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Wiring of divergent networks in the central auditory system

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Divergent axonal projections are found throughout the central auditory system. Here, we evaluate these branched projections in terms of their types, distribution, and putative physiological roles. In general, three patterns of axon collateralization are found: intricate local branching, long-distance collaterals, and branched axons (BAs) involved in feedback-control loops. Local collaterals in the auditory cortex may be involved in local processing and modulation of neuronal firing, while long-range collaterals are optimized for wide-dissemination of information. Rarely do axons branch to both ascending and descending targets. Branched projections to two or more widely separated nuclei or areas are numerically sparse but widespread. Finally, branching to contralateral targets is evident at multiple levels of the auditory pathway and may enhance binaural computations for sound localization. These patterns of axonal branching are comparable to those observed in other modalities. We conclude that the operations served by BAs are area- and nucleus-specific and may complement the divergent unbranched projections of local neuronal populations.

Keywords: branched axon, auditory system, collaterals, cortical, thalamocortical, brainstem

INTRODUCTION

A cardinal feature of axons is their divergent projections, which range from sparse branching in the thalamic input to different auditory cortex (AC) areas (Morel and Imig, 1987; Lee et al., 2004a; Kishan et al., 2008) to the many collaterals and thousand of boutons of single spiral Ia cochlear ganglion axons (Brown, 1981). Branched axons (BAs) are present throughout the auditory system (Fekete et al., 1984; Willard and Martin, 1984; Ojima, 1994; Hazama et al., 2004; Coomes et al., 2005; Kimura et al., 2005; Lee and Winer, 2008a,b,c) and can take many forms, from local (Brown et al., 1988a,b) to very distant (Hashikawa et al., 1995; Cetas et al., 1999; Huang and Winer, 2000), presumably allowing neurons to synchronize remote events or form multiple feature-specific representations.

Different patterns of axonal branching prevail at different levels of the auditory system (**Figures 1–3**). For instance, branching between different nuclei is common in the pathways to and from the medial nucleus of the trapezoid body (MTB; Morest, 1968; Spirou et al., 1990; Kuwabara and Zook, 1991, 1992; Kuwabara et al., 1991; Smith et al., 1991), while thalamocortical axons rarely project to different cortical fields, such as the primary auditory cortex (AI) and the anterior auditory field (AAF; Morel and Imig, 1987; Lee et al., 2004a,b). Other axons have both descending and ascending projections, e.g., from MTB cell axons projecting to the cochlear nucleus (CoN) and the inferior colliculus (IC), <1% project to both (Schofield, 1994).

In discussing the wide variety of branching patterns present in the auditory system, it is imperative to acknowledge that various methods allow the detection of different patterns of axonal branching, and that these different methods have inherent limitations in terms of the conclusions that can be drawn from their use. Thus, we review the technical considerations inherent in assessing axonal branching. An especially important caveat to establish at the outset, however, is that dual retrograde injections can only ascertain axonal branching to the specific regions within the nuclei injected; conclusions cannot be drawn about other forms of axonal branching from these studies. Nonetheless, the use of dual retrograde tracing has been useful in formulating hypotheses about neural function.

Abbreviations: AAF, anterior auditory field; AC, auditory cortex; AI, primary auditory area; AII, second auditory cortex; AVCN, anteroventral cochlear nucleus; BA, branched axon; CF, characteristic frequency; CN, central nucleus of the IC; CoN, cochlear nucleus; CT, corticothalamic; CTβ, cholera toxin β fragment; CTβG, cholera toxin β fragment, gold conjugated; DCoN, dorsal CoN; DL, double-labeled neuron; DLL, dorsal nucleus of the lateral lemniscus; DlP, dorsolateral periolivary area; DmP, DMPO, dorsomedial periolivary area; DZ, dorsal auditory zone; ED, dorsal posterior ectosylvian area; EE, excitatory–excitatory band; EI, excitatory–inhibitory response band; EI, intermediate posterior ectosylvian area; EV, ventral posterior ectosylvian area; IC, inferior colliculus; II, V, VI, auditory cortex layers; In, insular cortex; IL, intermediate nucleus of the lateral lemniscus; LA, lateral amygdaloid nucleus; La, lateral nucleus of the IC; LOC, lateral olivocochlear neurons; LSO, lateral superior olive; LT, LTB, lateral nucleus of the trapezoid body; MG, medial geniculate body; MGBd, MGd, dorsal division of the MG; MGBv, MGv, ventral division of the MGv; MGm, medial division of the MG; MOC, medial olivocochlear system; MSO, medial superior olive; MTB, medial nucleus of the trapezoid body; NA, nucleus angularis; NL, nucleus laminaris; NM, nucleus magnocellularis; P, posterior auditory area; PDL, percentage of double-labeled neurons; PIN, posterior intralaminar nucleus; PON, periolivary nuclei; PRh, perirhinal area; PVCN, posteroventral cochlear nucleus; RC, radiate multipolar cell; RP, rostral pole of the MG; SC, superior colliculus; SOC, superior olivary complex; SPN, superior paraolivary nucleus; TC, thalamocortical; Te, temporal cortex; Te3, third area of temporal cortex; TRN, thalamic reticular nucleus; VCN, ventral CoN; Ve, ventral auditory area; VIII, auditory nerve; VNLL, VL, ventral nucleus of the lateral lemniscus; VPO, ventral periolivary nucleus; VTB, ventral nucleus of the trapezoid body.

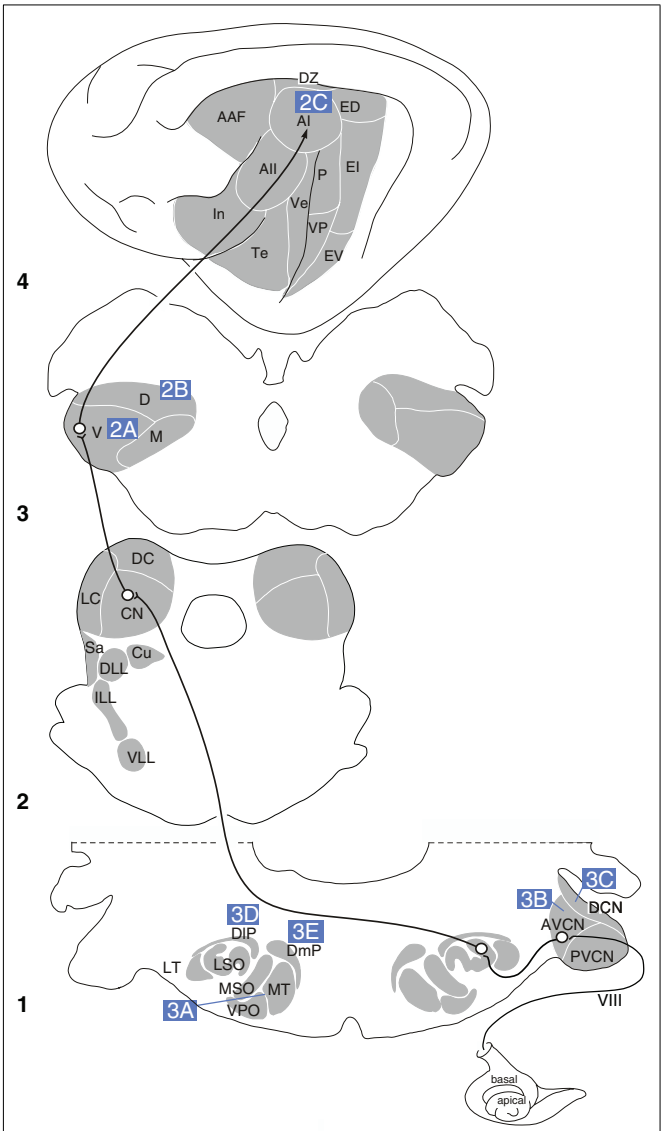

FIGURE 1 | The central auditory pathway. Key nuclei in the feline auditory system and elements of the lemniscal pathway from the medulla (1), midbrain (2), thalamus (3), and auditory cortex (4). Letters in blue boxes indicate the pathways depicted in **Figures 2** and **3**.

Although the functional implications of BAs are numerous (Morest, 1968; Kuwabara et al., 1991; Ojima et al., 1991, 1992; Li and Mizuno, 1997a,b; Kuwabara and Zook, 1999; Ye et al., 2000; Mulders and Robertson, 2002, 2003; Mulders et al., 2007), we are treating the function of BAs from the perspective of general organizational principles.

In the first two sections (see Branched Axons in the Auditory Cortical System, Branched Axons in the Auditory Brainstem and Midbrain), we review the existence, magnitude, and possible functions of BAs in the auditory cortex and thalamus as compared with those at earlier levels of the auditory system. These initial sections review the specifics of axonal branching in the auditory system, which the general reader may wish to skim in favor of the final sections (see Technical Considerations, Thematic Perspective, Alternatives to Collateralization in the Auditory Cortex, Collaterals in Other Modalities, and Summary), where we examine principles of axonal branching and evaluate the technical difficulties inherent in detecting BAs.

BRANCHED AXONS IN THE AUDITORY CORTICAL SYSTEM

THALAMOCORTICAL SYSTEM

All regions of the auditory cortex (AC) receive an input from the thalamus (Lee and Winer, 2008a). The principal source of auditory thalamocortical (TC) input, the medial geniculate body (MG), has tonotopic ventral (MGv) and rostral pole (RP) divisions, and non-tonotopic dorsal (MGd) and medial (MGm) divisions, which project in varying degrees to each of the 13 auditory cortical (AC) areas in the cat (Huang and Winer, 2000). Although focal regions within a thalamic nucleus can project broadly to multiple cortical areas based on anterograde tracing studies (Huang and Winer, 2000), axonal divergence of single neurons beyond a few millimeters is quite rare based on retrograde double labeling studies (Kishan et al., 2008). Thus, axonal branching in the auditory thalamocortical system is highly local, but with unique topographical features.

One of these features is the patchy distribution of TC BAs, which extend over 300–500 μm in layers IIIb and IV of the primate AC core (Hashikawa et al., 1995). In the lateral and posteromedial auditory cortical areas, larger (1000–1500 μm) patches arise from the MG anterodorsal and/or posterodorsal nuclei. In the rabbit, TC BAs form patches 1–2 mm apart in AI layers III and IV, with tangential layer I BAs up to 7 mm long (Cetas et al., 1999; **Figure 2A**). In the cat, similar patches are seen in AI, AAF, ventral, and the posterior AC (P) following injections of anterograde tracers into the MGv (Huang and Winer, 2000). More divergence occurs after similar MGd and MGm deposits, though not explicitly from BAs. Thick MGm axons in AC layer Ia project laterally across wide expanses, and vertical branches in layers II, IVb, and Va have fewer lateral BAs (Huang and Winer, 2000). Axons in layer IIIb also have many local BAs shorter than those in layers Ia and VIb.

The patchy distribution of MG afferents in AC may correlate with parvalbumin immunoreactivity and perhaps with modules of broadly and narrowly tuned neurons (Read et al., 2008) or binaural excitatory–excitatory/inhibitory (EE, EI) modules, though physiological–anatomical studies suggest that EE and EI columns are not linked by BAs (Middlebrooks and Zook, 1983). Similar patchy distributions in AC areas ostensibly lacking a binaural columnar arrangement imply that BAs are unrelated to binaurality. Intraareal BAs linking EE or EI columns are also sparse (Middlebrooks and Zook, 1983, but see Brandner and Redies, 1990).

Another canonical feature of the primary auditory cortical areas is the orderly spatial arrangement of neurons according to characteristic frequency (CF), i.e., tonotopy. A question that naturally arises is whether TC BAs contribute to the creation of the multiple AC CF maps (Morel and Imig, 1987) from the two representations in the MG (Imig and Morel, 1985a,b, 1985a,b)? Based on retrograde studies where different tracers are placed into matched isofrequency loci in different primary cortical areas, few double-labeled thalamic neurons are found (Morel and Imig,

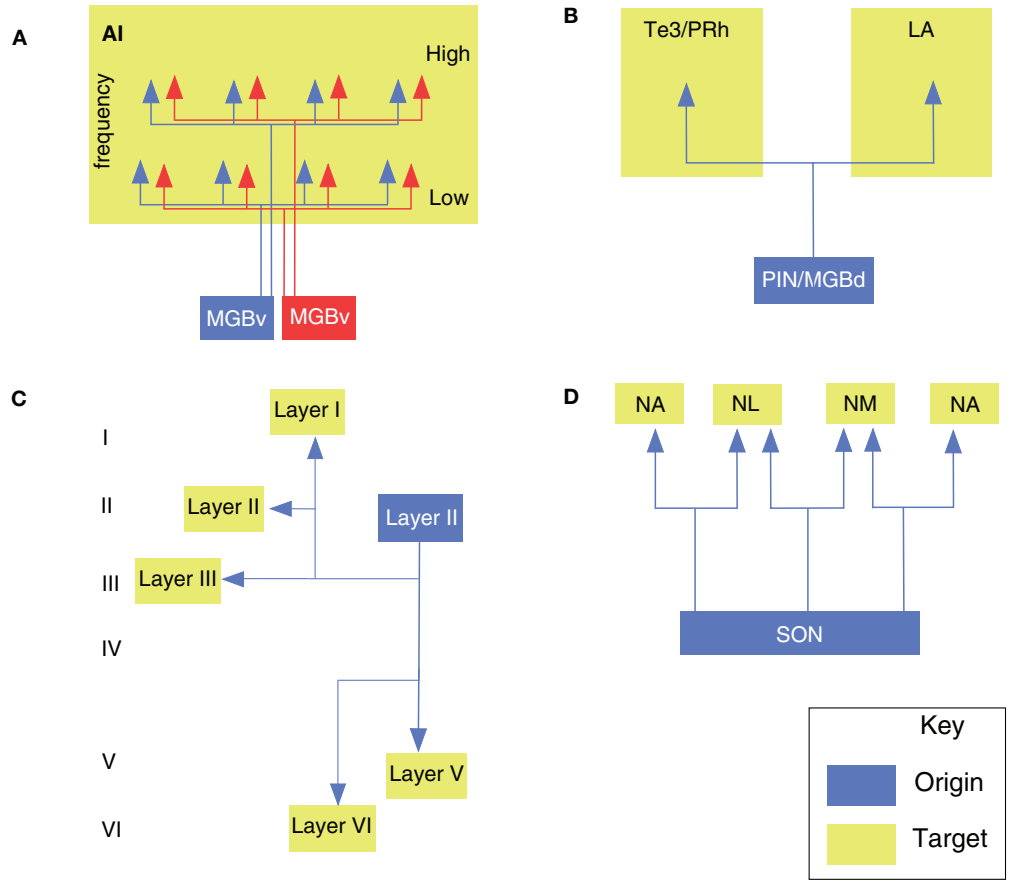

FIGURE 2 | Branched axonal projections in the auditory forebrain. (A) Clustered and periodic thalamocortical projections from medial geniculate body subdivisions to area AI (Velenovsky et al., 2003). **(B)** Posterior intralaminar (PIN) and dorsal division of the medial geniculate body branched projections to the non-primary auditory cortex (Te3/PRh) and lateral amygdala (LA; Doron and LeDoux, 2000). **(C)** Local, interlaminar, and collateral projections of an intracellularly labeled layer II pyramidal cell in AI (Ojima et al., 1991). **(D)** Avian olivary (SON) branched input to the laminaris (NL) and angularis (NA) nuclei (Burger et al., 2005).

1987), with some differences among the MGv and RP (Lee et al., 2004a; Kishan et al., 2008). Due to the paucity of double labeling in such studies, it appears that TC BAs do not create multiple CF maps in these areas.

Finally, the MG and intralaminar nuclei also project widely to non-auditory cortex. Thalamic BAs targeting both the lateral amygdaloid nucleus and the perirhinal or primary AC could influence autonomic and affective responses to auditory and multisensory stimuli (Namura et al., 1997). BAs may link some intralaminar nuclei with the dorsal (and, less so) ventral perirhinal cortex, and rarely arise from MGd/m neurons, though up to 17% of MGm cells project to perirhinal cortex and to the lateral amygdaloid nucleus (**Figure 2B**; **Table 1**). Although MGd cells project to both the frontal cortex and primary/non-primary AC, these originate from unbranched sources (Kurokawa and Saito, 1995). Thus, these TC parts of the auditory and motor pathways are segregated, despite extensive interdigitation of the projection cells. Overall, the few studies and diversity of relevant pathways make it difficult to specify the role of BAs in TC projections to non-auditory cortex.

CORTICOCORTICAL SYSTEM

Every area of the auditory cortex receives extensive input from local intrinsic cortical connections and extrinsic connections from other cortical areas in both hemispheres (Winer and Lee, 2007; Lee and Winer, 2008b,c), which provide ∼95% of the total input to an area (Lee et al., 2004a; Lee and Winer, 2011). As with the thalamocortical system, anterograde, axon-filling, and retrograde studies each provide complementary evidence about BAs in the corticocortical system.

On a local level, neurons in the auditory cortex branch within an area to create extensive divergent laminar circuits. In particular, layer II and III pyramidal cell axons branch proximally and distally to the cell body (Ojima et al., 1991; **Figure 2C**), forming an axonal network that extends across layers I–V, with two-to-five thick collaterals in layer III or V in addition to the main axon descending to the white matter for other cortical targets (Ojima et al., 1992). The horizontal branches in layer III or V run parallel to the pia for 500–2500 μm and emit, at a few distant points, local plexuses of secondary branches extending to upper and lower layers. This collateralization as a whole forms

a columnar terminal field in layers I through V with a branch-sparse gap in layer IV (**Figure 2C**). Each neuron has a number of vertical branches distributing around its cell body, forming a columnar terminal field, which is similar to that formed at distant points. Some non-projecting pyramidal neurons have thick, bifurcated axons with recurrent oblique or horizontal BAs; the latter extend 1–2 mm in layer V, and oblique branches project heavily in layers II–IV, with weaker input to layers I or II. Such cells may interact with those producing the synchronized oscillations arising in layer V (Silva et al., 1991). Several long-range dorsoventrally oriented BAs may link or segregate AI isofrequency loci in the cat (Read et al., 2001). Alternatively, they may synchronize cells with similar CF response properties, analogously to pyramidal neurons in visual cortex (Gray and Singer, 1989; Gray et al., 1989). Perhaps TC BAs complement these rich, local periodic projections.

As with the thalamocortical system, branched corticocortical projections that link similar CF regions are sparse, comprising <1% of AI and AAF cells projecting to matched CF regions (Lee et al., 2004a), although earlier studies using anterograde methods found extensive interconnections among matched CF regions (Imig and Reale, 1980), perhaps accounted for by neuronal populations that project in an unbranched manner to matched CF regions in different areas. Thus, long-range cortical BAs may be more rare than axon filling studies suggest. This implies that cortical BAs do not contribute significantly to spectral maps in different AC areas and illustrates a fundamental difference between the auditory forebrain and the brainstem, where axons subdivide profusely to innervate many different targets (Irvine, 1986). Intrinsic intraareal BAs across frequency laminae are also rare (Kishan et al., 2008), but may be more prevalent along an isofrequency contour.

Commissural AI axons may also target disparate areas, with homo- and hetero-topic terminal sites; a dual retrograde study found that some rat BAs target both sites (Rüttgers et al., 1990). However, <1% of AI or AAF neurons project commissurally to frequency-matched loci in both fields, and <4% of non-primary (AII, Te, and In) neurons project to two loci in their contralateral counterparts (Kishan et al., 2008).

CORTICOFUGAL PROJECTIONS

The auditory corticofugal system targets many thalamic, midbrain, and brainstem nuclei (Winer, 2006). Of these, the corticothalamic (CT) system is massive, with each major MG division receiving input from four or more AC areas (Winer et al., 2001). Two types of terminals arise from AI: small endings from thin axons of layer VI pyramidal neurons and large boutons from thick axons of layer V pyramidal neurons (Ojima, 1994; Winer et al., 1999; Llano and Sherman, 2008). Layer VI CT neurons typically project in a feedback manner to the thalamic nucleus from which they receives their major TC input, while layer V CT neurons project in a feedforward manner to a higher order thalamic nucleus (Winer et al., 2001; Sherman and Guillery, 2006).

Layer V CT pyramidal cell targets include MGm, MGd, and ventrolateral MGv, with thick horizontal BAs occurring in cortical layers V and VI forming heterogeneous en passant and spine-like boutons, and thin vertical axons ending above layer IV (Ojima et al., 1992), and with no BAs to the contralateral AI (Wong and Kelly, 1981), reserving collateralization to the ipsilateral AC. BAs crossing the cortical CF axis may enhance inhibition at other CFs, while those parallel to the isofrequency contours could have local roles (Ojima et al., 1991; Song et al., 2006).

Layer VI CT neurons branch extensively in both thalamus and cortex. Some layer VI CT cells have recurrent branches in cortical layer VI, then ascend to layers III and IV, where their processes form a dense plexus. In the thalamus, thin fiber BAs form dorsoventrally elongated bands parallel to MGv CF laminae (Rouiller and de Ribaupierre, 1990). Layer VI CT cells may activate local columnar neurons, while layer V CT neurons target more remote columns at the same or different CF. In addition, anterograde tracer deposits at separate frequency loci in the cat label terminals segregated in the MG, suggesting that microtopography complements BAs (Takayanagi and Ojima, 2006).

Corticothalamic projections include BAs to the thalamic reticular nucleus (TRN; Lam and Sherman, 2010). Layer V or VI axons traverse the TRN (Hazama et al., 2004); forming elongated slabs; these may be BAs of cells targeting the MGv. High- and low-CF loci in rat primary and non-primary AC areas converge in the MGv and target different TRN regions (Kimura et al., 2005). The TRN has inhibitory input to much of the MG, and some TRN neurons project to both the ventrolateral MGv and MGd, or to both the MGv *pars ovoidea* and MGm (Crabtree, 1998). This branching pattern might enable two AC tonotopic areas to convergently excite one MG region via direct CT projections, while divergently inhibiting separate MG regions via indirect reticulothalamic projections (Kimura et al., 2005). The AC also targets the midbrain, medulla, and striatum (Winer, 2006), and these corticofugal cells may also have intracortical BAs. Layer V corticostriatal neurons have vertical and short-range horizontal BAs. The vertical BAs form a dense network of terminal arbors in layers III and IV, perhaps reinforcing supragranular, reciprocal connections between AC CF loci projecting to similar striatal targets.

The corticocollicular system is also a rich substrate for axonal branching (Winer et al., 1998; Winer, 2006). Rat corticocollicular cells project to the caudal striatum (Moriizumi and Hattori, 1991b), and some corticofugal cells target the superior olivary complex (SOC) and IC, or the IC and the CoN, via BAs (Doucet et al., 2002, 2003). Some corticocollicular cells send BAs to the nucleus of the brachium of the IC (Saldaña et al., 1996). Retrograde experiments indicate that ∼5% of layer V neurons project to both IC (Willard and Martin, 1984; Coomes et al., 2005). Almost half of contralaterally projecting corticocollicular cells project bilaterally. Given the conservative estimates provided by retrograde tracers, all contralaterally projecting cells may target both ICs (Coomes et al., 2005), though no neurons appear to have BAs targeting both the IC and MG (Wong and Kelly, 1981).

BRANCHED AXONS IN THE AUDITORY BRAINSTEM AND MIDBRAIN

BRAINSTEM PROJECTIONS

Now, we consider the axonal branching patterns observed in the auditory brainstem and midbrain, in comparison with those of the auditory cortical systems described previously. Do similar branching patterns and principles apply across multiple stages of the auditory pathway? The numerous connections among brainstem

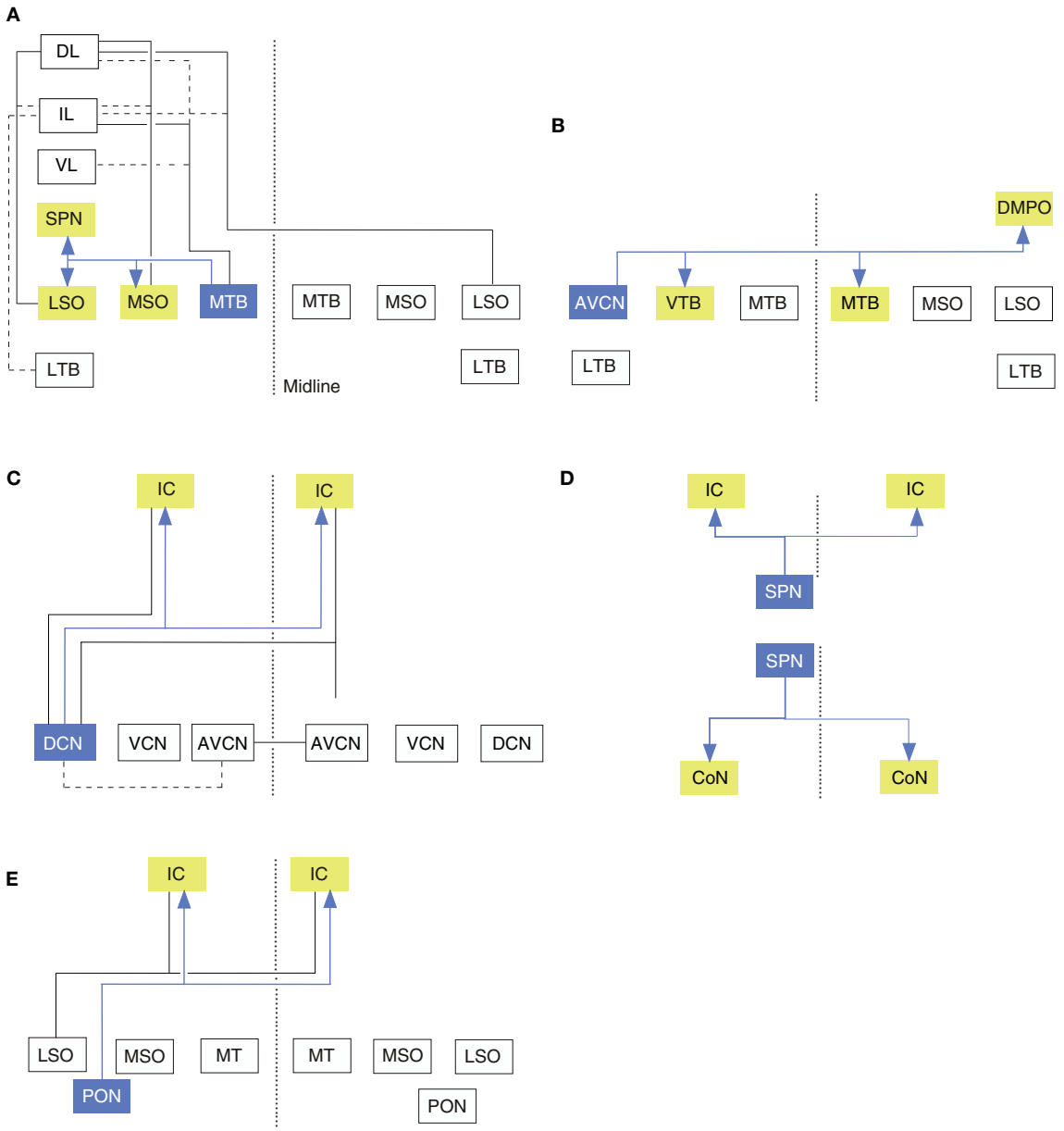

FIGURE 3 | Branched axonal projections in the auditory brainstem and midbrain. (A) Collateral projections from the medial nucleus of the trapezoid body to olivary and lateral lemniscal targets (Kuwabara and Zook, 1992). **(B)** Anteroventral cochlear nucleus collateral input to the ventral nucleus of the trapezoid body (VTB) and dorsomedial periolivary nucleus (Smith et al., 1991). **(C)** Cochlear nucleus branched projections to the inferior colliculus (IC; Schofield and Cant, 1996a; Schofield, 2002). **(D)** Branched ascending and descending projections from the superior paraolivary nucleus to the cochlear nucleus (CoN) and IC (Schofield, 1995). **(E)** Periolivary (PON) projections to the inferior colliculus (IC) and CoN. Dashed line in all panels represents the midline.

and midbrain nuclei might suggest different patterns of axonal branching exist at these stages. As noted in morphological studies, auditory BAs begin in the periphery (Lorente de Nó, 1981). At the earliest levels, type I auditory nerve fibers branch extensively in the CoN (Fekete et al., 1984). One main branch targets the ventral cochlear nucleus (VCoN) and the other ends in the dorsal cochlear nucleus (DCoN). Near this bifurcation, the parent trunk has few collaterals at low CFs, while axons at higher CFs have more numerous and complex axonal branches. Descending axons have 14–30 collaterals and, in the DCoN, the main trunk often makes parallel branches ending within 100 μm. Many BAs end in simple, en passant swellings, and others terminate diffusely in the neuropil. BAs

have regional morphologic variations, e.g., in the posteroventral cochlear nucleus, some have en passant swellings, while in the central part of the nucleus, fibers with a CF >4 kHz have many BAs that extend for hundreds of microns. These are parallel to octopus cell primary dendrites and could enhance the sharpness of tuning near the intensity threshold and broaden tuning at higher intensities. The ascending branch has 4–16 collaterals and ends in calyces of Held. These collaterals form complex, endbulb-like endings or en passant swellings and often remain within 100 μm of the parent branch, though one-third end in the anteroventral CoN. Small branches from high- and low-CF fiber may create heterotopic high frequency response zones in the VCoN (Fekete et al., 1984).

Cochlear nucleus afferents also branch. VCoN neurons send branches to matching frequency loci in the cat IC and contralateral DCoN (Adams, 1983a). Planar and radiate multipolar cells (T- and D-stellate cells, respectively) in the anterior VCoN branch to the DCoN and posterior VCoN, mainly to the multipolar cell area (Oertel et al., 1990). Radiate multipolar cells project to both the ipsilateral DCoN and the contralateral CoN (Doucet and Ryugo, 2006). Up to half the cells projecting to CoN also target the thalamic ventrobasal complex and may provide information about head and body position useful in sound localization or for somatic sensory–auditory interactions (Li and Mizuno, 1997a).

A prominent CoN target is the contralateral MTB (Morest, 1968), whose principal cells provide glycinergic input to the ipsilateral lateral superior olive (LSO) for interaural intensity difference computations (Smith et al., 1998). CoN projections form calyces of Held endings on MTB principal cells (Smith et al., 1991) and collateralize ipsilateral to the CoN of origin, targeting the lateral nucleus of the trapezoid body (LTB), posterior periolivary nucleus, or ventrolateral periolivary nucleus and end in large terminal swellings of variable shapes (**Figure 3B**; Spirou et al., 1990). En passant swellings are rare.

Most CoN BAs are precalycine. These traverse the MTB and ventral nucleus of the trapezoid body (VTB) toward the lateral lemniscus, forming branches in the anterolateral periolivary nucleus, the rostral LTB, and the VTB. Some fibers form collaterals at their branch point near the abducens nerve root, and branch sparsely before ending in the nucleus paragigantocellularis lateralis. Other precalycine collaterals target the dorsomedial and ventral periolivary nuclei and branch repeatedly within it (Kuwabara et al., 1991). About 40% of ipsilateral calyciferous branches end axosomatically in the ventral periolivary nucleus (VPO), 20% in the LTB and LSO, and 7% near the MTB in an area associated with the medial olivocochlear system (MOC). All axons have extensive BAs within the MTB, perhaps contributing to lateral inhibition. Other BAs end diffusely in the adjacent periolivary nuclei, the LTB, and the LSO, and 25% reach the lateral lemniscus (**Figure 3A**). Of the calycine collaterals, all terminate 20–80 μm from their origin in varicosities. Thus, ascending input to the MTB reaches parts of the ipsilateral lateral and medial olivocochlear system and diverse contralateral brain stem nuclei. MOC BAs to the CoN often converge with type II auditory nerve fiber endings (Benson and Brown, 2004), and areas targeted by such axons also project to the MOC, forming another prospective feedback-gain loop (Ye et al., 2000).

Perhaps unsurprisingly for brainstem projections, MTB axons are also collateralized (**Figure 3A**; Morest, 1968; Kuwabara et al., 1991). Principal cell axons send 2–6 BAs to the periolivary nuclei, superior paraolivary nucleus (SPN; the rodent homolog of the cat dorsomedial periolivary nucleus), and the VTB. Half of these axons also branch to the medial superior olive (MSO), and 25% branch to the lateral lemniscus. Recurrent MTB collaterals are also seen. The main axon often ends in a cascade of terminal BAs in the LSO; sometimes forming 1–2 thick perpendicular branches and then arborizing in the neuropil. MTB branches to the MSO are tonotopically organized (Smith et al., 1998).

Many brain stem neurons sample both the outputs of the MTB as well as collaterals bifurcating from input to the MTB, perhaps for monitoring or instructing gain control (Morest, 1968; Kuwabara et al., 1991). LSO-projecting neurons from the LTB also have collaterals to MSO (except in big brown bats), which, like MTB BAs, have axosomatic input on bipolar cells (Kuwabara and Zook, 1992). These inhibitory inputs may complement excitatory CoN afferents, perhaps preceding excitatory inputs because the contralateral calyciferous axons are much thicker than the CoN axons directly projecting to the contralateral MSO. Cell filling experiments in gerbil brain stem slices demonstrate that the MSO input to the SPN is highly branched, with >40% of thick, ascending MSO axons having one or more short BAs from their main trunk that ramify sparsely in the SPN (Kuwabara and Zook, 1999).

Not all brain stem projections have BAs. While some CoN efferent axons in the guinea pig target both CoN-projecting and IC-projecting cells in the SPN, their BAs may not be extensive (Schofield, 1995). Further, <1% of MTB neurons project to both the IC and CoN ipsilaterally, contralaterally, or have one ipsilateral and one contralateral target (Schofield, 1994).

PROJECTIONS OF THE INFERIOR COLLICULUS

The IC is the midbrain target for auditory input arising from earlier brainstem sources, e.g., the CoN, SOC, lateral lemniscal nuclei, AC, and many other non-auditory structures. The tonotopic central nucleus of the IC (CN) contains narrowly tuned neurons, while the cells in the dorsal cortex and lateral cortex (La) have broader frequency-tuning and multisensory properties. The IC projects to the MG, CoN, SOC, dorsal column nuclei, superior colliculi (SC), and other nuclei (for review see Winer and Schreiner, 2005).

The projection from the ventral nucleus of the lateral lemniscus to the CN has few BAs to different high- and low-frequency regions in the rat CN (Merchán and Berbel, 1996).

Such tonotopic precision is implicit in the narrow frequency tuning of anteroventral CoN cells (Bourk et al., 1981). In addition, in the rat lateral lemniscal nuclei, no neurons project to both the IC and the SC, or to both SCs, though cells in the dorsal nucleus of the lateral lemniscus may project to the SC deep layers for acoustic motor reflexes and head orientation (Tanaka et al., 1985).

The proportion of brainstem afferents that target both ICs via BAs may be species specific. In the cat IC, only 2% of LSO olivocollicular neurons project to both IC, while surprisingly, in the opossum, 20–25% of LSO olivocollicular neurons and almost all MSO olivocollicular cells project to both (Willard and Martin, 1984). Similar work in the guinea pig finds no branched projections in the LSO, MSO, or VCoN, but in the DCoN, 68% of ipsilateral

Table 1 | Retrograde studies of auditory branched projections.

System	Study and species	Method	Results
Thalamocortical	Middlebrooks and Zook (1983), Cat	EI band in AI: NY	MGv: none mentioned ($n = 3$)
		EE band in AI: PI (same CF)	
		Middle EE band in AI: NY	MGv: no%, but reported ($n = 1$)
		Ventral EE band in AI: PI (same CF)	
	Morel and Imig (1987), Cat	AI: HRP	MGv: 6.5 ($n = 5$, 6 sections)
		AAF: ^{3}H-BSA	RP: 6.0 ($n = 6$, 5 sections)
			MGv: 6.4 ($n = 1$, 2 sections)
		AI: ^{3}H-HRP	
		P: BSA	
	Brandner and Redies (1990), Cat	Dorsal AI: NY	MGv: no %, mentioned in one case ($n = 4$)
		Ventral and/or central AI: Bb	
		NY and Bb along AI isofrequency contour	MGv: none mentioned ($n = 2$)
	Kurokawa and Saito (1995), Rat	Te3: FG	MGd: 0 ($n = 6$)
		Fr1: FB	MGd: 0 ($n = 6$)
		Te1: NY	
		Fr1: FB	
	Namura et al. (1997), Rat	Dorsal perirhinal: DY	PIN: 3.3
		Lateral amygdaloid nucleus: FB	MGd[1]: 5
			SPFp: 11.3
			SPFm: 6.0
			MGm: 1.2 ($n = 1$)
		Ventral perirhinal: DY	PIN: 1.7
		Lateral amygdaloid nucleus: FB	MGd: 2.1
			SPFp: 3.7
			SPFm: 0
			MGm: 0 ($n = 1$)
		Te1: DY	0 ($n = 7$)
		Lateral amygdaloid nucleus: FB	
		Perirhinal: DY	0 ($n = 3$)
		Central amygdaloid nucleus: FB	
	Kishan et al. (2008), Cat	AI: CTβ	MGd: 1.5
		AAF: CTβG	MGm: 2.1
		Injected in frequency – matched loci	MGv: 1.4
			RP: 2.8 ($n = 4$)
		AI	MGd: 1.2
		Injected CTβ, CTβG at sites 3.3 mm apart	MGm: 2.8
			MGv: 0.6
			RP: 0 ($n = 1$)
		AII	MGd: 2.2
		Injected CTβ, CTβG at sites 3.3 mm apart	MGm: 3.9
			MGv: 2.1
			RP: 4.5 ($n = 1$)
		Te	MGd: 6.7
		Injected CTβ, CTβG at sites 1.7 mm apart	MGm: 4.9
			MGv: 5.8
			RP: 0.00 ($n = 1$)
		In	MGd: 3.9
		Injected CTβ, CTβG at sites 3.3 mm apart	MGm: 5.1
			MGv: 1.4
			RP: 0.00 ($n = 1$)

(Continued)

Table 1 | Continued

System	Study and species	Method	Results
Corticocortical	Rüttgers et al. (1990), Rat	DY and FB in regions of terminations of homotopic and heterotopic commissural projections	AI: no %, but reported
	Kishan et al. (2008), Cat	AI: CTβ AAF: CTβG Injected in frequency – matched loci	AI (i): 0.8 AAF (i): 0.6 AI (c): 0.8 AAF (c): 0.6 ($n=4$)
		AI Injected CTβ, CTβG at sites 3.3 mm apart from each other	AI (i): 0.1 AI (c): 1.4 ($n=1$)
		AII Injected CTβ, CTβG at sites 3.3 mm apart from each other	AII (i): 1.5 AII (c): 3.7 ($n=1$)
		Te Injected CTβ, CTβG at sites 1.7 mm apart from each other	Te (i): 1.3 Te (c): 1.8 ($n=1$)
		In Injected CTβ, CTβG at sites 3.3 mm apart from each other	In (i): 0.6 In (c): 1.1 ($n=1$)
Corticofugal	Wong and Kelly (1981), Cat	MG: HRP or NY Contra AI: NY or HRP	AI, layer V: 0 ($n=12$)
		IC: HRP or NY MG: NY or HRP	AI, layer V: 0 ($n=4$)
	Crabtree (1998), Cat	MGv, ventrolateral: FB or NY MGd: FB or NY	TRN: no %, always saw DLs ($n=3$)
		MGv, pars ovoidea: FB or NY MGm: FB or NY	TRN: no %, always saw DLs ($n=3$)
	Moriizumi and Hattori, 1991a, Rat	IC: TB Caudal striatum: DY	AI, layer V: 6.4% of IC projecting cells ($n=4$, pooled)
	Doucet et al. (2002), Rat	CoN: FB SOC: DY	AI: <10% ($n=2$, pooled)
	Doucet et al. (2003), Rat	CoN: FB IC: DY	AI: 10–20 ($n=4$)
		SOC: FB IC: DY	AI: 10–20 ($n=3$)
	Coomes et al. (2005), Guinea pig	Various combinations of FB, FG, red/green beads into both IC	Layer V of AC: 5.2 ($n=5$)
Brain stem	Adams (1983b), Cat	DCoN (c): EB or NY IC: HRP or EB (frequency matched with anatomical position)	VCoN (i): no %, but reported ($n=2$)
	Schofield (1994), Guinea pig	Various combinations of FB, FG, green beads into CoN and IC	MTB: <1% ($n=3$)
		CoN (i), IC (c) or CoN (c), IC (i) (same tracers)	MTB: <1% ($n=13$)
	Li and Mizuno (1997a), Rat	CoN: FG VB (c): TMRDA	Dorsal column (i): 50.7% of CoN-projecting STN: 30% of CoN-projecting ($n=1$, from figure)
	Doucet and Ryugo (2006), Rat	DCoN: BDA CoN (c): DY (large)	VCoN: 3.6% of planar multipolar No % for RC-multipolar, but reported ($n=3$)
IC afferents	Glendenning and Masterton (1983), Cat	Various combinations of DB, NY, Bb, PI, and DPD into both IC	LSO: 2% ($n=18$)
	Tanaka et al. (1985), Rat	DAPI and PI into both IC IC: PI or DAPI SC: DAPI or PI	LL: no %, but reported ($n=3$) LL: 0 ($n=3$)

(Continued)

Table 1 | Continued

System	Study and species	Method	Results
	Willard and Martin (1984), Opossum	TB and NY into both IC	AC: 6 CoN: <3% Dorsal columns: 6.67–12 DLL: <5 LSO core: 20–25% MSO: 100% ($n=8$)
	Moriizumi and Hattori (1991), Rat	AC (widely): TB IC: DY	Caudal globus pallidus: 0 ($n=2$)
	Schofield (1991), Guinea pig	Various combinations of FB, FG, green beads into CoN and IC	SPN: 1.7% of IC-projecting 3.3% of CoN-projecting ($n=3$)
	Schofield and Cant (1992), Guinea pig	CoN (i), IC (c) or CoN (c), IC (i) (same tracers) Various combinations of FB, FG, green beads into both IC	SPN: 0 ($n=4$ each) DLPO, LTB: <1% LSO, MSO: 0 ($n=4$)
	Schofield and Cant (1996a), Guinea pig	Various combinations of FB, FG, red/green beads into CoN (c) and IC	DCoN: 68.4% to IC (i) also project to IC (c) VCoN: 0
	Merchán and Berbel (1996), Rat	High frequency CNIC: HRP Low frequency CNIC: Biocytin	VLL: no %, very few reported
	Li and Mizuno (1997b), Rat	VB: TMRDA La: FG	Dorsal column nuclei and STN: no %, many reported ($n=8$)
	Li and Mizuno (1997a), Rat	CoN (i): FG IC (c): TMRDA CoN (c): FG IC (c): TMRDA	Gr: 60% of CoN-projecting Cu: 72.4% of CoN-projecting STN: 42.9% of CoN-projecting ($n=1$, from figure) Gr: 60% of CoN-projecting Cu: 61.5% of CoN-projecting STN: 36.4% of CoN-projecting ($n=1$, from figure)
IC efferents	Hashikawa (1983), Cat	CoN: PI, NY, Pr, or Bb MG: PI, NY, Pr, or Bb CoN: PI, NY, Pr, or Bb MG (c): PI, NY, Pr, or Bb PN: PI, NY, Pr, or Bb SC: PI, NY, Pr, or Bb	IC: 0 ($n=1$) IC: 0 ($n=1$) IC: <1% ($n=1$)
	González-Hernández et al. (1991), Rat	IC (c): NY MG: FB	IC: 5–10% of tectothalamic ($n=7$)
	Schofield (2001), Guinea pig	Various combinations of FB, FG, red/green beads into both CoN	IC: <1% ($n=12$)
	Coomes and Schofield (2004), Guinea pig	Various combinations of FB, FD, FG, FR, red/green beads into CoN, MG CoN (c), MG (i) (same tracers) CoN (i), MG (c) (same tracers) CoN (c), MG (c) (same tracers) CoN (c), MG (c) (same tracers)	IC: <1% ($n=6$) IC: <1% ($n=5$) IC: <1% ($n=3$) IC: 0 ($n=4$) IC: 0 ($n=4$)
	Okoyama et al. (2006), Rat	FG and FR into MG and CoN FG and FR into IC (c), MG FG and FR into CoN, IC (c)	IC: 0 ($n=11$) IC: <1% ($n=8$) IC: 0 ($n=10$)

(Continued)

Table 1 | Continued

System	Study and species	Method	Results
		FG and FR into both CoN	IC: 0 ($n = 6$)
		FG and FR into CoN (c), SOC	IC: 0 ($n = 3$)

[1]Originally counted as being part of the supragenicular nucleus, which is considered as part of the MGd; c, contralateral; i, ipsilateral; [3]H-BSA, tritiated bovine serum albumin; AAF, anterior auditory field; AC, auditory cortex; AI, primary auditory area; AII, second auditory cortex; Bb, bisbenzimide; BSA, bovine serum albumin; CoN, cochlear nucleus; CN, central nucleus of the IC; CTβ, β subunit of cholera toxin; CTβG, gold conjugate of CTβ; Cu, cuneate nucleus; DCoN, dorsal CN; DLPO, dorsolateral periolivary nucleus; DNLL, dorsal nucleus of the LL; DY, diamidino yellow; EB, Evans blue; EE, excitatory–excitatory band; EI, excitatory–inhibitory response band; FB, fast blue; FD, fluorescein–dextran; FG, fluorogold; FR, fluororuby; Fr1, frontal cortex; Gr, gracile nucleus; HRP, horseradish peroxidase; IC, inferior colliculus; La, lateral nucleus of the IC; In, insular cortex; LL, lateral lemniscus; LTB, lateral nucleus of the trapezoid body; LOC, lateral olivocochlear neurons; LSO, lateral superior olive; MG, medial geniculate body; MGd, dorsal division of the MG; MGm, medial division of the MG; MGv, ventral division of the MGv; MTB, medial nucleus of the trapezoid body; MOC, medial olivocochlear system; MSO, medial superior olive; NY, nuclear yellow; PI, propidium iodide; PIN, posterior intralaminar nucleus; PN, pontine nuclei; Pr, primulin; RC-multipolar, radiate multipolar cells projecting contralaterally; RP, rostral pole of the MG; SC, superior colliculus; SOC, superior olivary complex; SPFm, medial portion of the subparafascicular nucleus; SPFp, posterior portion of the subparafascicular nucleus; STN, spinal trigeminal nucleus; TB, true blue; Te, temporal cortex; Te1, primary auditory area; Te3, non-auditory temporal cortex; TMRDA, tetramethylrhodamine–dextran amine; TRN, thalamic reticular nucleus; VCN, ventral CN; VNLL, ventral nucleus of the LL.

IC-projecting cells have BAs to the contralateral IC (**Figure 3C**; Schofield and Cant, 1996b). Compared with the corticofugal system (see above), in both the guinea pig and the opossum, ∼6% of AC neurons project bilaterally to the IC.

Branched brainstem projections to the IC and other targets are also rare. In the SPN, ∼2% of IC-projecting cells branch to the CoN (**Figure 3D**; Schofield, 1991). Similarly, in the guinea pig SOC, only 1% of IC-projecting neurons send axons to the CoN (**Figure 3E**; Schofield, 2002). These few branched projections originate in the ventral periolivary region, including the anteroventral periolivary nucleus and the VTB, but no cells project to both targets contralaterally, or to one ipsilaterally – and the other contralaterally. In addition, some non-auditory afferents also have BAs (Moriizumi and Hattori, 1991a,b; Li and Mizuno, 1997a,b).

Within the IC itself, local connections are highly collateralized as revealed by intracellular filling studies in the cat (Oliver et al., 1991). These intrinsic BAs sometimes parallel the dendrites, extending for hundreds of microns (as in the CoN), while other IC neurons have non-oriented CN BAs. This diversity suggests extensive IC computational roles for local BAs and interneurons (Oliver et al., 1991). Axons of these cells extend toward the brachium of the IC, and many likely project to the MG (Winer et al., 1996). Some of these tectothalamic neurons are inhibitory (Winer et al., 1996; Peruzzi et al., 1997; Bartlett and Smith, 2002; Lee and Sherman, 2010), providing a source of feedforward inhibition that is unique to the auditory system.

However, most long-range IC projections have few BAs. Few colliculobulbar neurons target both CoNs in the guinea pig (Schofield, 2001) and rat (Okoyama et al., 2006). Instead, the IC may exert descending divergent influence disynaptically through contact with cells that projecting bilaterally to the CoN, particularly in the VTB and anteroventral periolivary nucleus (Schofield and Cant, 1999). As in the brain stem, IC neurons with ascending and descending projections are rare, with reports suggesting that no or few cells project to both the CoN and the MG in the cat (Hashikawa, 1983), rat (Okoyama et al., 2006), and guinea pig (Coomes and Schofield, 2004), and <1% project to both the SC and the pontine nuclei (Hashikawa, 1983). IC neurons branching to the MG and the contralateral IC also target the contralateral CoN, and comprise 1–10% of all tectothalamic cells (González-Hernández et al., 1991; Okoyama et al., 2006). Similarly, few axons target both the contralateral IC and the SOC or CoN.

TECHNICAL CONSIDERATIONS

Many approaches have been used to characterize BAs. Dual retrograde tract tracing (Hayes and Rustioni, 1979; Kuypers et al., 1980; Jones, 1983) can provide a profile of BA projections, as the many labeled cells permit quantitative analyses (**Table 1**). However, these studies presume equivalent uptake affinity, injection site size and efficacy, visualization methods, the interaction of damage with uptake, and transport rate (Schofield et al., 2007). To label significant numbers of cells, sufficiently large deposits can complicate the collection of quantitative data. Thus, for example, injections restricted to a single binaural response bands may be too small to label sufficient cells to provide reliable statistically appropriate estimates of double-labeled cells (DLs; Kishan et al., 2008).

Negative results are also problematic. Few DLs suggest that the injected regions do not receive BAs, though other areas might, or that the tracers were neither equivalent spatially nor equally likely to be transported. If BAs are oriented selectively, and the injections are not aligned appropriately, DL estimates would be spurious. Finally, dual retrograde tracing methods are limited since BAs to only a few sites can be detected, even if multiple targets are present. Thus, dual retrograde tracing likely underestimates the divergence of axonal projections.

In comparison, focal anterograde injections may overestimate the degree of single axon divergence by labeling fibers-of-passage or filling closely apposed neurons that project to separate loci. However, both anterograde and axon filling studies can demonstrate recurrent, local, and distant BAs. Some BAs are too near their source to be detected reliably by retrograde means (Winer, 1986), and anterograde or filling approaches do not require a precise or systematic injection orientation to reveal them. Anterograde studies may not reveal the full range of targets since incomplete filling of fine or long processes or insufficient transport time may confound estimates.

Intracellular filling studies are highly constrained by sample size (Fekete et al., 1984; Ojima et al., 1991). While a few axons may have collaterals (or, alternatively, lack branches), it is uncertain whether these are representative. As in anterograde studies, incomplete staining or insufficient transport time can constrain firm conclusions or population values except when many axons can be filled and their targets visualized (Brown, 1981; Humphrey et al., 1985).

THEMATIC PERSPECTIVE

Branched axons are common in the auditory cortical system, as well as in the auditory midbrain and brainstem. However, several general principles are evident from a comparison across processing levels. First, most axons branch according to one of three patterns: intricate local BAs, long-distance collaterals, and BAs involved in feedback-control loops. Second, cells rarely project to both ascending and descending targets, suggesting that these streams are well segregated and that descending projections play specific roles rather than merely feedback or modulatory ones (Guinan, 2006; Winer, 2006). Third, some neurons have both ascending and contralateral targets, e.g., CoN neurons projecting to the IC and the contralateral CoN (Adams, 1983b), and IC neurons targeting the MG and the contralateral IC (González-Hernández et al., 1991). Most projections are contra- or ipsi-lateral because of the acoustic chiasm (Glendenning and Masterton, 1983); thus, these BAs may enhance binaural computations for sound localization or otherwise modulate ascending input from an ear with contralateral influence. This may not pertain to descending projections since corticothalamic neurons are not commissural (Wong and Kelly, 1981). Fourth, bilateral projection neurons are part of at least the corticofugal and olivocochlear streams, with ∼5% of corticocollicular neurons projecting to both IC (Willard and Martin, 1984; Coomes and Schofield, 2004), and a similar proportion of MOC cells targeting both cochleae (Thompson and Thompson, 1986; Robertson et al., 1987a,1987a,b; Aschoff and Ostwald, 1988). Such bilaterally projecting neurons in ascending pathways are differentially distributed in various nuclei.

ALTERNATIVES TO COLLATERALIZATION IN THE AUDITORY CORTEX

In the auditory cortex, one might predict that BAs would be an ideal way to create multiple independent representations of frequency, aurality, amplitopy, or other dimensions required for computation (Ehret, 1997). It is somewhat unexpected that BAs to matched frequency regions are comparatively rare, especially in the forebrain (Lee et al., 2004a), where the emergence of multiple CF maps (Reale and Imig, 1980) suggest that they might be more common.

A robust alternative mechanism is provided by heterotopic projections that arise from interleaved thalamic and cortical neurons situated in close proximity and serving presumably similar physiologic roles but whose targets are separated widely (Lee et al., 2004b; Lee and Winer, 2005). Three obvious advantages accrue to this arrangement. First, precise branching to multiple targets is unnecessary, and neurons that target multiple cortical areas can migrate as a group and assemble their connectivity with comparative ease relative to the precision required by multiple branches that must terminate in exact register in different targets. Second, and perhaps most critically, heterotopic arrangements enable easy coordination of activity across large spatial territories, a prospectively problematic issue when coordinating diverse spatiotemporal patterns across vast expanses of brain (Lee et al., 2004b; Winer et al., 2004). Third, they provide a simple mechanism enabling the precise coordination of discharge patterns among resident thalamic or cortical neurons, either via local circuit neurons or, in their absence (Winer and Larue, 1996), via the BAs of excitatory neurons.

A second alternative is that the terminal plexus of many axons is highly divergent, and can span wide arrays, as in the TC axons in visual (Ferster and LeVay, 1978), somatic sensory (Landry and Deschênes, 1981), and auditory (Velenovsky et al., 2003) cortex. Such axons engage large areas and could readily initiate or sustain parallel intracortical and corticocortical modularity (DeFelipe et al., 1986) in networks larger than the comparatively finer scale of interneuronal projections (Kisvárday et al., 1994). The complexity of these axons belies point-to-point models of connectivity (Brandner and Redies, 1990).

COLLATERALS IN OTHER MODALITIES

Comparable, and perhaps even more extensive, collaterals systems exist in other modalities. The complexity of the subcortical auditory pathway frustrates direct comparisons with the visual, somatic sensory, or autonomic systems. Nonetheless, some comparisons can be drawn. For example, primary phrenic afferents send BAs to different spinal cord laminae (Goshgarian and Roubal, 1986), as do Ia muscle spindle (Brown and Fyffe, 1978), and Ib Golgi tendon organ (Brown and Fyffe, 1978) afferents. Many cuneate nucleus inputs are collateralized (Weinberg et al., 1990), resembling type I ganglion cell axons near the CoN. Retinofugal fibers to the lateral geniculate nucleus (LGN) ramify within the LGN (Conley and Fitzpatrick, 1989), resembling type I ganglion axons within the CoN.

Forebrain connections are compared more readily. The visual TC system may have more interareal BAs and intraareal BAs to matched functional domains than the somatic sensory or auditory systems. Retinotopically matched deposits in areas 17 and 18 double label 3–16% of neurons in the LGN A lamina (Bullier, 1984; Birnbacher and Albus, 1987; Salin et al., 1989), while matched somatotopic injections (SI) in the primary and secondary somatosensory areas only double label 2.3% of cells (Fisher et al., 1983).

Horizontal BAs are also present in all modalities. In the visual system, extensive lateral collaterals, similar to those seen in AI link loci with similar functional properties (Gilbert and Wiesel, 1979; Michalski et al., 1983; LeVay, 1988). There are also horizontal connections in higher-level areas such as the macaque inferior temporal cortex (Tanigawa et al., 2005), and long-range horizontal collaterals from SI pyramidal cells may target neurons in other fields (DeFelipe et al., 1986).

As in AI, some rat SI CT cells have local collaterals to neurons in the same column, while others project remotely (Zhang and Deschênes, 1997). Mirroring the absence of AI corticofugal BAs to diverse targets, <2% of SI cells have BAs to the corticostriatal, corticorubral, corticopontine, and corticospinal pathways

(Akintunde and Buxton, 1992). In the somatic sensory (Bourassa et al., 1995) and visual (Bourassa and Deschênes, 1995) systems, the CT fibers arising from axons of layer V neurons in V1 or SI were collaterals of corticotectal or corticopontine axons, unlike the auditory CT system. This suggests modality specific rules for BAs, whose ontogeny and functional specificity remain for further investigation.

SUMMARY

The floridness of axonal branching throughout the central auditory system, and other modalities, is indicative of the functional importance of divergent processing in sensory systems. Such branching ranges across scales, from intrinsic branches that modulate firing in local circuits, to long-range collaterals that widely disseminate information. Yet, it remains an open question whether BAs as a wiring principle is more efficient from an ontological and developmental standpoint, compared with the targeting of separate loci by unbranched neuronal ensembles. In addition, the degree to which separate branches have similar synaptic properties and efficacy in terms of transmitting auditory information remains to be investigated. Indeed, widely varying synaptic properties at separate axonal branches would have profound effects on the divergent dissemination of auditory information. Thus, defining the functional role of axonal divergence will require a convergence of future theory and experiments.

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