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A periodic network of neurochemical modules in the inferior colliculus

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Abstract

A new organization has been found in shell nuclei of rat inferior colliculus. Chemically specific modules with a periodic distribution fill about half of layer 2 of external cortex and dorsal cortex. Modules contain clusters of small glutamic acid decarboxylase-positive neurons and large boutons at higher density than in other inferior colliculus subdivisions. The modules are also present in tissue stained for parvalbumin, cytochrome oxidase, nicotinamide adenine dinucleotide phosphate-diaphorase, and acetylcholinesterase. Six to seven bilaterally symmetrical modules extend from the caudal extremity of the external cortex of the inferior colliculus to its rostral pole. Modules are from ~800 to 2200 μm long and have areas between 5000 and 40 000 μm^2. Modules alternate with immunonegative regions. Similar modules are found in inbred and outbred strains of rat, and in both males and females. They are absent in mouse, squirrel, cat, bat, macaque monkey, and barn owl. Modules are immunonegative for glycine, calbindin, serotonin, and choline acetyltransferase. The auditory cortex and ipsi- and contralateral inferior colliculi project to the external cortex. Somatic sensory influences from the dorsal column nuclei and spinal trigeminal nucleus are the primary ascending sensory input to the external cortex; ascending auditory input to layer 2 is sparse. If the immunopositive modular neurons receive this input, the external cortex could participate in spatial orientation and somatic motor control through its intrinsic and extrinsic projections.

Key words: GABAergic organization; Glutamic acid decarboxylase; Parvalbumin; Module; External cortex; Rat auditory system

1. Introduction

Brain subdivisions have been identified classically using architectonic methods to define nuclei in subcortical structures (Morest, 1965) and layers in the cerebral cortex (Lorente de Nó, 1938). More recent approaches reveal compartmental organization within nuclei and in layers otherwise considered as homogeneous. One such organizational feature, the modules, are periodic, subnuclear zones that are chemically (Wong-Riley et al., 1998), architectonically (Buzás et al., 2001), or connectionally (Mana and Chevalier, 2001) distinct. Modules have intricate patterns of organization that have been revealed with histochemical (Johnson et al., 2002) or immunoconnectional (Graf et al., 2002) probes and which may have functional significance. In some systems, such as rat barrel representation in the somatic sensory thalamus (Sugitani et al., 1990), these local regions may be specialized for intrinsic processing.

Such a modular organization is not a common feature in the auditory system. Other than frequency-specific and immunocytochemically identified processing domains confined to a few nuclei in the brainstem of highly adapted echolocating bats (Vater et al., 1992; Winer et al., 1995), such domains are remarkable for their virtual absence. Perhaps the auditory system dif-

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Abbreviations: AChE, acetylcholinesterase; C, caudal; CG, central gray; CN, central nucleus of IC; CO, cytochrome oxidase; D, dorsal; DC, dorsal cortex of IC; EC, external cortex of IC; GABA, γ-aminobutyric acid; GAD, glutamic acid decarboxylase; IAØ, interaural zero; IC, inferior colliculus; L, lateral; LL, lateral lemniscus; M, medial; Mes V, mesencephalic trigeminal nucleus; NADPH-d, nicotinimide adenine dinucleotide phosphate-diaphorase; Parv, parvalbumin; R, rostral; RP, rostral pole of IC; V, ventral

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fers significantly from the visual (Wallace, 1988), somatic sensory (Rainey and Jones, 1983), and olfactory (Meister and Bonhoeffer, 2001) systems, where such modules seem to be more abundant.

The first study to report an unusual structure in the external cortex (EC) of inferior colliculus (IC) described "...patches of GABAergic terminals and cell bodies in layer 2..." (Mugnaini and Oertel, 1985). We confirm that finding and now describe their novel modular organization in the EC, where any systematic distribution of auditory function has been elusive. Single EC cells respond to auditory and somatic stimuli in the cat (Aitkin et al., 1978), but there is no evidence for a tonotopic organization nor has any precise somatotopic representation been described in opossum (RoBards, 1979) or cat (Aitkin et al., 1981).

This is the first report in the auditory system other than in bats (Vater et al., 1992; Winer et al., 1995) of a periodic distribution of neurochemical foci that is modular. It suggests that there are two complementary patterns of γ-aminobutyric acid (GABA) expression in the IC, namely, a continuous local pattern in the central nucleus and nuclei of the commissure and brachium (Chernock et al., 2003a), and a second, more focal modular distribution of GABAergic neurons and puncta in EC.

2. Materials and methods

2.1. Animals

Six adult male rats, and one female Sprague–Dawley, one male Lewis, and one male Long–Evans rat, each weighing 200–400 g, were studied. All husbandry and anesthetic procedures followed accepted and approved animal care and use guidelines established by the University of California at Berkeley office of laboratory animal care and the National Institutes of Health. Rats were anesthetized with sodium pentobarbital (Abbott Laboratories, North Chicago, IL, USA; 100 mg/kg, i.p.) until areflexive, then perfused intracardially. Transverse or parasagittal sections were processed for immunocytochemistry or histochemistry. More than 40 ICs stained for glutamic acid decarboxylase (GAD) or parvalbumin (Parv) from other mammals and birds were available for reference. Tissue was processed with the same antisera adjusted to species-specific dilutions for the rat (Winer and Larue, 1988, 1989), cat (Oliver et al., 1994; Prieto et al., 1994), mustached bat (Winer et al., 1992), and owl (Winer and Larue, 1996).

2.2. Immunostaining

Brains prepared for GAD immunocytochemistry were perfused with 0.5% zinc salicylate in 10% formalin (Mugnaini and Dahl, 1983) then cryoprotected with 30% sucrose in saline (pH 6.5). Sections 25 μm thick were cut on a freezing microtome in the transverse or parasagittal plane. GAD processing began with blocking serum for 1 h, then primary rabbit anti-GAD (Sigma-Aldrich, St. Louis, MO, USA; 1:2000) overnight. Tissue was incubated in goat anti-rabbit for 60 min. For Parv immunostaining, sections were blocked for 1 h, incubated in mouse anti-Parv (Swant, Bellinzona, Switzerland; 1:5000) overnight, then placed in secondary horse anti-mouse solution for 1 h. Immunostaining followed published protocols for glycine (Winer et al., 1995), calbindin (Zettel et al., 1991), serotonin and choline acetyltransferase (Campbell et al., 1987). Every fourth section was Nissl-stained for cytoarchitectonic analysis.

2.3. Histochemistry

Rats were perfused intracardially with 1% paraformaldehyde/1.5% glutaraldehyde. Brains were dissected, and 50 μm thick sections were cut in the parasagittal or transverse plane. Incubation followed in 0.1% nicotinamide adenine dinucleotide phosphate-diaphorase (NADPH-d) for 5–6 h at 37°C (Druga and Syka, 1993). For cytochrome oxidase (CO) histochemistry, the incubation was in cytochrome *c*/diaminobenzidine for 2 h at 37°C before postfixation in 10% formaldehyde (Tootell et al., 1983). For acetylcholinesterase (AChE) staining, unfixed tissue was cut to 50 μm on a vibratome (Oxford), mounted on slides and incubated overnight in sodium acetate buffer pH 5.0, to which had been added copper sulfate, glycine, *S*-acetylcholine iodide, and ethopropazine. After water rinses, slides were developed in 1% sodium sulfide and postfixed in 4% paraformaldehyde (Koelle and Friedenwald, 1949).

2.4. Computer reconstructions

The auditory brainstem and neurochemical modules were reconstructed in three dimensions from transverse and parasagittal sections using the Neurolucida system and Neuroexplorer software (MicroBrightField, Colchester, VT, USA). In every other transverse section, the perimeter of the section, the IC, and the modules were outlined and measured. Fiducial marks were used to align sections and to adjust sections processed with different methods to a common final size. With Neuroexplorer, the outlines were serially reconstructed in one plane then rotated to show the three dimensional configuration of midbrain modules.

EC neurons immunopositive for GAD or Parv were plotted with the Neurolucida system coupled to a computer-controlled stage. Somatic cross-sections were

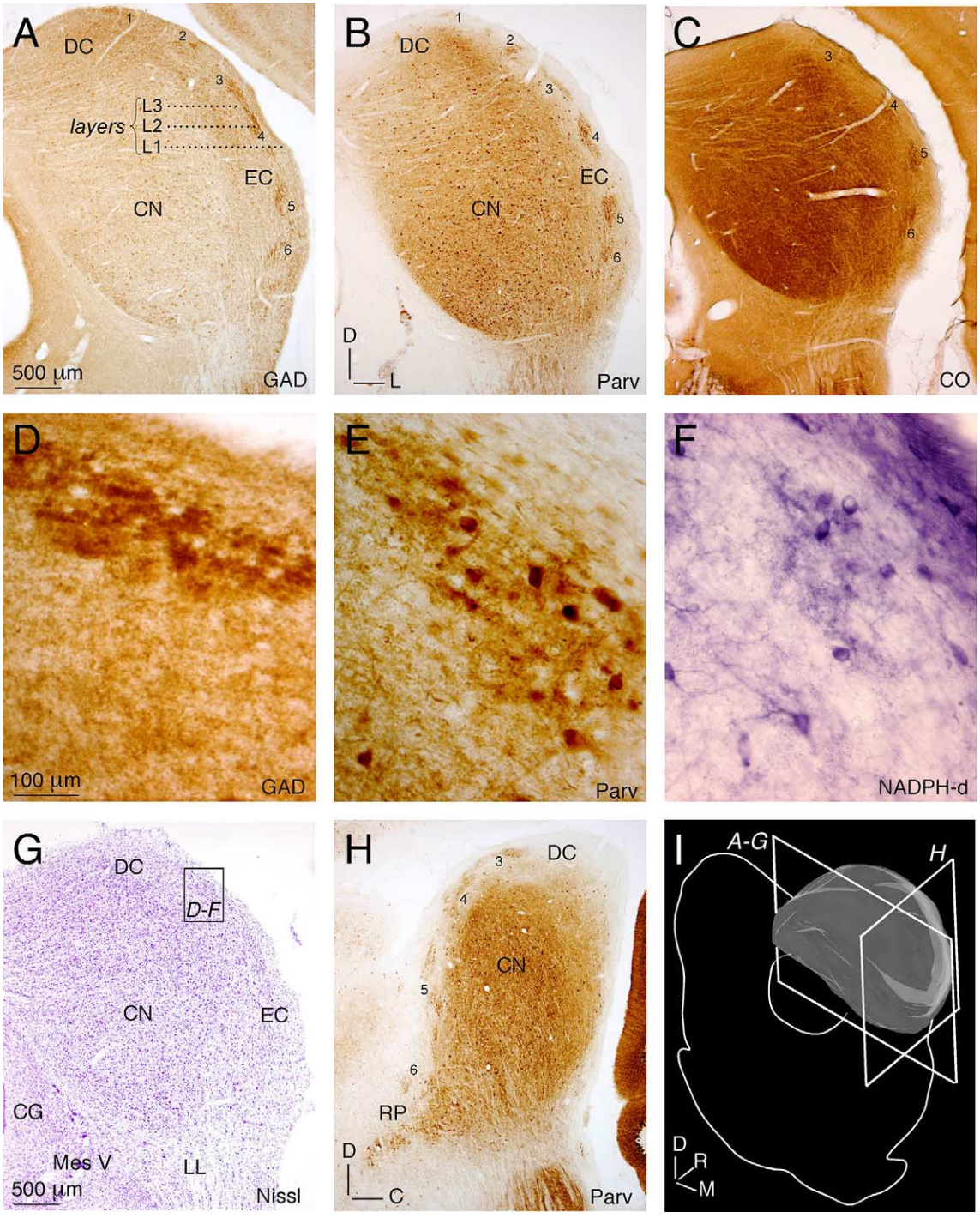

Fig. 1. Modular and architectonic organization of rat IC. (A–G) Transverse sections. (A) Discrete modules (1–6) of GAD immunoreactivity were confined to the EC. EC had three layers: a fibrous perimeter (L1), a modular region (L2), and an inner, lighter staining layer (L3). (B) The immunostaining in layer 2 zones (1–6) colocalized with Parv in adjoining sections. (C) Modules were positive for CO. (D) Density of GAD staining in a module was above background. (E) In a Parv-stained module the immunopositive neurons were clustered. (F) NADPH-d-stained puncta were darker in modules. (G) Layer 1 of EC was evident in a Nissl stain. (H) Continuity between modules was apparent in a parasagittal section that intercepted their long axes. (I) Planes of section (boxes). Planapochromat, N.A. 0.02, ×40.

measured with a minimum convex polygon fitted to the neuron's soma when this profile had at least one dendrite. Modules were drawn with a drawing tube and an oil immersion objective.

3. Results

3.1. GAD immunostains clusters of neurons and axon terminals in the external cortex

Shell nuclei of the IC, including EC, dorsal cortex (DC) and the rostral pole (RP), contained intensely immunostained clusters of neurons and axon terminals in GAD material (Fig. 1A), Parv-stained sections (Fig. 1B), and in other material (Fig. 1C,F). These immuno- or histochemically positive areas had local staining that was above background consistently. In transverse sections midway through the IC, six to seven discrete elongated or ovoid regions were found ~200 μm beneath the dorsal and lateral surfaces (Fig. 1A,B,H). These zones were defined as modules. The long modular axis extended into the RP (Fig. 2B) and the individual clusters (Fig. 1B: 1–6) were in caudo-rostral continuity (Fig. 3A: 1–7). Modules were 800–2200 μm long and between 5000 and 40 000 μm^2 in area ($n = 28$).

The modules in DC, layer 2 of EC, and in the RP were distinguished by a unique population of GAD-positive neural somata and a much higher local concentration of puncta than in non-modular parts of these nuclei (Fig. 1B). The internal modular architecture is described below.

Some modules (Fig. 2A: 1,2; C: 7) were more solitary and others (Fig. 2B: 3–6) fused to form band-like aggregates interrupted by equally large immunonegative zones. Some modules varied in cross-sectional area (Fig. 3A: 3–6) and others were more uniform (Fig. 3A: 1, 2) along their caudo-rostral length.

Many modules were symmetrical bilaterally (Fig. 3B: 1, 2). They were conserved with respect to number, position, and size in GAD (Figs. 1D and 3B: 1), Parv (Figs. 1E and 3B: 4), NADPH-d (Fig. 1F), CO (Fig. 1C) and AChE (Fig. 3B: 7) material. Their structure was neither gender-dependent nor highly individualized, as their size and shape were comparable between specimens in a strain and in both genders (Fig. 3B: 3). These patterns were similar in both outbred (Lewis) (Fig. 3B: 5) and inbred (Long–Evans) (not shown) strains.

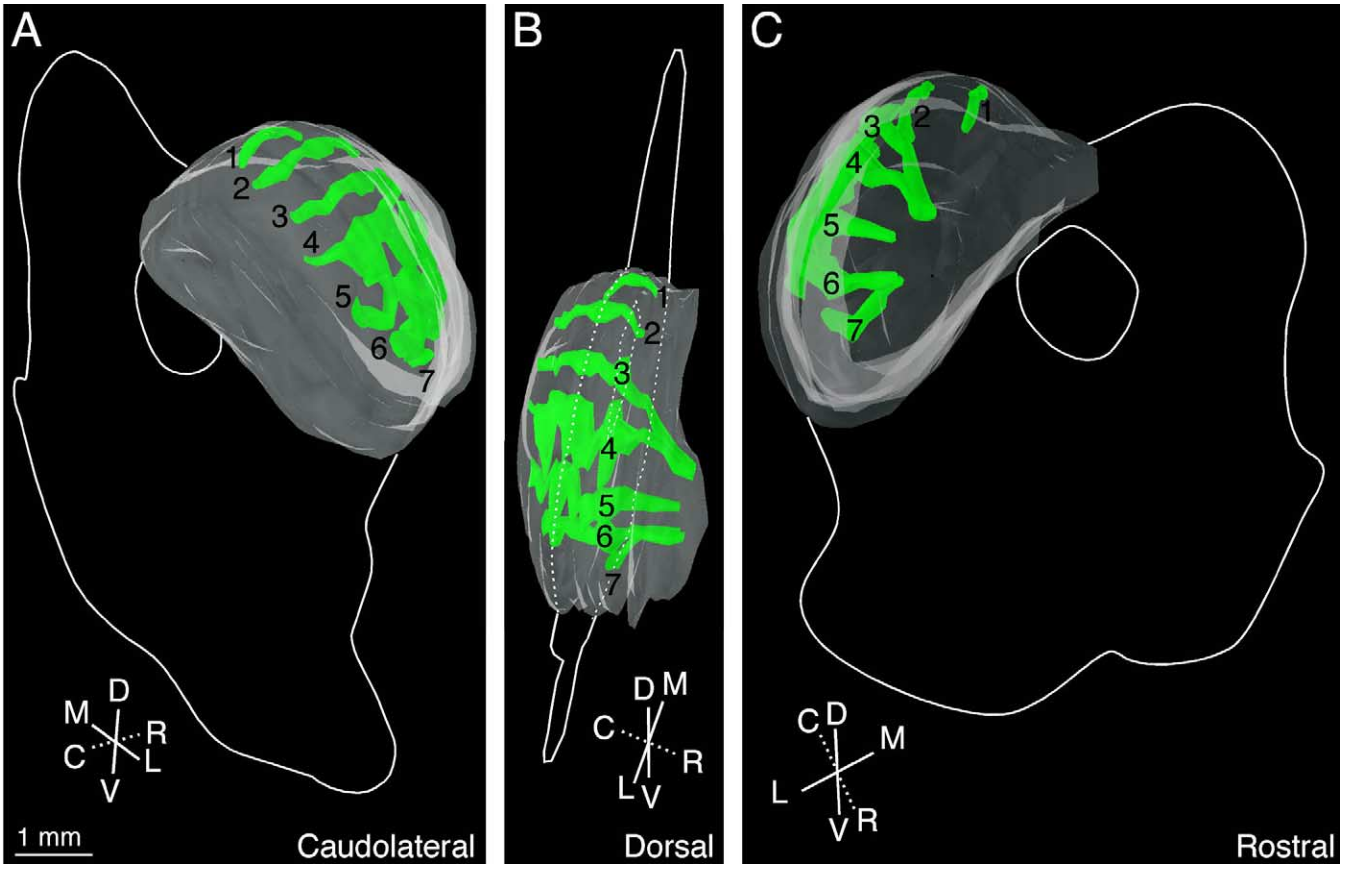

Fig. 2. Reconstructions of modules in three dimensions projected onto the IC and rotated. (A) The caudolateral view showed the modules (1–7) embedded in layer 2 of the EC without entering the caudal cortex. (B) From a superior perspective, the modules were periodic along the caudo-rostral axis. Modules 3–7 extended into the RP. (C) Modules converged medially as they projected rostrally.

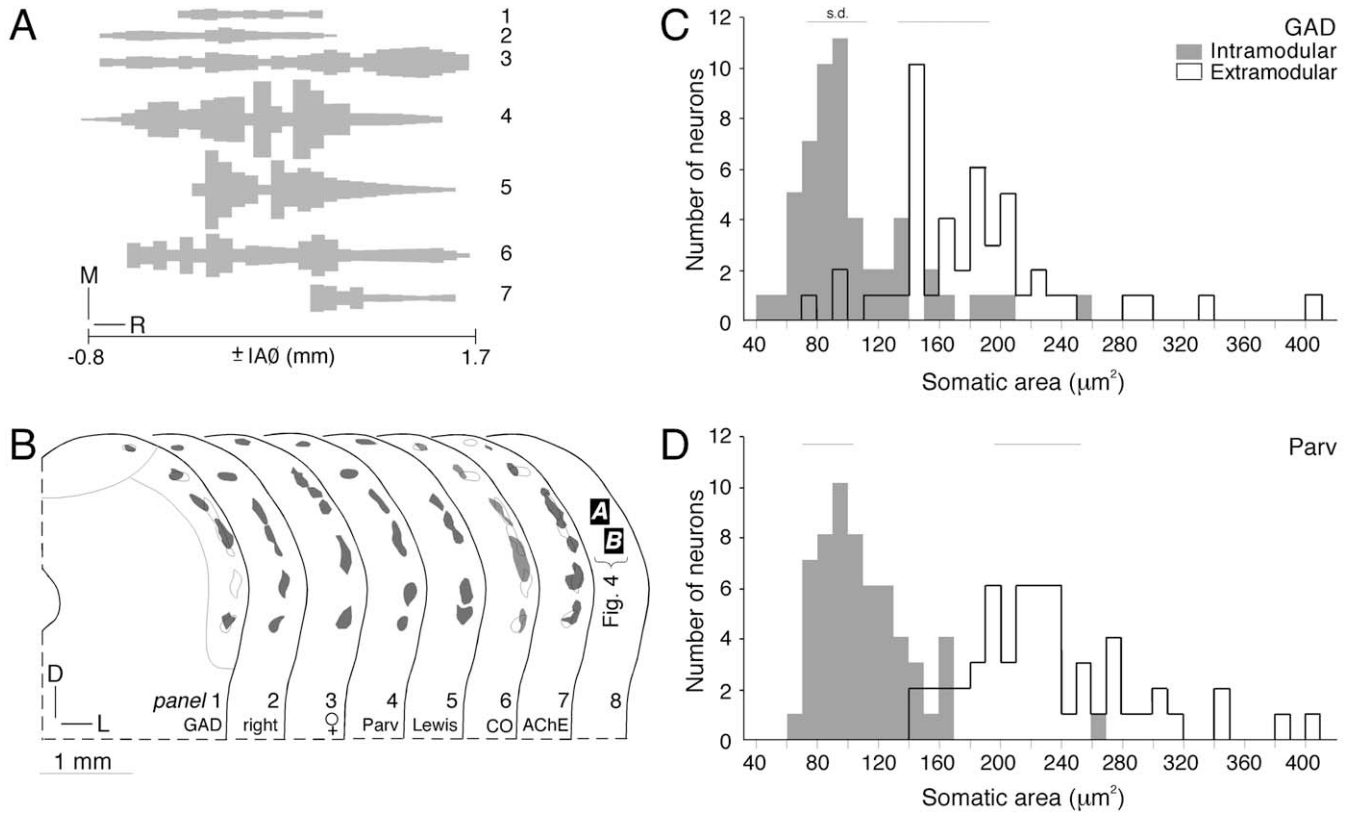

Fig. 3. Analyses of modules. (A) Modules (1–7) projected onto a flattened surface contour to show their continuity, periodicity, shape, and variations along the anteroposterior axis. Modules 3–6 were largest and most complex. (B) Comparisons of GAD immunostaining from the left and right IC in the male Sprague–Dawley strain (1, 2), from a female (3), in an adjacent Parv section (4), from a GAD-immunostained section in the Lewis strain (5), and in CO- (6) and AChE- stained sections (7). The modules had similar spatial and areal positions. Modular outlines from panel 2 were superimposed onto panels 1, 6, and 7. Boxes A and B (8), loci of observations in Fig. 4. (C) Somatic size comparison of intra- and extramodular GAD-immunostained neurons. The size difference for both GAD and Parv (D) was statistically significant. Fine horizontal lines, standard deviation. (D) The range of Parv-positive somatic sizes was larger than that of Parv-negative cells.

In EC, CO-positive zones resembling visual cortical blobs in shape (Livingstone and Hubel, 1984) colocalized to the GAD-positive and Parv-positive modules (Fig. 3B: 6). NADPH-d and CO both identified comparable patches of neuropil, much as they do in other systems (Wiencken and Casagrande, 2000), and they also colocalized with the GAD-positive EC modules (Fig. 1C,F), thus distinguishing them as sites of high metabolic activity. The CO marker identified boutons and axon terminals. The AChE preparations also showed patchy staining (Paxinos and Watson, 1998) that often overlapped with the GAD-positive modules (Fig. 3B: 7). When superimposed, there was considerable, though not perfect, congruence of modules identified with different markers (Fig. 3B: 4, 6, 7), between modules in male and female rats (Fig. 3B: 3), in both sides of the IC (Fig. 3B: 2), and between strains (Fig. 3B: 5).

3.2. Comparison of GAD and Parv immunoreactivity

Modular GAD-positive neurons (Fig. 3C) were significantly smaller (mean somatic size 93 ± 20 μm^2) than those found outside modules (173 ± 30 μm^2; F-test, $P = 0.0036$). The largest GABA-positive perikarya in EC were outside modules, and they were not targets of the clustered modular GAD-positive terminals. The populations of non-modular GAD-positive and Parv-positive neurons are not statistically different (F-test, $P = 0.58$; Fig. 3C,D) but the difference in mean somatic size (173 versus 222 μm^2) may reflect the fact that Parv and GABA do not always colocalize (Polgar and Antal, 1995; Soares-Mota et al., 2001).

The GAD immunostaining was more intense in the modular neuropil (Fig. 4A), while Parv immunostaining was more concentrated in cell bodies and preterminal processes (Fig. 4B). There were significantly more GAD-positive puncta in the modular neuropil, including boutons and preterminal axons (Fig. 4A). Many large boutons in modules were found near the somata of GAD-positive cells. Parv-positive (Fig. 4B: drawn neurons) and -negative neurons (Fig. 4B: gray profiles) clustered within modules.

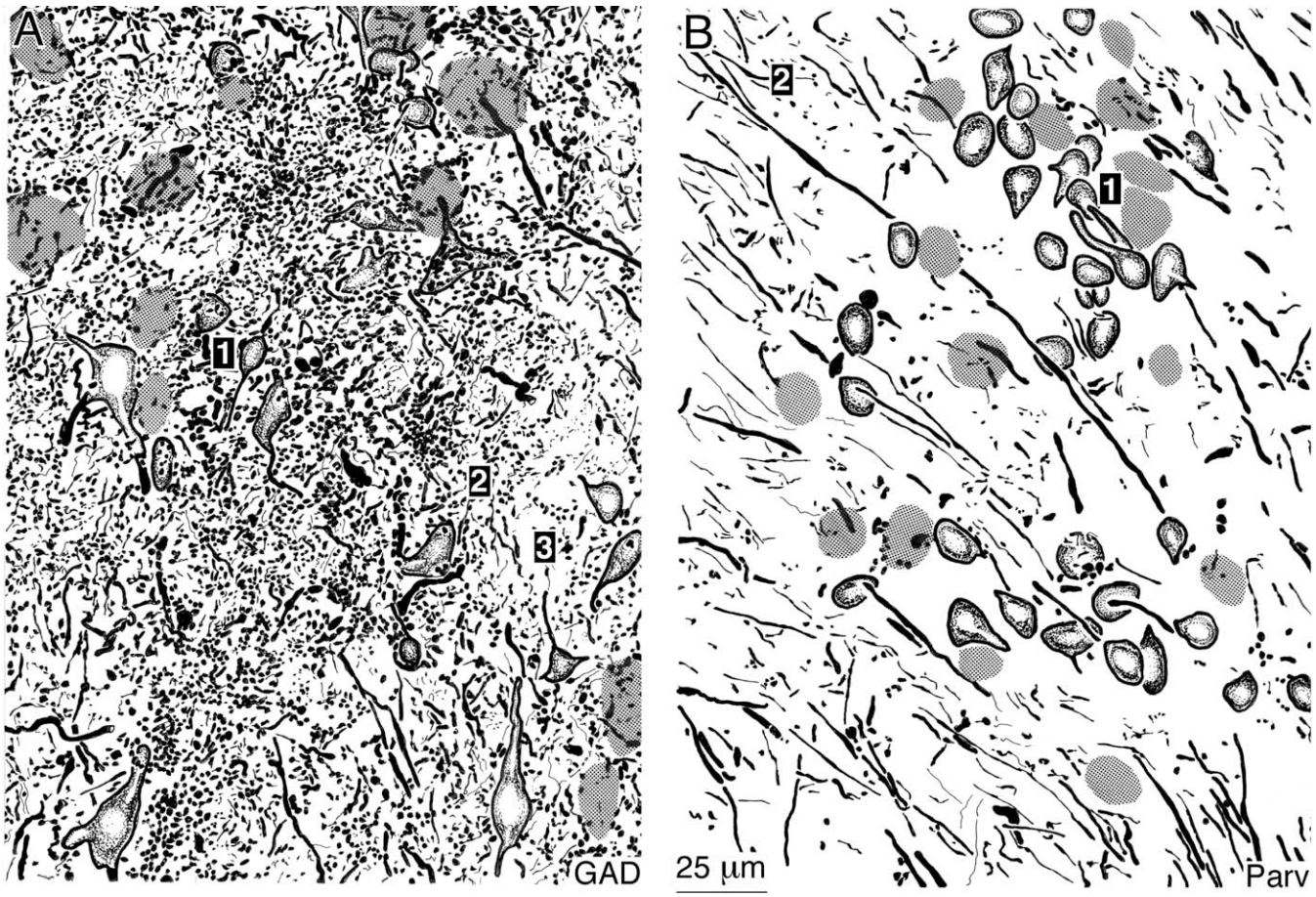

Fig. 4. Drawings of modules. The locus of these observations was shown in Fig. 3B: 8 (boxes). (A) In GAD preparations, the modules had more puncta and smaller neurons (1) than did extramodular regions. The border between intra- (2) and extramodular (3) neuropil was sharp (e.g., lower right side). Gray profiles, immunonegative cells. (B) A Parv-positive module showed the local concentration of immunostained neurons (1). Extramodular zones had no such cells and few small, immunoreactive profiles (2). Planapochromat, N.A. 1.32, ×2000.

3.3. Other immunoprobes and comparative analysis

Immunostaining for glycine, serotonin, calbindin, and choline acetyltransferase revealed no modular arrangement. The GAD-positive modules were absent in mice (*Mus musculus*), bats (*Antrozous pallidus* and *Pteronotus parnellii*), gray squirrel (*Sciureus carolinensis*), cat (*Felis catus*), macaque monkey (*Macaca mulatta*) and barn owl (*Tyto alba*). Omission controls for all immunoprobes and histochemical assays showed no specific staining.

4. Discussion

We report a neurochemically specific modular organization in a particular subdivision of the rat IC. These modules may have functional importance since their neurons and axon terminals are immunostained selectively for GAD, and because they contain a subpopulation of GAD-positive neurons that might contribute to local GABAergic operations within the IC or to extrinsic processes in other nuclei. Unless noted otherwise, all references are to the rat.

4.1. Potential sources of modular neuropil

Without direct physiological data, we can offer only speculations on modular function. Connectional data provide a useful frame of reference for proposing functional correlates. Convergence within EC of input from the spinal trigeminal tract and dorsal column nuclei (Li and Mizuno, 1997) suggests the integration of ascending somatic sensory and corticofugal auditory influences. Such joint input may coordinate auditory and somatic sensory spatial interactions. EC modules likely receive auditory corticofugal axons (Herrera et al., 1994; Druga et al., 1997), a projection whose effects on IC function are complex. These include, in the cat, influences on vigilance and attention (Jane et al., 1965) and on processing audio-spinal reflex information (Wright and Barnes, 1971), and on transmission from

the auditory midbrain to the thalamus (Mitani et al., 1983). In the owl, there is possible modulation of local receptive field organization via intrinsic collicular connections (Wagner, 1990). In the bat, GABAergic IC neurons have a role in direction-dependent sharpening of frequency tuning curves (Jen and Zhang, 2000).

Other possible sources of modular afferents are the substantia nigra (Olazábal and Moore, 1989) and pallidum (Shammah-Lagnado et al., 1996). Neither the trigeminal, nigral, nor pallidal inputs are likely sources of the GABAergic puncta in EC modules since none of these project periodically or are clustered. Alternatively, they may project to the modules non-topographically. Since ascending auditory input to the nuclei containing modules is modest (Coleman and Clerici, 1987; González-Hernández et al., 1996), their primary role may pertain to intercollicular processing and cortically mediated influence (Saldaña et al., 1996). The absence of connectional periodicity sets the IC apart from the superior colliculus, where segregation and periodicity is a common form of organization (Illing, 1996). In fact, the IC modules appear to be unrelated to any known afferent system.

4.2. Putative targets of modular neurons

The principal outputs of the EC are all subdivisions (Chernock et al., 2003b) of the ipsilateral (González-Hernández et al., 1991) and contralateral (Coleman and Clerici, 1987) IC, the medial geniculate body (LeDoux et al., 1987), the pontine nuclei (Burne et al., 1981), and the cochlear nucleus (Caicedo and Herbert, 1993). Since many modular cells are GAD-positive, cortical stimulation (Mitani et al., 1983), which is glutamatergic (Feliciano and Potashner, 1995), might elicit a concerted wave of GABAergic EC modular output that could affect the auditory thalamus (Peruzzi et al., 1997) or the subcollicular targets of EC (Caicedo and Herbert, 1993). Projections from EC and RP contribute to the maturation of the auditory space map in the guinea pig superior colliculus (Thornton and Withington, 1996) and avian tectum (Knudsen and Knudsen, 1983), each of which is consistent with a multimodal role.

4.3. Possible functional roles

Within the IC, the modules might affect inhibitory receptive field subregions of postsynaptic neurons with a role in aurality, like those in the mustached bat (Park and Pollak, 1993; Klug et al., 1995). In the owl such cells may participate in spatial representation (Knudsen and Konishi, 1978) or lateral inhibitory interactions (Wagner, 1990).

EC projections to the pontine nuclei could ultimately reach cerebellar territories concerned with skeletomotor adjustments in human postural control (Tanaka et al., 2001) or motor timing (Ivry et al., 1988), rat startle reflex (Leitner and Cohen, 1985), or in head orientation in cat (Beitel, 1999). Most EC projections to the cat cochlear nuclei target the dorsal cochlear nuclei, potentially reaching neurons that may themselves receive olivocochlear input (Mulders and Robertson, 2000). Perhaps such projections coordinate activity in the tectocochlear and olivocochlear systems.

4.4. Other subcortical modules

No analogous modules have been reported in the cochlear nucleus (Mugnaini, 1985), superior olivary complex (Moore and Moore, 1987), medial geniculate body (Winer and Larue, 1988), or auditory cortex (Winer and Larue, 1989). The dorsal nucleus of the lateral lemniscus (Ueyama et al., 1999) and medial nucleus of the trapezoid body (Webster et al., 1990) have a more homogeneous, rather than a modular, pattern of GAD immunoreactivity.

In the superior colliculus both chemically specific and metabolically active patches (Chevalier and Mana, 2000) resemble EC modules. Possible inputs to these patches in the intermediate gray layers include multiple sensory systems. In the cat, terminals from the RP of IC, itself a site of modular organization, end here (Harting and Van Lieshout, 2000). In the rat, the trigeminal system (Yasui et al., 1993), the substantia nigra (Mana and Chevalier, 2001) and the retinal projection (Linden and Perry, 1983) each overlap with chemically specific superior collicular patches, presumably contributing to multisensory processing. Perhaps the IC modules act in an analogous way for hearing.

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