrated an excitatory, glutamatergic, component based on the synaptic uptake and retrograde transport of tritiated D-aspartate. But combining retrograde labelling with immunohistochemistry for GABA or its synthesising enzyme GAD67 reveals a substantial minority of labelled neurons are GABAergic (González-Hernández et al. 1996; Nakamoto et al. 2013). In rat, 18% of retrogradely labelled commissural neurons in the IC were GABA positive (González-Hernández et al. 1996; Hernández et al. 2006). Given that around 20-25% of neurons in the IC of rat are GABAergic (Merchán et al. 2005) the percentage of inhibitory commissural projections suggests the commissural projection is

representative of the population of GABAergic neurons in the IC. In guinea pig, co-labelling of commissurally identified neurons with GAD67 found that approximately 10% of intercollicular projections were GABAergic, but the number differed between subdivisions from only 4% in ICc, to between 12-21% in the different cortical subdivisions (Nakamoto et al. 2013). These numbers probably reflect species differences, but there also appears to be a gradient in the number of GABAergic neurons contributing commissural input from dorsal to ventral through ICd and ICc which might account for some of the differences observed between studies (González-Hernández et al. 1996). These authors report up to 68% of commissural neurons in ICd are GABAergic with fewer located in more ventral regions. Such a gradient may also explain why (Zhang et al. 1998) failed to find any GABAergic labelled cells among commissural neurons labelled with fluorogold following injections placed ventrally in ICc. The contribution of different proportions of GABAergic neurons between different regions of IC indicates disparate roles of fibres with the CoIC, related to their afferent sources and efferent targets.

While glutamate or GABA are the neurotransmitters of most commissural neurons, a small number of neuropeptide Y and encephalin-labelled commissural neurons have been identified in the cortical subdivisions of the IC (Nakagawa et al. 1995). Further investigation of the diversity of the neurotransmitters expressed by CoIC fibres is required.

2.5 Neuronal morphologies in IC contributing to commissural connections

There is no systematic study of the neuronal types in IC that form the commissural projection. However, several reports using retrograde tracers or intracellular labelling show that IC neurons of widely differing morphologies are sources of commissural input (Adams 1980; Druga and Syka 1984; Gonzalez Hernandez et al. 1986; Coleman and Clerici 1987; Moore 1988; González-Hernández et al. 1996; Saint Marie 1996; Okoyama et al. 2006). The task of comparing these studies is somewhat hampered by the different terminologies applied in naming the neuronal types. However, it appears safe to say that the two major classes of neurons that feature in cytoarchitecture of the frequency-band laminae of the ICc (neurons with flattened disc shaped dendritic fields and stellate neurons – also termed flat and less flat types (Oliver and Morest 1984; Malmierca et al. 1993; Oliver 2005; Malmierca and Hackett 2010) are both found in the commissural population in the central nucleus, together with mainly stellate types in ICd.

In one of the few quantitative studies, Okoyama et al (2006) report that the most frequently encountered types were small- and medium-sized disc-shaped neurons (c.a. 10 and 15 µm soma diameter respectively) together with medium-sized stellate neurons. Neurons of both categories with large diameter soma (>20 µm) were observed, but much less frequently. These two major morphological classes are also present in studies that targeted the excitatory (Saint Marie 1996) or inhibitory (GABAergic) (González-Hernández et al. 1996; Nakamoto et al. 2013) components of the commissural projection. Following injection of tritiated aspartate to retrogradely label glutamatergic neurons, Saint Marie (1996) reported labelled neurons in ICc and ICd of the contralateral IC, including 'fusiform' cells lying parallel to the orientation of the frequency band laminae, thus presumed disc-shaped neurons. Gonzalez-Hernandez et al. (1996) and Nakamoto et al. (2013) combined retrograde labelling with immunohistochemistry to identify GABAergic neurons projecting from one IC to the other. Labelling was most pronounced in ICd and the dorsal part of ICc. The labelled neurons constituted a heterogeneous population of morphologies and diameters with multipolar (stellate) and fusiform types representing soma diameters from 12 µm to over 20 µm. Comparison of these findings with the population analysis of GABAergic neuron size in the IC by Ito et al (Ito et al. 2009), suggests that GABAergic of all sizes contribute to the commissural projection.

Intracellular and juxtacellular labelling techniques *in vivo* or *in vitro* produce smaller samples of neurons than retrograde studies, but have the advantage that labelling of dendritic arbors is more complete, and axons can often be traced along at least part of their length. Such studies have described labelled neurons with axons directed towards or into the commissure (Smith 1992; Reetz and Ehret 1999; Wallace et al. 2012). Consistent with the retrograde studies discussed above, in the ICD, most of these neurons are 'multipolar' (putative stellate or less flat) cells (Smith 1992), but in the central nucleus, some have flattened dendritic arbors characteristic of neurons that aligned to form the frequency-band laminae (Reetz and Ehret 1999; Wallace et al. 2012).

2.6 Inputs and outputs of commissural neurons

Knowledge of the inputs and outputs of commissural neurons is essential to delineate their microcircuitry. Although we know relatively little about their sources of inputs, given their number and distribution in IC, it would be surprising if commissural neurons were not the recipients of extensive input from both intrinsic and external sources.

One significant source of input to commissural neurons comes from the auditory cortex. Nakamoto et al. (2013) in guinea pig used anterograde and retrograde tracers in combination to demonstrate that commissurally projecting neurons receive extensive input from the ipsilateral auditory cortex. These contacts were seen on neurons in ICD and ICC, and cortico-collicular endings were found on both presumed excitatory and identified inhibitory commissural neurons. Intriguingly, as suggested by Nakamoto et al. (2013), cortical input to commissural neurons might provide the primary route whereby the IC is influenced by the *contralateral* auditory cortex.

In support of this hypothesis, spontaneous and sound evoked firing in IC were found to be influenced by electrical stimulation of either contralateral or ipsilateral auditory cortex, but the latency of the contralateral effect was longer than that for ipsilateral stimulation (11.4 vs 7.2ms) (Torterolo et al. 1998). The longer latency of the contralateral response is consistent with the possibility that the auditory cortex influences the contralateral IC indirectly via the commissure.

With respect to the output connections of commissural neurons, studies *in vitro* show that the majority of ICC neurons activated by stimulating the commissure are also driven by stimulation of the lateral lemniscus (Moore et al. 1998; Reetz and Ehret 1999). In contrast, neurons in ICD receiving commissural input were not, or only weakly, driven by the stimulation of the lateral lemniscus (Smith 1992). These data support the notion of different populations of commissural neurons suggested by the anatomical findings discussed above (see Figure 2).

GABAergic neurons projecting to GABAergic neurons in the contralateral IC have been demonstrated (Lee et al. 2015), and cell-dependent monosynaptic tracing in mouse has extended this finding. Chen et al. (2018) report differences in the proportions of inhibitory neurons projecting to glutamatergic and GABAergic neurons in the other IC. About a third of GABAergic neurons projected to glutamatergic neurons, and this proportion was similar for GABAergic neurons located in either ICC or ICD. However, there was a marked, location-dependent difference in the proportion of GABAergic neurons projecting to *GABAergic* neurons, with about 60% of those in ICD projecting to GABAergic neurons compared with only 20% of those in ICC. These data suggest that commissural connections predominantly drive dis-inhibitory circuits in the ICD.

Amongst the GABAergic neurons targeted by commissural connections are the large GABAergic neurons with diameters >16.5 µm. These neurons, characterised by their dense axosomatic synapses associated with terminals expressing vesicular glutamate transporter 2 (VGLuT2) (Altschuler et al. 2008; Ito et al. 2009), constitute the inhibitory connection from the IC to MGB (Winer et al. 1996; Ito

et al. 2009). These neurons receive excitatory inputs from several external and intrinsic sources, including from the contralateral IC, although these inputs are considerably sparser than from ipsilateral intrinsic neurons (Ito and Oliver 2014; Ito et al. 2015).

Intracellular labelling demonstrates that some neurons that send axons toward the commissure also make axon collaterals that head towards the brachium or the lateral lemniscus. Although it was not possible to trace them to their terminals, this observation is consistent with commissural neurons also making ascending or descending connections external to the IC (Reetz and Ehret 1999). More definitive double labelling tracer studies have also addressed this question. González-Hernández et al. (1991) observed that around 10% of neurons that project to MGB also project to the contralateral IC in rat, but suggested that this number increases to 25-30% in areas where neurons labelled each or the tracers most overlap. In contrast, Okoyama et al. (2006) report only around 1% of double labelled neurons in the IC in the same species following injections into both the contralateral colliculus and the ipsilateral MGB. Furthermore, the latter study showed a complete absence of neurons contributing to both the commissural and the descending pathways from the IC to the cochlear nucleus or the superior olive. These conflicting findings await to be resolved.

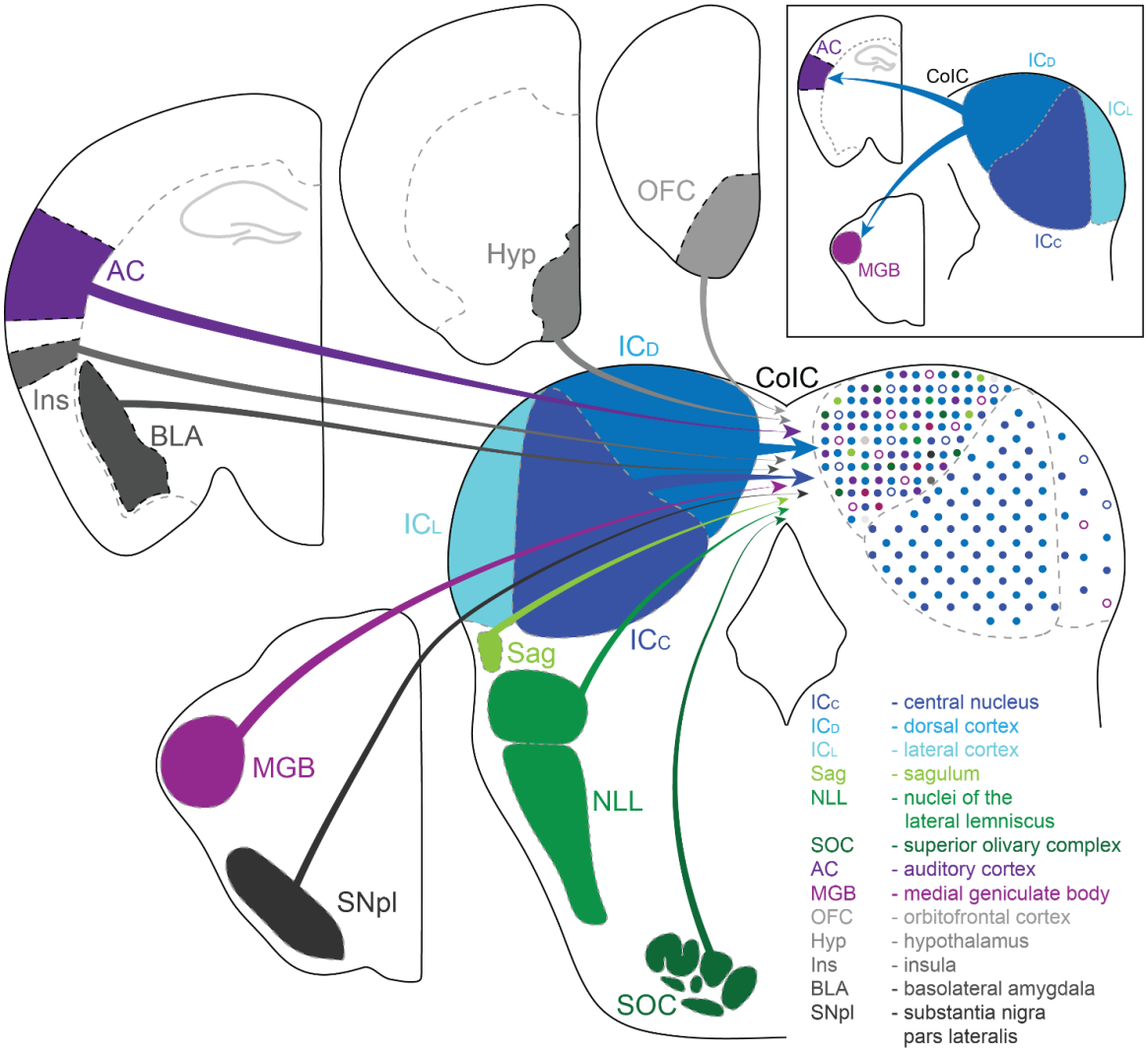

Figure 3

Summary of the sources and terminal sites of fibres projecting through the commissure of the IC. By far the largest part of the projection originates in the contralateral IC from the central nucleus (ICc) and

the dorsal cortex (ICD). Other centres in the brainstem, diencephalon and cerebral cortex make up smaller part of the projection and primarily terminate in the ICD. Coloured stippling in the subdivisions of the IC, corresponding to the colour of the incoming projections, indicates the regions where these inputs terminate. Inset top right shows that the IC also sends a minor projection to the contralateral medial geniculate body (MGB) and auditory cortex via the CoIC.

Figure 3 near here

2. 7 Overview of anatomical findings

The sources and projections of commissural fibres are summarised in Figure 3. Together, the anatomical findings discussed emphasise several points about the organisation of the commissure. Commissural connections are responsible for extensive interaction between the two ICs. The commissure mediates excitatory and inhibitory connections roughly in proportion to the percentages in which those neuronal types are found in the IC, and cells with a wide variety of morphologies project from one side to the other. These projections, if not connecting point-to-point, are at least weighted towards the interconnection of homologous points on the fibrodendritic lamina of the ICC, while in ICD there appear to be two populations of commissural neurons with distinct patterns of connections.

Our knowledge of the micro-circuitry of the IC is rudimentary. The extent to which commissural neurons also project to the main external targets of the IC, the brainstem and the thalamus, is controversial, but within the IC their projections to output neurons converge with other inputs. It is not known if commissural neurons are directly reciprocal, though this seems likely. Commissural neurons receive feedback from the auditory cortex, providing a route for the contralateral auditory cortex to influence the IC, over and above the relatively sparse *direct* projections from the contralateral cortex.

Overall, the anatomical findings reveal the ICs so intimately bound to one another by the commissure, it is hard to avoid the conclusion that they function as a single entity.

3.0 Functional properties of commissural projections

What might be the function of such interconnections? In comparison to our knowledge of the anatomical organisation of the CoIC, our understanding of its function is far more limited. The interconnection of the left and right sides of the brain points to a commissural role in binaural interactions, including the neural representation of sounds in azimuth. However, the extent of coupling between the two ICs suggests equally extensive and wide-ranging effects on auditory processing. What knowledge we have about the functional role of commissural connections derives primarily from electrophysiological studies *in vitro*, and *in vivo*.

3.1 In vitro studies

Electrical stimulation in brain slices, has been used to study the effects of commissural fibres on their contralateral neuronal targets. Interestingly, for neurons recorded in the central nucleus, the predominant response with stimulation of the commissure is a short latency EPSP followed by a short or, more often, long latency IPSP (Moore et al. 1998; Reetz and Ehret 1999). In contrast, although some neurons in ICD and ICL had only a short latency EPSP or ISPS, a short latency IPSP followed by an EPSP and often a second, long latency, IPSP was the dominant pattern (Smith 1992; Li et al. 1999). The short latency responses are consistent with monosynaptic excitatory and inhibitory connections, while the longer latency inhibitory effects indicate at least a di-synaptic pathway. Admittedly, the number of neurons studied in this way is relatively small, but these findings support the suggestion made earlier

that there are different patterns of synaptic organisation for commissural connections between the cortices of the IC, and those of the central nucleus.

Pharmacological approaches in these studies showed that the long latency component of the inhibition was blocked by the perfusion of AMPA glutamatergic-receptor antagonists, confirming that the long-latency inhibitory component is mediated by di- or poly-synaptic pathways in which GABAergic neurons are driven by excitatory commissural fibres (Smith 1992; Moore et al. 1998). Thus, although excitatory fibres in the commissure outnumber inhibitory fibres by around 4:1, inhibitory effects arising from commissural activation could occur more frequently than expected by this ratio. For some commissurally activated neurons in ICD, it was also possible to uncover an NMDA-receptor mediated component, suggesting that these inputs may play a role in processing involving learning and plasticity (Smith 1992; Li et al. 1999), as might be expected given the role of the ICD in learning-induced auditory plasticity (Bajo et al. 2010).

3.2 In vivo studies

The main advantage of *in vivo* recording for auditory studies is it can be combined with physiologically relevant sound stimulation. In the current context, such recordings have been combined with stimulating or inactivating the commissural pathway.

In principle, inactivating commissural inputs, and thus removing their normative influence, might be more informative for understanding the physiology of commissural connections. Two approaches have been used: the application of drugs, either by pressure injection (Malmierca et al. 2003; Malmierca et al. 2005), or microdialysis (Orton and Rees 2014; Orton et al. 2016) into one IC, or local cooling of one IC (Orton et al. 2012; Orton and Rees 2014; Orton et al. 2016). A limitation of pressure injection is the proximity of the recording site to the site of injection and the mechanical instability that often accompanies the injection. This is a particular problem for single unit studies where the recording is highly sensitive to mechanical disturbance. Micro-iontophoresis avoids these issues, but the volume of drug delivered, and therefore the region of influence of the drug, is small, and, given the organisation of commissural connections, requires positioning the pipette to match the location of the recording site in the other IC. A better combination of mechanical stability and extended region of influence is obtained by delivering a drug via a microdialysis cannula (Orton and Rees 2014; Orton et al. 2016). An alternative to blocking commissural activity is to activate the commissure via electrical stimulation of the contralateral IC (Mei et al. 2012b). This method allows direct activation of commissural fibres with control over the pattern of stimulation. However, it may not mimic physiological activity, and could result in effects arising from the antidromic activation of neurons in the contralateral IC.

In vivo studies demonstrate that modulating commissural input has wide-ranging effects on neurons in the contralateral IC, with evidence for effects on frequency response areas, rate level functions and the processing binaural cues.

Frequency response areas or receptive field in the IC can be subdivided into several categories according to their shape. Many neurons have a V-shaped response area, redolent of auditory nerve fibres (LeBeau et al. 2001; Palmer et al. 2013). The other broad group, termed non-V, contains several patterns, some of which appear to have been sculpted by inhibition from a V-type response (Egorova et al. 2001; LeBeau et al. 2001; Alkhatib et al. 2006; Palmer et al. 2013). While distinct sub-types appear to occur within this group, detailed analysis of thousands of response areas suggest they do not

constitute discrete classes, but lie on a continuum (Palmer et al.). Experiments where recording is combined with iontophoresis of GABAergic antagonists shows differential effects on these two groups: V-shaped response areas show increased firing rate over the whole response area, with little change in receptive field area. In contrast neurons in the non-V group often show changes in receptive field shape, often reverting to a more V-like appearance (LeBeau et al. 2001).

Interestingly, inactivation of the commissural connections produces changes in frequency response areas reminiscent of those seen with inhibitory blockade (LeBeau et al. 2001; Malmierca et al. 2003; Orton and Rees 2014). V-shaped response areas typically showed an increase or reduction in firing over the whole response area, whereas in non-V type responses changes in firing rate were accompanied by an increase or decrease in receptive field area and shape (Figure 4) (Orton and Rees 2014). The parallels between these observations and those in which inhibitory inputs to the recorded neuron are blocked by GABAergic antagonists, suggest that commissural connections contribute to the inputs defining receptive field shape, and these can be facilitatory or inhibitory in their action.

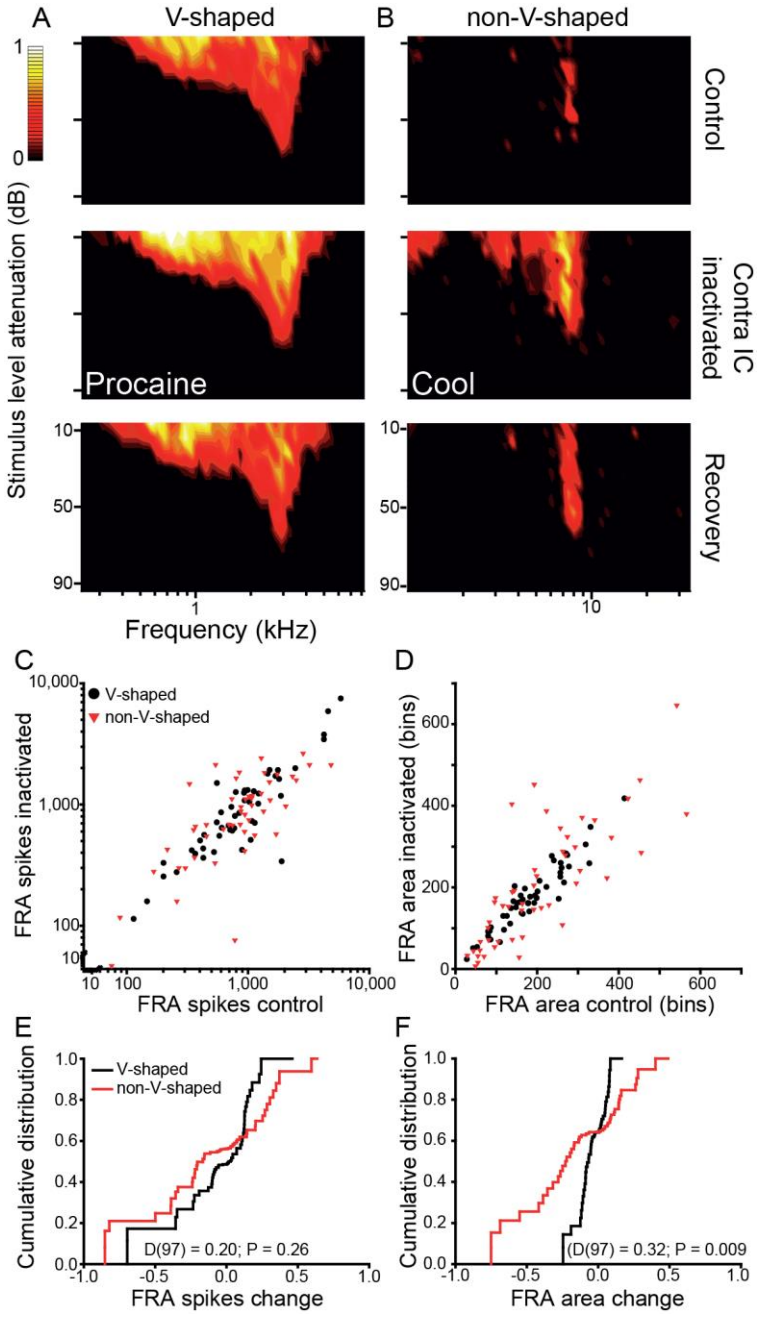

Figure 4

*Influence of commissural input on frequency responses in the IC. V-shaped (**A**) and nonV-shaped (**B**) response areas for single neurons recorded in the IC of guinea pig. Control (top), during inactivation of the contralateral IC by procaine infusion or cooling (middle), and after recovery (bottom). Responses in each example normalised to the maximum value across conditions. On deactivation of the contralateral IC, the V-shaped response area showed an elevation in firing, but little change in area or shape. In contrast, the nonV-shaped response area expanded, and firing increased at frequencies to which the neuron responded in the control condition. Comparison of firing (**C**, total number of spikes) and area (**D,** above threshold bins) in the control and deactivated conditions for the populations of V-shaped (black) and nonV-shaped (red) frequency response areas (FRAs). Cumulative distributions for change in firing (**E)** and area (**F)** for V and nonV groups. While the range of change in firing was similar between the two groups, the nonV group showed a larger range of area change than the V group. (Modified from Orton and Rees, 2014.)*

Figure 4 near here

Electrical stimulation of one IC leads to changes in firing rate and broadening or narrowing of V-shaped tuning curves for neurons in the other IC, in some cases accompanied by a change in best frequency (Mei et al. 2012a; Cheng et al. 2013). The direction of such changes depended on the difference between the frequency represented by the stimulation site in one IC and the recording site in the other. Where such a difference existed the best frequency shifted towards that of the stimulation site (Mei et al. 2012b; Cheng et al. 2013). These effects appear to involve plasticity, since they are sustained for 1-2 hours following 30 mins of stimulation. It is not clear to what extent these effects implicate commissural interactions between different frequency-band laminae.

As expected given changes in frequency response areas, stimulation or inactivation in the IC also influences the relationship between firing rate and sound level of neurons in the opposite side, as exemplified by rate-level functions (RLFs). Electrical stimulation can elicit increases or decreases in firing rate, although the majority of neurons were inhibited by stimulation of the contralateral IC (Cheng 2016; Mei 2012). Facilitation was generally only observed with small BF differences whereas inhibition occurred over a wider range of best frequency differences, again raising the possibility of interactions between within and between laminae. In general, rate level responses were suppressed by electrical stimulation with increased slope, and a reduction in dynamic range, but no change in the degree of monotonicity. As with the effects on frequency responses, there was evidence of the involvement of short-term plasticity.

Blockade of commissural inputs, either by cooling or microdialysis of procaine, in guinea pig resulted in shifts in RLFs towards higher sound levels and reduced non-monotonicity, effects that were, in the main, due to changes in responsivity at supra-threshold sound levels (Orton and Rees 2014). As a consequence of these changes, there was an overall reduction in the ability of neurons to discriminate sound levels, suggesting that physiologically commissural input enhances the neural representation of sound level.

Although in all these studies there was evidence for both excitatory and inhibitory commissural effects, inhibitory effects appear to occur disproportionately to the known distribution of glutamatergic and GABAergic fibres in the commissure (see Section 2.4) (Malmierca et al. 2005; Mei et al. 2013; Orton and Rees 2014). This finding concurs with the findings of *in vitro* studies (see Section 3.1) demonstrating that inhibitory effects are mediated not only mono-synaptically, but also by di- or poly-synaptic circuits in which excitatory commissural fibres target local inhibitory neurons in the contralateral IC.

As we suggested earlier, it seems intuitive that commissural interactions might impact binaural processing. Physiological studies *in vivo* lend some support to this view (Malmierca et al 2005; Orton et al 2016). Orton et al (2016) addressed this issue by inactivating the IC by cooling or procaine infusion while recording neuronal responses to stimuli of varying interaural time or level difference (ITD, ILD) in the opposite IC. The dominant effect of IC inactivation was a reversible reduction or increase in firing rate at all values ITD or ILD. Across the population of recorded neurons, there was no evidence for a change in the range of ITD or ILDs encoded in the absence of commissural input. Nevertheless, analysis of firing rates for the control and inactivated conditions (Figure 5) indicated, both for ITD and ILD, that response gain was reduced following commissural inactivation. Commensurate with this reduction in gain, discriminability of these binaural cues was also reduced. Taken together, these findings suggest that in normal operation, commissural inputs enhance the ability of IC neurons to discriminate changes in the position of sounds in azimuthal space.

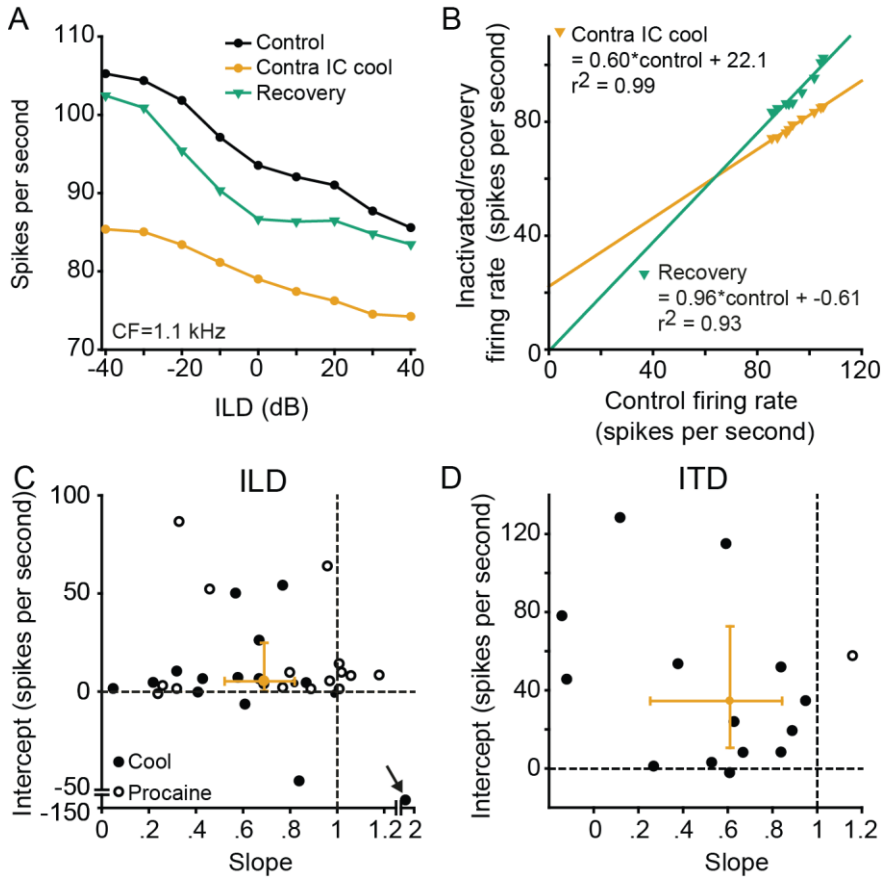

Figure 5

The influence of commissural input on response gain to interaural time and level differences in the IC. ***A.*** *Interaural level difference (ILD, sound level in ear ipsilateral to recorded IC relative to contralateral ear) functions for a single neuron: control (black), during deactivation of the contralateral IC (yellow) and after recovery (green).* ***B*** *Data in (A) replotted as firing rate in the inactivated (yellow) or recovery conditions (green) as a function of control. The difference in slope and intercept between these two functions denotes a divisive and additive gain change in the inactivated condition.* ***C & D*** *Summary plots showing the change in slope and intercept as in (**B**) for units tested with ILD (**C**) and ITD (**D**) stimuli. Overall, for both cues of azimuthal location, removal of commissural input leads to a reduction in slope and a more positive intercept, consistent with normal commissural input enhancing response gain in a multiplicative and subtractive manner. (From Orton et al, 2016.)*

Figure 5 near here

An important caveat that applies to all the methodologies used thus far to manipulate commissural inputs is that they might influence the contralateral IC via routes other than the commissure. These alternative pathways could go via the auditory cortex, given that both ipsilateral and contralateral cortices influence the IC, the latter, in part, via a commissural projection (Nakamoto et al. 2013). Alternatively, the descending projections from the IC to the superior olivary complex or the cochlear nucleus could also modulate the ascending input into the IC. The possibility seems less likely in view of the fact that when the IC is inactivated through cooling, the effect on sound-evoked local field potentials recorded in the opposite IC is predominantly on the later potentials rather than on the initial afferent volley (Orton et al 2012).

Some of the technical limitations of the methods used to investigate commissural function thus far could be surmounted with the application of optogenetics, which confers the possibility of targeting only those neurons that contribute to the commissural projection, a feat not possible with methods that globally modulate IC function. Furthermore, given evidence that commissural neurons may be a distinct subset of IC neurons (Okoyama et al. 2006), the ability to manipulate them in the absence of influencing IC neurons that project to upstream or downstream targets would be a distinct advantage.

3.3 Behavioural studies

If commissural inputs are important for sound processing in the IC, then the loss of commissural input might be expected lead to behavioural deficits in sound processing. Transecting the commissure is difficult and not reversible, and there is only one study in the literature where this has been reported (Moore et al. 1974). In this behavioural study of sound localisation in cat, transection of the commissure of the IC was either performed alone, or preceded or followed by transections of the trapezoid body and/or the corpus callosum to demonstrate their cumulative effects. Only a lesion to the trapezoid body was reported to impact sound localisation. Unfortunately, the study has limited utility since only two sound sources were used, situated either side of the animal's midline, thus it tested lateralisation rather than localisation. Subsequent studies have confirmed that following unilateral lesions within various structures in the ascending auditory pathway, animals can retain the ability to lateralise sound sources, but may not be able to localise them (Jenkins and Masterton 1982).

In the absence of studies involving commissural transection, we can look to studies in animals or human where there is a lesion in one IC. These reports vary in the tests conducted and the effects observed, but are consistent in reporting deficits in sound localisation in the spatial hemifield contralateral to the lesion (Kelly and Kavanagh 1994; Litovsky et al. 2002) (Jenkins and Masterton 1982; Champoux et al. 2007). The extent of the lesion varied from study to study, but the most marked deficits occurred where damage extended to the nuclei of the lateral lemniscus (Kelly and Kavanagh 1994).

For the current discussion, the question is whether such unilateral lesions had any impact on responses to stimuli presented in the hemifield ipsilateral to the lesion, the 'intact hemifield'? Such effects would be expected if signals to the IC, via the commissure, from the lesioned side, were ordinarily important. Although the other IC is not *necessary* for localisation in the 'intact hemifield', there is evidence that performance in that hemifield is affected by a lesion to the other IC. Litovsky et al.'s (2002) patient showed impaired performance, relative to controls, when localising targets close to the midline in the 'intact hemifield', and in animal studies, pre-lesion performance was consistently worse than post-lesion performance in the 'intact hemifield' (Kelly and Kavanagh 1994). Although these were small effects and could have alternative explanations, we should be cautious about ruling out the importance of the commissural pathway on the basis of these studies. Most behavioural studies tested localisation using clicks or brief noise bursts, in which the main interaural cue is stimulus onset time, rather than

on-going interaural time and level differences. Furthermore, tests were conducted in quiet conditions using constant intensity stimuli, and did not fully reflect the more demanding conditions of real-world listening.

4 Speculations regarding the function of commissural projections

The anatomical and physiological evidence accumulated so far suggest the CoIC's extensive connections exert wide-ranging effects on sound processing that encompass at least the encoding of frequency, level and location.

Insights into why the colliculi are interconnected may be gained by considering why is it important for one colliculus to know about the responses of its twin in response to events in the acoustic environment? One possibility is that the signal in one IC alone is insufficient to define the properties of a sound source unambiguously. For example, consider how the location of a sound source is represented in the two ICs. Signals encoding interaural time and level differences reach the ICs having been extracted in the medial and lateral nuclei, respectively, of the superior olivary complex (Grothe et al. 2010). The neural representation of these azimuthal cues is organised in mirror symmetric hemispheric channels. As a sound source moves from one extreme of azimuth to the other, the firing rate of neurons in one IC increases while those in the other decrease in a negatively correlated manner. However, when considering the neural activity in one IC alone, such a rate-coded representation might not code the stimulus invariantly. As represented schematically in Figure 6, the change in firing rate of neurons in the right IC to a sound that moves from the midline to the left side (green arrow and green dot) would be indistinguishable from that to a sound on the midline that increases in overall level (blue arrow, blue dot). These stimulus changes are distinguishable, however, if the firing rates in *both* ICs are compared. The increase in level results in an increased firing rate in both ICs, whereas the change in azimuth leads to a reduction in firing in the left IC and an increase in the right. Although such an analysis is doubtless an oversimplification of reality, it serves to demonstrate how signals sent back and forth across the commissure to signal the mutual state of each IC could be important for resolving such ambiguities.

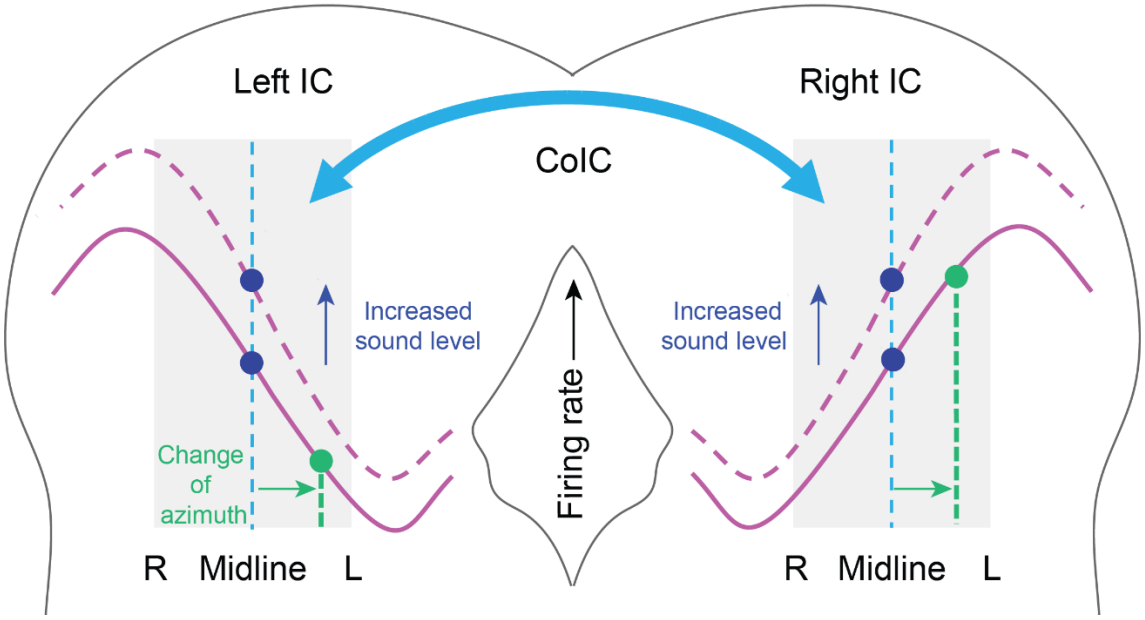

Figure 6

Schematic diagram demonstrating ambiguous stimulus representation when based on firing rates in one IC (see text for discussion). The solid magenta curves represent the response functions of IC neurons to changes in stimulus azimuth in the hemispheric channel model for sound localisation. The dashed magenta curves represent the firing to similar stimuli, but at a higher sound pressure level. As a stimulus moves from the midline to the left, the firing rate in the contralateral (right) IC increases (green arrow and green dot), but the same firing rate is obtained from a stimulus in the midline at higher level (blue arrow and blue dot). This ambiguity is resolved if the firing in both ICs is considered. A shift in azimuth leads to firing in the two ICs changing in opposite directions (green arrows and green dots), whereas changes in level lead to firing rates changing in the same direction (blue arrows and blue dots). Connecting the two ICs via the CoIC could provide each IC with information about the status of the other.

Figure 6 near here

Other roles for the commissure are suggested by anatomical and physiological findings. One important aspect of real-world hearing is the need to adjust response properties of neurons to keep them within their operating range as overall sound levels in the acoustic environment changes. Stimulus-dependent gain control in the IC has been shown to keep neurons within their operating range so maintaining their responsiveness to tones as noise levels increase (Rees and Palmer 1988; Dean et al. 2005; Robinson and McAlpine 2009). It is interesting that modulation of commissural activity leads to shifts in the operating ranges of rate-level functions (Mei et al. 2012a; Orton and Rees 2014; Mei et al. 2016).

Finally, there is increasing evidence of the important influence that corticofugal and other descending inputs have on auditory processing, including mediating various forms of plasticity (Suga and Ma 2003; Bajo et al. 2010; Bajo and King 2013). Such descending inputs might also mediate the types of feedback interactions postulated in predictive coding (Bastos et al. 2012). Particularly intriguing in this context is the evidence for a crossed cortical input to the contralateral IC mediated by commissural connections (Nakamoto et al. 2013).

5. Conclusion

This chapter has highlighted the extent to which the two inferior colliculi are tightly interconnected by commissural connections that closely integrate many aspects of their complex circuitry. The wide-ranging effects of the commissural system on the coding of fundamental parameters of sound: frequency, level and spatial location, is consistent with the possibility that responses of virtually all neurons in one IC are influenced by those in the other. Thus, functionally, the two ICs appear to operate as a single entity.

Existing studies have only scratched the surface in discovering the role of commissural connections, and it is important to avoid the fallacy of basing an understanding of commissural function on the answers to what might be the wrong questions! And it is more than likely that the adequate stimulus (Sherrington 1906) necessary to reveal the critical contribution of the CoIC have yet to be identified. Furthermore, it is increasingly evident that the inferior colliculus does much more than just integrate ascending sensory information. It receives a multitude of inputs from diverse sources, including those of corticofugal (Bajo and King 2013) and neuromodulatory origin (Hurley and Sullivan 2012; Gittelman et al. 2013), that have thus far received little attention. A more complete understanding of the function of the CoIC may require experiments in an awake behaving preparation where the full impact of these diverse inputs can be assessed.

Acknowledgements

Some of our own work discussed in this chapter was supported by grants from the Wellcome Trust (066348) and BBSRC (BB/J0008680/1) to AR.

Figure Legends

Figure 1

***A**. Coronal section (50-µm thick) of the tectal midbrain in guinea pig stained for myelin with osmium tetroxide to show the commissure of the inferior colliculus (CoIC). Commissural fibres can be seen crossing the midline and fanning out into each IC. Fibres of the lateral lemniscus can be seen entering the ICs from below. **B**. Photomicrograph showing injections of two different tracers into the same frequency band lamina in the IC of rat. The best frequency at the injection sites was determined by electrophysiological recording to sound to be 10-10.5 kHz. The injection of tetramethyl-rhodamine dextran (TRD) in the dorsal cortex (IC$_D$, yellow circle) and biotinylated dextran amine (BDA) into the central nucleus (IC$_C$, red circle). A V-shaped plexus of intrinsic axons is labelled ipsilateral to the injections with a central wing in IC$_C$ that extends into IC$_D$, and a lateral wing that turns into the lateral cortex (IC$_L$). **C**. In the contralateral IC, commissural fibres are labelled in mirror image distribution to those ipsilateral, with retrogradely labelled neuronal somata scattered amongst them. **D**. Camera lucida drawings from sections at different locations along the rostro-caudal axis, showing the locations of somata labelled by the injection in the central nucleus (red dots) and the dorsal cortex (black dots) respectively. **E.** Three dimensional reconstructions in the coronal plane of the locations of the injection sites (left) and of retrogradely labelled somata (right) for the case shown in **B-D.** The injection in the IC$_C$ labels somata (red points) in the contralateral IC$_C$ and IC$_D$. Somata labelled following an injection in the IC$_D$ (yellow points) are restricted to the cortical regions. (Some of the latter appear in this view to be in the IC$_C$, but viewing from other orientations shows them to be in the cortex rostral and caudal to the IC$_C$.) Neurons in the IC$_L$ do not give rise to commissural projections. D, dorsal; L, lateral. (B-E adapted from Malmierca et al., 2009).*

Figure 2

Schematic diagrams to illustrate the patterns of commissural connections between the different subdivisions of the inferior colliculus (IC) based on retrograde labelling following tracer injections like those in Fig 1.

***A.** An injection (dotted circle) into the central nucleus (IC$_C$) results in fibro-dendritic labelling of a V-shaped axonal plexus (grey) in both ICs (see Fig 1B). Retrogradely labelled somata (filled dots) are observed over the length of the lamina in the contralateral (right) IC, consistent with each of these neurons making divergent commissural projections (thin arrows) to the injection site and sites along the lamina. Cell counts show the projection is weighted (broad arrow) to a point on the lamina (solid circle) corresponding to that of injection site. **B.** Neurons in the dorsal cortex make two types of projection: an injection in ICC retrogradely labels neurons in the deeper layers of the dorsal cortex (open squares) in line with the lamina, while an injection in IC$_D$ labels neurons distributed more diffusely in the dorsal cortex (solid squares).*

Figure 3

Summary of the sources and terminal sites of fibres projecting through the commissure of the IC. By far the largest part of the projection originates in the contralateral IC from the central nucleus (ICC) and the dorsal cortex (ICD). Other centres in the brainstem, diencephalon and cerebral cortex make up smaller part of the projection and primarily terminate in the ICD. Coloured stippling in the subdivisions of the IC, corresponding to the colour of the incoming projections, indicates the regions where these inputs terminate. Inset top right shows that the IC also sends a minor projection to the contralateral medial geniculate body (MGB) and auditory cortex via the CoIC.

Figure 4

*Influence of commissural input on frequency responses in the IC. V-shaped (**A**) and nonV-shaped (**B**) response areas for single neurons recorded in the IC of guinea pig. Control (top), during inactivation of the contralateral IC by procaine infusion or cooling (middle), and after recovery (bottom). Responses in each example normalised to the maximum value across conditions. On deactivation of the contralateral IC, the V-shaped response area showed an elevation in firing, but little change in area or shape. In contrast, the nonV-shaped response area expanded, and firing increased at frequencies to which the neuron responded in the control condition. Comparison of firing (**C**, total number of spikes) and area (**D,** above threshold bins) in the control and deactivated conditions for the populations of V-shaped (black) and nonV-shaped (red) frequency response areas (FRAs). Cumulative distributions for change in firing (**E)** and area (**F)** for V and nonV groups. While the range of change in firing was similar between the two groups, the nonV group showed a larger range of area change than the V group. (Modified from Orton and Rees, 2014.)*

Figure 5

*The influence of commissural input on response gain to interaural time and level differences in the IC. **A.** Interaural level difference (ILD, sound level in ear ipsilateral to recorded IC relative to contralateral ear) functions for a single neuron: control (black), during deactivation of the contralateral IC (yellow) and after recovery (green). **B** Data in (A) replotted as firing rate in the inactivated (yellow) or recovery conditions (green) as a function of control. The difference in slope and intercept between these two functions denotes a divisive and additive gain change in the inactivated condition. **C & D** Summary plots showing the change in slope and intercept as in (**B**) for units tested with ILD (**C)** and ITD **(D)** stimuli. Overall, for both cues of azimuthal location, removal of commissural input leads to a reduction in slope and a more positive intercept, consistent with normal commissural input enhancing response gain in a multiplicative and subtractive manner. (From Orton et al, 2016.)*

Figure 6

Schematic diagram demonstrating ambiguous stimulus representation when based on firing rates in one IC (see text for discussion). The solid magenta curves represent the response functions of IC neurons to changes in stimulus azimuth in the hemispheric channel model for sound localisation. The dashed magenta curves represent the firing to similar stimuli, but at a higher sound pressure level. As a stimulus moves from the midline to the left, the firing rate in the contralateral (right) IC increases (green arrow and green dot), but the same firing rate is obtained from a stimulus in the midline at higher level (blue arrow and blue dot). This ambiguity is resolved if the firing in both ICs is considered. A shift in

azimuth leads to firing in the two ICs changing in opposite directions (green arrows and green dots), whereas changes in level lead to firing rates changing in the same direction (blue arrows and blue dots). Connecting the two ICs via the CoIC could provide each IC with information about the status of the other.

Bibliography

Adams, J. C. (1980). "Crossed and descending projections to the inferior colliculus." Neuroscience Letters **19**: 1-5.

Adams, J. C. and Mugnaini, E. (1984). "Dorsal nucleus of the lateral lemniscus: A nucleus of GABAergic projection neurons." Brain Research Bulletin **13**: 585-590.

Adams, J. C. and Wenthold, R. J. (1979). "Distribution of putative amino acid transmitters, choline acetyltransferase and glutamate decarboxylase in the inferior colliculus." Neuroscience **4**: 1947-1951.

Afifi, A. and Kaelber, W. W. (1965). "Efferent Connections of the Substantia Nigra in the Cat." Exp Neurol **11**: 474-482.

Alibardi, L. (1998). "Ultrastructural and immunocytochemical characterization of commissural neurons in the ventral cochlear nucleus of the rat." Annals of Anatomy - Anatomischer Anzeiger **180**: 427-438.

Alkhatib, A., Biebel, U. W. and Smolders, J. W. T. (2006). "Inhibitory and excitatory response areas of neurons in the central nucleus of the inferior colliculus in unanesthetized chinchillas." Experimental Brain Research **174**: 124-143.

Altschuler, R. A., Tong, L., Holt, A. G. and Oliver, D. L. (2008). "Immunolocalization of vesicular glutamate transporters 1 and 2 in the rat inferior colliculus." Neuroscience **154**: 226-232.

Aparicio, M. A., Viñuela, A. and Saldaña, E. (2010). "Projections from the inferior colliculus to the tectal longitudinal column in the rat." Neuroscience **166**: 653-664.

Arnott, R. H., Wallace, M. N., Shackleton, T. M. and Palmer, A. R. (2004). "Onset Neurones in the Anteroventral Cochlear Nucleus Project to the Dorsal Cochlear Nucleus." JARO **5**: 153-170.

Bajo, V. M. and King, A. J. (2013). "Cortical modulation of auditory processing in the midbrain." Frontiers in Neural Circuits **6**.

Bajo, V. M., Merchan, M. A., Lopez, D. E. and Rouiller, E. M. (1993). "Neuronal morphology and efferent projections of the dorsal nucleus of the lateral lemniscus in the rat." J Comp Neurol **334**: 241-262.

Bajo, V. M. and Moore, D. R. (2005). "Descending projections from the auditory cortex to the inferior colliculus in the gerbil, <I>Meriones unguiculatus</I>." The Journal of Comparative Neurology **486**: 101-116.

Bajo, V. M., Nodal, F. R., Moore, D. R. and King, A. J. (2010). "The descending corticocollicular pathway mediates learning-induced auditory plasticity." Nat Neurosci **13**: 253-260.

Barnes, W. T., Magoun, H. W. and Ranson, S. W. (1943). "The ascending auditory pathway in the brain stem of the monkey." The Journal of Comparative Neurology **79**: 129-152.

Bastos, Andre M., Usrey, W. M., Adams, Rick A., Mangun, George R., Fries, P. and Friston, Karl J. (2012). "Canonical Microcircuits for Predictive Coding." Neuron **76**: 695-711.

Brown, M. C., Drottar, M., Benson, T. E. and Darrow, K. (2013). "Commissural axons of the mouse cochlear nucleus." Journal of Comparative Neurology **521**: 1683-1696.

Cant, N. (2013). "Patterns of convergence in the central nucleus of the inferior colliculus of the Mongolian gerbil: organization of inputs from the superior olivary complex in the low frequency representation." Frontiers in Neural Circuits **7**.

Cant, N. B. and Benson, C. G. (2006). "Organization of the inferior colliculus of the gerbil (*Meriones unguiculatus*): Differences in distribution of projections from the cochlear nuclei and the superior olivary complex." The Journal of Comparative Neurology **495**: 511-528.

Cant, N. B. and Gaston, K. C. (1982). "Pathways connecting the right and left cochlear nuclei." The Journal of Comparative Neurology **212**: 313-326.
Champoux, F., Paiement, P., Mercier, C., Lepore, F., Lassonde, M. and Gagné, J. P. (2007). "Auditory processing in a patient with a unilateral lesion of the inferior colliculus." European Journal of Neuroscience **25**: 291-297.
Chen, C., Cheng, M., Ito, T. and Song, S. (2018). "Neuronal organization in the inferior colliculus revisited with cell-type-dependent monosynaptic tracing." The Journal of Neuroscience.
Chen, L., Kelly, J. B. and Wu, S. H. (1999). "The commissure of Probst as a source of GABAergic inhibition." Hearing Research **138**: 106-114.
Cheng, L., Mei, H. X., Tang, J., Fu, Z. Y., Jen, P. H. S. and Chen, Q. C. (2013). "Bilateral collicular interaction: Modulation of auditory signal processing in frequency domain." Neuroscience **235**: 27-39.
Coleman, J. R. and Clerici, W. J. (1987). "Sources of projections to subdivisions of the inferior colliculus in the rat." The Journal of Comparative Neurology **262**: 215-226.
Coomes, D. L. and Schofield, B. R. (2004). "Separate projections from the inferior colliculus to the cochlear nucleus and thalamus in guinea pigs." Hearing Research **191**: 67-78.
Coomes, D. L., Schofield, R. M. and Schofield, B. R. (2005). "Unilateral and bilateral projections from cortical cells to the inferior colliculus in guinea pigs." Brain Research **1042**: 62-72.
Dean, I., Harper, N. S. and McAlpine, D. (2005). "Neural population coding of sound level adapts to stimulus statistics." Nat Neurosci **8**: 1684-1689.
Doucet, J. R., Lenihan, N. M. and May, B. J. (2009). "Commissural Neurons in the Rat Ventral Cochlear Nucleus." Journal of the Association for Research in Otolaryngology **10**: 269-280.
Druga, R. and Syka, J. (1984). "Ascending and descending projections to the inferior colliculus in the rat " Physiologica Bohemoslovaca **33**: 31-42.
Egorova, M., Ehret, G., Vartanian, I. and Esser, K. H. (2001). "Frequency response areas of neurons in the mouse inferior colliculus. I. Threshold and tuning characteristics." Experimental Brain Research **140**: 145-161.
Faye Lund, H. and Osen, K. K. (1985). "Anatomy of the Inferior Colliculus in Rat." Anatomy and Embryology **171**: 1-20.
Gittelman, J. X., Perkel, D. J. and Portfors, C. V. (2013). "Dopamine Modulates Auditory Responses in the Inferior Colliculus in a Heterogeneous Manner." Journal of the Association for Research in Otolaryngology **14**: 719-729.
González-Hernández, T., Mantolán-Sarmiento, B., González-González, B. and Pérez-González, H. (1996). "Sources of GABAergic input to the inferior colliculus of the rat." Journal of Comparative Neurology **372**: 309-326.
González-Hernández, T. H., Galindo-Mireles, D., Castañeyra-Perdomo, A. and Ferres-Torres, R. (1991). "Divergent projections of projecting neurons of the inferior colliculus to the medial geniculate body and the contralateral inferior colliculus in the rat." Hearing Research **52**: 17-21.
Gonzalez Hernandez, T. H., Meyer, G. and Ferres-Torres, R. (1986). "The commissural interconnections of the inferior colliculus in the albino mouse." Brain Research **368**: 268-276.
Grothe, B., Pecka, M. and McAlpine, D. (2010). "Mechanisms of Sound Localization in Mammals." Physiological Reviews **90**: 983-1012.
Henkel, C. K. and Shneiderman, A. (1988). "Nucleus Sagulum - Projections of a Lateral Tegmental Area to the Inferior Colliculus in the Cat." Journal of Comparative Neurology **271**: 577-588.
Hernández, O., Rees, A. and Malmierca, M. S. (2006). "A GABAergic component in the commissure of the inferior colliculus in rat." NeuroReport **17**: 1611-1614.
Hurley, L. M. and Sullivan, M. R. (2012). "From behavioral context to receptors: serotonergic modulatory pathways in the IC." Frontiers in Neural Circuits **6**.
Hutson, K. A., Glendenning, K. K. and Masterton, R. B. (1991). "Acoustic chiasm. IV: Eight midbrain decussations of the auditory system in the cat." J Comp Neurol **312**: 105-131.
Ito, T., Bishop, D. C. and Oliver, D. L. (2009). "Two Classes of GABAergic Neurons in the Inferior Colliculus." Journal of Neuroscience **29**: 13860-13869.

Ito, T., Hioki, H., Sohn, J., Okamoto, S., Kaneko, T., Iino, S. and Oliver, D. L. (2015). "Convergence of lemniscal and local excitatory inputs on large GABAergic tectothalamic neurons." Journal of Comparative Neurology **523**: 2277-2296.

Ito, T. and Oliver, D. L. (2014). "Local and commissural IC neurons make axosomatic inputs on large GABAergic tectothalamic neurons." Journal of Comparative Neurology **522**: 3539-3554.

Jenkins, W. M. and Masterton, R. B. (1982). "Sound localization: effects of unilateral lesions in central auditory system." Journal of Neurophysiology **47**: 987-1016.

Kelly, J. B. and Kavanagh, G. L. (1994). "Sound localization after unilateral lesions of inferior colliculus in the ferret (Mustela putorius)." Journal of Neurophysiology **71**: 1078-1087.

Kudo, M. and Niimi, K. (1978). "Ascending projections of the inferior colliculus onto the medial geniculate body in the cat studied by anterograde and retrograde tracing techniques." Brain Research **155**: 113-117.

LeBeau, F. E. N., Malmierca, M. S. and Rees, A. (2001). "Iontophoresis in vivo demonstrates a key role for GABA(A) and glycinergic inhibition in shaping frequency response areas in the inferior colliculus of guinea pig." Journal of Neuroscience **21**: 7303-7312.

Lee, C. C., Yanagawa, Y. and Imaizumi, K. (2015). "Commissural functional topography of the inferior colliculus assessed in vitro." Hearing Research **328**: 94-101.

Li, Y., Evans, M. S. and Faingold, C. L. (1999). "Synaptic response patterns of neurons in the cortex of rat inferior colliculus." Hearing Research **137**: 15-28.

Litovsky, R. Y., Fligor, B. J. and Traino, M. J. (2002). "Functional role of the human inferior colliculus in binaural hearing." Hearing Research **165**: 177-188.

Loftus, W. C., Bishop, D. C. and Oliver, D. L. (2010). "Differential Patterns of Inputs Create Functional Zones in Central Nucleus of Inferior Colliculus." Journal of Neuroscience **30**: 13396-13408.

Malmierca, M. S., Blackstad, T. W., Osen, K. K., Karagulle, T. and Molowny, R. L. (1993). "The central nucleus of the inferior colliculus in rat - a Golgi and computer reconstruction study of neuronal and laminar structure." Journal of Comparative Neurology **333**: 1-27.

Malmierca, M. S. and Hackett, T. A. (2010). Structural organization of the ascending auditory pathway.In: The Auditory Brain. A. Rees and A. Palmer, Eds. Oxford, OUP**:** 9-41.

Malmierca, M. S., Hernández, O., Antunes, F. M. and Rees, A. (2009). "Divergent and point-to-point connections in the commissural pathway between the inferior colliculi." Journal of Comparative Neurology **514**: 226-239.

Malmierca, M. S., Hernandez, O., Falconi, A., Lopez-Poveda, E. A., Merchan, M. and Rees, A. (2003). "The commissure of the inferior colliculus shapes frequency response areas in rat: an in vivo study using reversible blockade with microinjection of kynurenic acid." Experimental Brain Research **153**: 522-529.

Malmierca, M. S., Hernandez, O. and Rees, A. (2005). "Intercollicular commissural projections modulate neuronal responses in the inferior colliculus." European Journal of Neuroscience **21**: 2701-2710.

Malmierca, M. S., Rees, A., Lebeau, F. E. N. and Bjaalie, J. G. (1995). "Laminar Organization of Frequency-Defined Local Axons within and between the Inferior Colliculi of the Guinea-Pig." Journal of Comparative Neurology **357**: 124-144.

Marsh, R. A., Fuzessery, Z. M., Grose, C. D. and Wenstrup, J. J. (2002). "Projection to the inferior colliculus from the basal nucleus of the amygdala." Journal of Neuroscience **22**: 10449-10460.

Mei, H.-x., Cheng, L. and Chen, Q.-C. (2013). "Neural interactions in unilateral colliculus and between bilateral colliculi modulate auditory signal processing." Frontiers in Neural Circuits **7**.

Mei, H.-X., Cheng, L., Tang, J., Fu, Z.-Y., Jen, P. H. S. and Chen, Q.-C. (2012a). "Modulation of amplitude sensitivity by bilateral collicular interaction among different frequency laminae." Neuroscience Letters **517**: 13-17.

Mei, H.-X., Cheng, L., Tang, J., Fu, Z.-Y., Wang, X., Jen, P. H. S. and Chen, Q.-C. (2012b). "Bilateral Collicular Interaction: Modulation of Auditory Signal Processing in Amplitude Domain." PLOS ONE **7**: e41311.

Mei, H.-X., Tang, J., Fu, Z.-Y., Cheng, L. and Chen, Q.-C. (2016). "Plastic Change in the Auditory Minimum Threshold Induced by Intercollicular Effects in Mice." Neural Plasticity **2016**: 8.

Merchán, M., Aguilar, L. A., Lopez-Poveda, E. A. and Malmierca, M. S. (2005). "The inferior colliculus of the rat: Quantitative immunocytochemical study of GABA and glycine." Neuroscience **136**: 907-925.

Merzenich, M. M. and Reid, M. D. (1974). "Representation of the cochlea within the inferior colliculus of the cat." Brain Research **77**: 397-415.

Milinkeviciute, G., Muniak, M., Pongstaporn, T., Cho, A. and Ryugo, D. (2015). Circuitry between the dorsal cochlear nucleus and the inferior colliculus in the mouse. Assoc. Res. Otolaryngol. Abs.:.

Mizuno, N., Sauerland, E. K. and Clemente, C. D. (1968). "Projections from the orbital gyrus in the cat. I. To brain stem structures." The Journal of Comparative Neurology **133**: 463-475.

Moore, C. N., Casseday, J. H. and Neff, W. D. (1974). "Sound localization: the role of the commissural pathways of the auditory system of the cat." Brain Research **82**: 13-26.

Moore, D. R. (1988). "Auditory brainstem of the ferret: Sources of projections to the inferior colliculus." The Journal of Comparative Neurology **269**: 342-354.

Moore, D. R., Kotak, V. C. and Sanes, D. H. (1998). "Commissural and lemniscal synaptic input to the gerbil inferior colliculus." Journal of Neurophysiology **80**: 2229-2236.

Moore, R. Y. and Goldberg, J. M. (1966). "Projections of the inferior colliculus in the monkey." Exp Neurol **14**: 429-438.

Morest, D. K. and Oliver, D. L. (1984). "The neuronal architecture of the inferior colliculus in the cat: defining the functional anatomy of the auditory midbrain." Journal of Comparative Neurology **222**: 209-236.

Nakagawa, H., Ikeda, M., Houtani, T., Ueyama, T., Baba, K., Kondoh, A., Yamamoto, T., Yamashita, T. and Sugimoto, T. (1995). "Immunohistochemical evidence for enkephalin and neuropeptide Y in rat inferior colliculus neurons that provide ascending or commissural fibers." Brain Research **690**: 236-240.

Nakamoto, K. T., Sowick, C. S. and Schofield, B. R. (2013). "Auditory cortical axons contact commissural cells throughout the guinea pig inferior colliculus." Hearing Research **306**: 131-144.

Needham, K. and Paolini, A. G. (2006). "Neural timing, inhibition and the nature of stellate cell interaction in the ventral cochlear nucleus." Hearing Research **216-217**: 31-42.

Okoyama, S., Ohbayashi, M., Ito, M. and Harada, S. (2006). "Neuronal organization of the rat inferior colliculus participating in four major auditory pathways." Hearing Research **218**: 72-80.

Olazabal, U. E. and Moore, J. K. (1989). "Nigrotectal projection to the inferior colliculus: horseradish peroxidase transport and tyrosine hydroxylase immunohistochemical studies in rats, cats, and bats." J Comp Neurol **282**: 98-118.

Oliver, D. L. (1984). "Neuron Types in the Central Nucleus of the Inferior Colliculus That Project to the Medial Geniculate-Body." Neuroscience **11**: 409-424.

Oliver, D. L. (2005). Neuronal Organisation of the Inferior Colliculus.In: The Inferior Colliculus. J. A. Winer and C. E. Schreiner, Eds. New York, Springer**:** 69-114.

Oliver, D. L. and Morest, D. K. (1984). "The Central Nucleus of the Inferior Colliculus in the Cat." Journal of Comparative Neurology **222**: 237-264.

Orton, L. D., Papasavvas, C. A. and Rees, A. (2016). "Commissural Gain Control Enhances the Midbrain Representation of Sound Location." The Journal of Neuroscience **36**: 4470-4481.

Orton, L. D., Poon, P. W. F. and Rees, A. (2012). "Deactivation of the inferior colliculus by cooling demonstrates intercollicular modulation of neuronal activity." Frontiers in Neural Circuits **6**.

Orton, L. D. and Rees, A. (2014). "Intercollicular commissural connections refine the representation of sound frequency and level in the auditory midbrain." eLife **2014;3:e03764**.

Palmer, A. R., Shackleton, T. M., Sumner, C. J., Zobay, O. and Rees, A. (2013). "Classification of frequency response areas in the inferior colliculus reveals continua not discrete classes." The Journal of Physiology **591**: 4003-4025.

Powell, E. W. and Hatton, J. B. (1969). "Projections of the inferior colliculus in cat." J Comp Neurol **136**: 183-192.

Rees, A. and Palmer, A. R. (1988). "Rate-intensity functions and their modification by broad-band noise for neurons in the guinea-pig inferior colliculus." J.Acoust.Soc.Am. **83**: 1488-1498.

Reetz, G. and Ehret, G. (1999). "Inputs from three brainstem sources to identified neurons of the mouse inferior colliculus slice." Brain Research **816**: 527-543.
Robinson, B. L. and McAlpine, D. (2009). "Gain control mechanisms in the auditory pathway." Current Opinion in Neurobiology **19**: 402-407.
Rockel, A. J. and Jones, E. G. (1973). "Observations on the fine structure of the central nucleus of the inferior colliculus of the cat." J Comp Neurol **147**: 61-92.
Rose, J. E., Greenwood, D. D., Goldberg, J. M. and Hind, J. E. (1963). "Some discharge characteristics of single neurons in the inferior colliculus of the cat. I. Tonotopical organization, relation of spike-counts to tone intensity, and firing patterns of single elements." Journal of Neurophysiology **26**: 294-320.
Saint Marie, R. L. (1996). "Glutamatergic connections of the auditory midbrain: Selective uptake and axonal transport of D-[3H]aspartate." The Journal of Comparative Neurology **373**: 255-270.
Saldaña, E., Aparicio, M. A., Fuentes-Santamaría, V. and Berrebi, A. S. (2009). "Connections of the superior paraolivary nucleus of the rat: projections to the inferior colliculus." Neuroscience **163**: 372-387.
Saldana, E., Feliciano, M. and Mugnaini, E. (1996). "Distribution of descending projections from primary auditory neocortex to inferior colliculus mimics the topography of intracollicular projections." Journal of Comparative Neurology **371**: 15-40.
Saldaña, E. and Merchán, M. (2005). Intracollicular connections.In: The Inferior Colliculus. J. A. Winer and C. Schreiner, Eds. New York, Springer**:** 155-181.
Saldana, E. and Merchan, M. A. (1992). "Intrinsic and Commissural Connections of the Rat Inferior Colliculus." Journal of Comparative Neurology **319**: 417-437.
Saldaña, E., Viñuela, A., Marshall, A. F., Fitzpatrick, D. C. and Aparicio, M. A. (2007). "The TLC: A Novel Auditory Nucleus of the Mammalian Brain." The Journal of Neuroscience **27**: 13108-13116.
Schofield, B. R. and Cant, N. B. (1996a). "Origins and targets of commissural connections between the cochlear nuclei in guinea pigs." The Journal of Comparative Neurology **375**: 128-146.
Schofield, B. R. and Cant, N. B. (1996b). "Projections from the ventral cochlear nucleus to the inferior colliculus and the contralateral cochlear nucleus in guinea pigs." Hearing Research **102**: 1-14.
Sherrington, C. S. (1906). The integrative action of the nervous system. New Haven, CT, Yale University Press.
Shneiderman, A., Oliver, D. L. and Henkel, C. K. (1988). "Connections of the Dorsal Nucleus of the Lateral Lemniscus - an Inhibitory Parallel Pathway in the Ascending Auditory-System." Journal of Comparative Neurology **276**: 188-208.
Shore, S. E., Godfrey, D. A., Helfert, R. H., Altschuler, R. A. and Bledsoe, S. C. (1992). "Connections between the cochlear nuclei in guinea pig." Hearing Research **62**: 16-26.
Smith, P. H. (1992). "Anatomy and physiology of multipolar cells in the rat inferior collicular cortex using the in vitro brain slice technique." J. Neurosci. **12**: 3700-3715.
Suga, N. and Ma, X. F. (2003). "Multiparametric corticofugal modulation and plasticity in the auditory system." Nature Reviews Neuroscience **4**: 783-794.
Torterolo, P., Zurita, P., Pedemonte, M. and Velluti, R. A. (1998). "Auditory cortical efferent actions upon inferior colliculus unitary activity in the guinea pig." Neuroscience Letters **249**: 172-176.
van Adel, B. A., Kidd, S. A. and Kelly, J. B. (1999). "Contribution of the commissure of Probst to binaural evoked responses in the rat's inferior colliculus: interaural time differences." Hear Res **130**: 115-130.
van Noort, J. (1969). The Structure and Connections of the Inferior Colliculus. An Investigation of the Lower Auditory System Assen, Van Gorcum.
Wallace, M. N., Shackleton, T. M. and Palmer, A. R. (2012). "Morphological and physiological characteristics of laminar cells in the central nucleus of the inferior colliculus." Front Neural Circuits **6**: 55.
Whitley, J. M. and Henkel, C. K. (1984). "Topographical organization of the inferior collicular projection and other connections of the ventral nucleus of the lateral lemniscus in the cat." The Journal of Comparative Neurology **229**: 257-270.

Willard, F. H. and Martin, G. F. (1984). "Collateral innervation of the inferior colliculus in the North American opossum: A study using fluorescent markers in a double-labeling paradigm." Brain Research **303**: 171-182.

Winer, J. A., Chernock, M. L., Larue, D. T. and Cheung, S. W. (2002). "Descending projections to the inferior colliculus from the posterior thalamus and the auditory cortex in rat, cat, and monkey." Hearing Research **168**: 181-195.

Winer, J. A., Saint Marie, R. L., Larue, D. T. and Oliver, D. L. (1996). "GABAergic feedforward projections from the inferior colliculus to the medial geniculate body." Proceedings of the National Academy of Sciences of the United States of America **93**: 8005-8010.

Woollard, H. H. and Harpman, J. A. (1940). "The connexions of the inferior colliculus and of the dorsal nucleus of the lateral lemniscus." Journal of Anatomy **74**: 441-458.

Zhang, D. X., Li, L., Kelly, J. B. and Wu, S. H. (1998). "GABAergic projections from the lateral lemniscus to the inferior colliculus of the rat." Hear Res **117**: 1-12.