Modular construction of nervous systems: a basic principle of design for invertebrates and vertebrates

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1. INTRODUCTION

As evinced by the proliferation of papers in the last 30 years[48,62,83,147,148,200,204,205,220,224,225 ,227] it is now well accepted that an iterative columnar or modular organization of the neocortex is characteristic of mammalian sensory[98,147,200,225,247], motor[12,75,78] and frontal association areas[55,78,79,102]. This does not imply that all mammalian neocortical areas are thus arranged; exceptions occur, particularly in the rodents[102].

The basic unit, module or column, is modeled on the vertical cylinders of neocortical tissue described by Lorente de Nó[135]. Initially described from anatomical data, these modules are thought to act both in parallel and in series; the biological equivalents of modern microprocessor chips. Subunits within these modules are arguably the smallest neural building block[148,225]. These subunits, approximately 30 μm in diameter, are columns of 110-260 neurons whose interconnections are mostly vertical[148]. Each `minicolumn' originates as a developmentally cohesive unit[128,177,184] and probably provides a specific type of excitation or inhibition within the column[225]. In this review, I am concerned with the larger neural modules and their functional homologues and analogues throughout the animal kingdom.

Numerous researchers have corroborated and extended Mountcastle's[147] initial documentation of the distinctive physiological roles played by the cortical columns. These modules are not merely autonomous units acting as serial relay stations with internal integrative functions; they exhibit extensive lateral interconnections as demonstrated by several experimental viewpoints. Golgi methods show that branches from cells in adjacent modules are highly interwoven; intracellular fills of physiologically characterized local interneurons reveal arborizations that reach across several compartments[74]; horizontal or tangential views of the cortex marked with activity-dependent substances demonstrate that contiguous, simultaneously active modules can be combined into slabs of tissue 200-800 μm across and several millimeters long[130]. However, in Mountcastle's[147] view, it is pericolumnar inhibition, the ability of active columns to be functionally isolated from inactive neighbors, that is one of their most important properties.

While cortical columns are often discussed as spanning the width of the neocortex, the generality of this idea is still under debate[21,247]. Also, columns may not be evident in all cortical areas. For example, the 'barrels' recognizable within rodent somatosensory cortex are only visible in the particular subfields of this area that receive afferent input from the head and distal forelimbs[247].

Modules are not limited to the neocortex (Table I). Architectonic compartments of similar widths also occur in subcortical and midbrain areas. 'Islands' or `striosomes' in mammalian basal ganglia and 'patches' in the human superior colliculus have been recognized by autoradiographic, immunohistochemical and classical staining methods[76,82,84-89]. However, their physiological roles are the subjects of much speculation.

That the brains of the more complex invertebrates contain functionally and anatomically discrete lobes of neuropil is equally well known [36,196,239,249,250], although perhaps by a different subset of neuroscientists. While

these lobes vary greatly in size (Table II), most lie within the size range of neocortical columns. Larger invertebrate lobes tend to be internally compartmentalized. What is less widely recognized, is that ganglia along invertebrate nerve cords also contain identifiable neuropil compartments[4] that again are similarly sized (Table III).

TABLE I

Examples of vertebrate neural compartments

Sizes are diameters or short and long diameters for ellipsoidal modules, estimated from published literature. Volumes estimated using formulae for spheres (1), cylinders (2) or ellipsoids (3)[223]. Note that OD and orientation columns have been demonstrated to be connected slabs of tissue[97,99,101,221,242]. Striosomes are also connected compartments[87,88]. Best estimates of volumes should be made from original tissue. Volumes are calculated here to give the reader some idea of comparative sizes.

Structure	*Size (μm)*	*Location*	*Volume (mm^3)*	
Olfactory bulb glomerulus	100–200	rabbit cortex[205]	0.00052–0.0042	(1)
	250–750	rat cortex[102]	0.0082–0.065	(1)
Ocular dominance column	385 × 1500	monkey cortex[137,242]	0.18	(2)
	(300–400) × 1500	cat cortex[33,97]	0.11–0.18	(2)
	(700–800) × 2500	human cortex[33,96]	0.96–1.3	(2)
Orientation hypercolumn	570 × 2000	monkey cortex[100,242]	0.51	(2)
	870 × 1500	cat cortex[97,221]	0.89	(2)
Somatosensory barrel	(50–170) × (100–380)	mouse cortex[247]	0.00020–0.0086	(2)
Frontal association column	(300–750) × 2000	monkey cortex[79,100]	0.14–0.88	(2)
Bands in superior colliculus	200–400	human midbrain[82]	0.0042–0.034	(1)
Striosomes of caudate nucleus	500 × (500–800)	human[87]	0.065–0.17	(3)
	300 × (300–500)	cat, monkey[87]	0.014–0.039	(3)
Islands of basal ganglia	300 × (300–600)	monkey[76]	0.014–0.057	(3)

The properties of neural compartments vary, both between phyla and between brain areas. The cellular components and circuitry within the modules are the most obvious source of variability, although among mammalian cortical modules the neuronal constituents are surprisingly uniform[33,148,225]. Many invertebrate modules, often called neuropils, are spherical or ellipsoidal lobes of tissue, rather than long cylinders and they can often be visualized without the use of specialized staining methods. On the other hand, vertebrate compartments arise in greater number and make up larger fields of tissue. And in most cases, methods that rely on their specific architectonic and pharmacological or physiological attributes must be used to make them visible.

TABLE II

Representative spherical and ellipsoidal lobes from invertebrate brains

Sizes are diameters or short and long diameters for ellipsoidal lobes. Volumes for optic, superior frontal and vertical lobes are data calculated by Maddock and Young[139]. Sizes listed for these and all other lobes are estimated from published figures. All other volumes are estimated from published formulae for spheres (1) or cylinders (2)[223] and are included to give the reader some idea of comparative module size. Note that the large lobes are not single modules. * denotes lobes with subunits

Structure	*Size (μm)*	*Location*	*Volume (mm^3)*	
Antennal lobe (with glomeruli)	500	cockroach brain[67]	0.065	(1)
	450	moth brain[49]	0.048	(1)
	150	locust brain[244]	0.0018	(1)
Olfactory lobe (with glomeruli)	200 × 380	crayfish brain[197]	0.012	(2)
	1800	lobster brain*[142]	3.05	(1)
Accessory lobe (with glomeruli)	350	crayfish brain[197]	0.022	(1)
	950	lobster brain[142]	0.45	(1)
Optic lobe	1500 × 2300	cuttlefish brain*[139,252]	232.4	
	3300 × 6500	octopus brain*[139,249]	79.0	
Superior frontal lobe (with lobules)	1000 × 1800	cuttlefish brain*[139]	5.52	
	1000 × 3000	octopus brain*[139,249]	5.27	
Vertical lobe (with lobules)	800 × 3100	octopus brain*[250]	6.18	
	1200 × 3000	cuttlefish brain*[249]	1.95	

Invertebrate neuropils satisfy most of Mountcastle's[148] criteria that distinguish cortical columns. Thus, invertebrate modules (1) are input—output processing devices with connections to a limited number of regions in the nervous system, (2) can map several variables simultaneously, such as sensory modality or position of bodily musculature, topology of connection and/or receptive field, (3) maintain specific connections in an orderly fashion between brain regions, retaining any topological relationships between and through areas, (4) can be identified by unique sets of parameters and (5) allow for selective signal processing by routing specific parameters to particular output destinations. As the number of replicated and functionally alike modules within any one ganglion of an invertebrate brain or nervous system is usually less than 5, with only rare exceptions

such as the 7 or 8 putative neuropils in *Octopus* arm ganglia[90], it is unlikely that most invertebrate modules will satisfy Mountcastle's 6th criterion: that topographic representations shift across a field of modules. However, modules may indeed interact to form laterally inhibited networks. As will be discussed below (see Section 4. Neuropil substructure), such topographic representations occur *within* invertebrate modules.

The striking dimensional similarity between vertebrate and invertebrate modules (Tables I—III) motivated me to try to understand what commonalities might underlie their existence. In this review, I examine some of the characteristics of neural compartments and argue that the modular construction of nervous tissue is at least a remarkable case of evolutionary convergence or at most an organizing principle of nervous systems that developed millions of years ago as animals evolved increasingly complex behavioral and integrative capabilities.

2. RECOGNITION OF VERTEBRATE MODULES

Based upon his studies of Golgi-stained material, Lorente de Nó[135] suggested that the neocortex is composed of numerous `elementary units', local synaptically connected circuits that arc composed of incoming thalamic afferents, intracortical processes and intrinsic cortical neurons. He described these elementary units as columns or cylinders of tissue that encompass all of the cortical layers and act as parallel circuits. Mountcastle[147], experimenting upon a somatosensory area in the cat, demonstrated that such elementary units are indeed physiologically active circuits, but was unable to correlate these units with specific cortical eytoarchitectonic features. Undaunted, Ile speculated that these cylinders are one to several cells wide and that each centers upon an afferent thalamic axon. This axon then activates a narrow set of cortical neurons within it radius of about 250 μm. According to Mountcastle, such columns are interconnected, [Inc! depending upon the stimulus modality, may overlap in horizontal extent. In more recent reviews[111,224] overlapping sets of columns centered upon bundles of thalamic axons or corticocortical afferents have been described. The neuronal composition of modules is discussed below in more detail (see subsection 5.1. Cellular basis for modules).

TABLE III

Examplary neuropils from some invertebrate ganglia

Sizes are diameters or short and long diameters for ellipsoids, estimated from published micrographs. Volumes are estimated from published formulae for spheres (1), cylinders (2) or ellipsoids (3)[223]. * Neuropils in one hemiganglion. *Octopus* stellate neuropil estimated as 1/2 cylinder.

Structure	*Size* (μm)	*Location*	*Volume* (mm^3)	
Ventral Association Center	200	locust thorax[234]	0.0042	(1)
Horseshoe Neuropil	150 × 300	crayfish abdomen*[211]	0.0053	(2)
Auditory neuropil	200	locust thorax[191]	0.0042	(1)
Lateral Neuropil	150 × 275	crayfish abdomen*[211]	0.0049	(2)
	250	insect metathorax[209]	0.0082	(1)
Leech neuropil	100 × 250	leech ganglion[71]	0.0033	(3)
Stellate dorsal neuropil	300 × 1400	*Octopus* ganglion[251]	0.93	
Brachial ganglion	400 × 1000	*Octopus* arm[90]	0.13	(2)
Stomatogastric neuropil	300 × 600	lobster ganglion[115]	0.057	(3)

In only a few cases have brain modules been recognized from anatomical studies that do not depend upon the use of El particular histochemical, immunocytological or autoradiographic technique. Using Nissel stains and Golgi methods, Woolsey and Van der Loos[247] confirm Lorente de Nó's[135] conclusions and identify distinctive cytoarchitectonic compartments in a somatosensory region of the mouse cerebral cortex.. These barrel-shaped compartments are delineated by a dense periphery of stellate cell perikarya which surround a core that is relatively free of cell somata[70]. Barrels range from 1.00-500 μm in diameter with barrels in the posteromedial subfield being larger and more ellipsoidal than those in the anterior area[247]. Unlike other cortical compartments, these barrels only occur in cortical layer IV. As Woolsey and Van der Loos[247] review, the field of cortex containing these barrels receives sensory afferents from the head and distal forelimbs, as discovered through evoked-potential mapping studies. The 5 rows of ellipsoidal barrels in the posteromedial field are associated in a unitary and somatotopic fashion with mystacial vibrissae that are arranged in 5 rows parallel to the bridge of the animal's nose.

Perhaps the best known system of cortical modules that has been described from correlated physiological and anatomical evidence is the system of orientation and ocular dominance columns in the visual cortex. From an extensive series of single-cell electrophysiological recordings, neurons that respond most strongly to the visual presentation of a straight line segment at a particular angular orientation were found to occur in columns perpendicular to the surface of the cortex. These columns, 25-50 μm in diameter, probably correspond to Mountcastle's minicolumns[148,225]. A set of neighboring minicolumns that responds to all orientations is termed a hypercolumn and is about 570 μm wide in monkeys. One hypercolumn is considered to be one module[74,137,230] The anatomical arrangement of orientation columns into hypercolumns was confirmed with the use of the 2-[^{14}O deoxy-u-glucose (2-DG) method[114]. Adjacent hypercolumns were also found to be grouped into slabs of tissue one hypercolumn wide[97,99,101,221,242]. Recent work has shown that orientation hypercolumns can only be demonstrated in the middle cortical layers (II—IV) by single unit recording techniques[21], whereas autoradiographic techniques display them in all cortical layers. Bauer el al.[21] suggest that columnar organization may not extend past layer IV.

A second set of modules containing cells that respond preferentially to input from one eye also occur within discrete columns. In this case, a hypercolumn also contains two individual ocular dominance (OD) columns that receive input from the left and right eyes (Table 1)[74,136,242], but a module is considered to be a column responding to one eye. OD columns can be visualized by using degeneration techniques[99], the 2-DG method or by injecting a fluorescent or radio-labeled tracer into one eye. The tracer is then carried transneuronally into the cortex[221,242.] Again, adjacent OD hypercolumns that receive input from the same eye, can be demonstrated to be connected slabs of tissue with a transverse periodicity of about 770 μm[136]. As with orientation columns, there is disagreement over the vertical extent of OD columns[136,137]. Although the inter-relationship of these two compartment sets is often modeled as perpendicular, the reality of their interconnection is still under study. Recent data show no obvious geometrical pattern and have led Lowel et al.[136] to conclude that the neuronal interactions leading to the development of these two columnar systems follow similar principles, but that the two systems arise from different populations of cells.

Other sets of functionally distinct architectural systems overlap with the OD and orientation columns. For example, the upper cortical layers display a patchy array of staining for cytochrome oxidase activity[241]. Patches rich in enzyme activity contain cells with poor orientation selectivity but with good color specificity. Inter-patch regions have cells with the opposing selectivity. The spatial relationships and interconnections of the cellular components of these systems are also under study[241]. Research done on other cortical visual areas has demonstrated similar architectonic patterns[231,241.]

Neural compartments also occur in the basal ganglia (Table I), the subcortical nuclei involved in sensorimotor integration3 and in the superior colliculus[82]. These cytoarchitectonic units have been discovered relatively recently as most are not visible in conventionally stained tissue[82]. From studies of histochemically or immunocytochemically treated tissue, several overlapping yet pharmacologically distinct compartmental systems have emerged. A mosaic of alternating regions of low and high acetylcholinesterase activity occur within the striatum of cats, monkeys and humans[87,88]. In the human caudate nucleus, `striosomes', areas of low cholinergic activity, are about 500 μm in diameter and extend for several millimeters. Striosomes tend to be round or elliptical in sections, but from serial reconstructions it is apparent that they are connected in a labyrinthine fashion. Their spatial distribution is also not random; striosomes tend to be prominent in the head and rostral half of the caudate nucleus.

In the rhesus monkey striatum, striosome-like patches have recently been identified with classical staining methods$_{76}$. 'Islands', 300-600 μm in diameter, composed of tightly packed, densely stained neuronal somata, are each enclosed by a ring of fibers and embedded in a matrix of more loosely packed, lighter staining cells. Like striosomes they are most prominent in the caudate nucleus, but their anatomical relationship to striosomes is still not well understood.

The use of antisera to Metenkephalin and substance P in cats has disclosed additional systems of patches. In the caudate nucleus, compartments of Metenkephalin immunoreactivity occur as discrete patches 200-500 μm wide. Patches of both low and high substance P immunoreactivity were also found in this region[89]. The enkephalin-rich patches align with the striosome pattern , while the substance P immunoreactive regions do not[89]. In another set of studies, dopamine 'islands', areas that express high tyrosine hydroxylase-like immunoreactivity, co-localize with striosomes late in development but not in the early fetus[84,85]. From studies of the pathways used by various sets of axons, Graybiel and her associates have found that afferent connections from the cortex, thalamus and amygdala terminate in clusters in the caudate nucleus and putamen, some of which coincide with striosomes, depending upon the source. Efferent fibers likewise stem from clusters, some of which also overlap with striosomes[64,83].

The basal ganglia are thus thought to be composed of at least two sets of physiologically distinct compartments. It is not known if these compartments are physiological circuits like cortical columns. As yet, one can only speculate about their importance. Graybiel[83] suggests that these striatal modules may serve to maximize the efficiency of important local connections and to constrain modulatory influences to specific target areas.

3. INVERTEBRATE MODULES

Used in the traditional sense, `neuropil' is a general term that describes any synaptic field of densely packed fine fibers of dendritic and/or axonal origin[37,119]. When modified with a descriptive word or phrase, this term is also used to name specific lobes or regions of synaptic tissue that have obvious histological boundaries (Table III), each with a particular motor, sensory or associative function[4,108,155,173,190-192,211,212,217]. For example, Boyle[30] lists some 25 functionally unique lobes in the brain of *Octopus vulgaris*, which were originally described from anatomical studies and lesioning experiments by Young[250] and Boycott[29]. By comparison, the brains of most decapod crustaceans contain only 11 architectonically distinct neuropils[196]. It is these identifiable neuropils that I infer to be analogs of the brain compartments described above.

In the Annelida, Arthropoda and Mollusca, the 3 phyla whose members are the subjects of most invertebrate neurobiological research, the brain is thought to result from the fusion of several anterior ganglia[36,196,199,239,249,250]. Internally, each ganglion is a heterogeneous structure, composed of axonal tracts, commissures and regions of neuropil, all partially or completely enclosed by a rind of neuronal somata[4,24,36,56,71,91,92,113,174,196,211-213,234,249,250]. As with vertebrate nervous systems, various methods, such as silver impregnations, Golgi methods, the osmium-ethyl gallate technique, cobalt backfilling and intracellular marking procedures must be employed to reconstruct the cytoarchitectonics of the various brain regions[125,194,216,218,243,244].

Many of the largest lobes of invertebrate brains exceed 2000 μm in one dimension (Table II), approximately the height of neocortical columns, but are more voluminous than the largest cortical columns (Tables I and II). The large invertebrate lobes are often subdivided into several neuropils and in these instances a lobe contains multiple modules. For example, the vertical lobe in the brain of *Octopus vulgaris* (Fig. 1), which is involved in short term memory and in the learning and control of complex behaviors, is formed from 5 long lobules. Each lobule is 650-800 μm wide; extends for the length of the lobe, about 3100 μm in mature adults[249,250]; and has a relatively thick cortex of neuronal somata. Thus, the central neuropil of each lobule is actually only about 350 μm across, yielding a volume of about 0.3 mm (ref. 3), well within the range of cortical modular volumes. Another *Octopus* associative center, the superior frontal lobe, is composed of 3 lobules[249,250]. Similarly, the optic lobes (Fig. 2) of many arthropods contain several different layers of neuropil[36,196,219], each of which is considered one module.

Lobes and neuropils are not limited to the brains of large invertebrates. Many homologues of the neuropils seen in crustacean brains occur in insect brains[27,36,47,49,66,67,244] and similar lobes and neuropils exist in the brains of annelid worms[24,36,92]. Identifiable neuropil regions also exist in the ganglia of the ventral nerve cords in arthropods and annelids[71,91,211,212,234] (Table III). However, even though homologous neuropils usually occur in

each ganglion along the chain, the constituents of a neuropil in any one ganglion will depend upon the behavioral activities of the segment and the ganglion's role in their coordination.

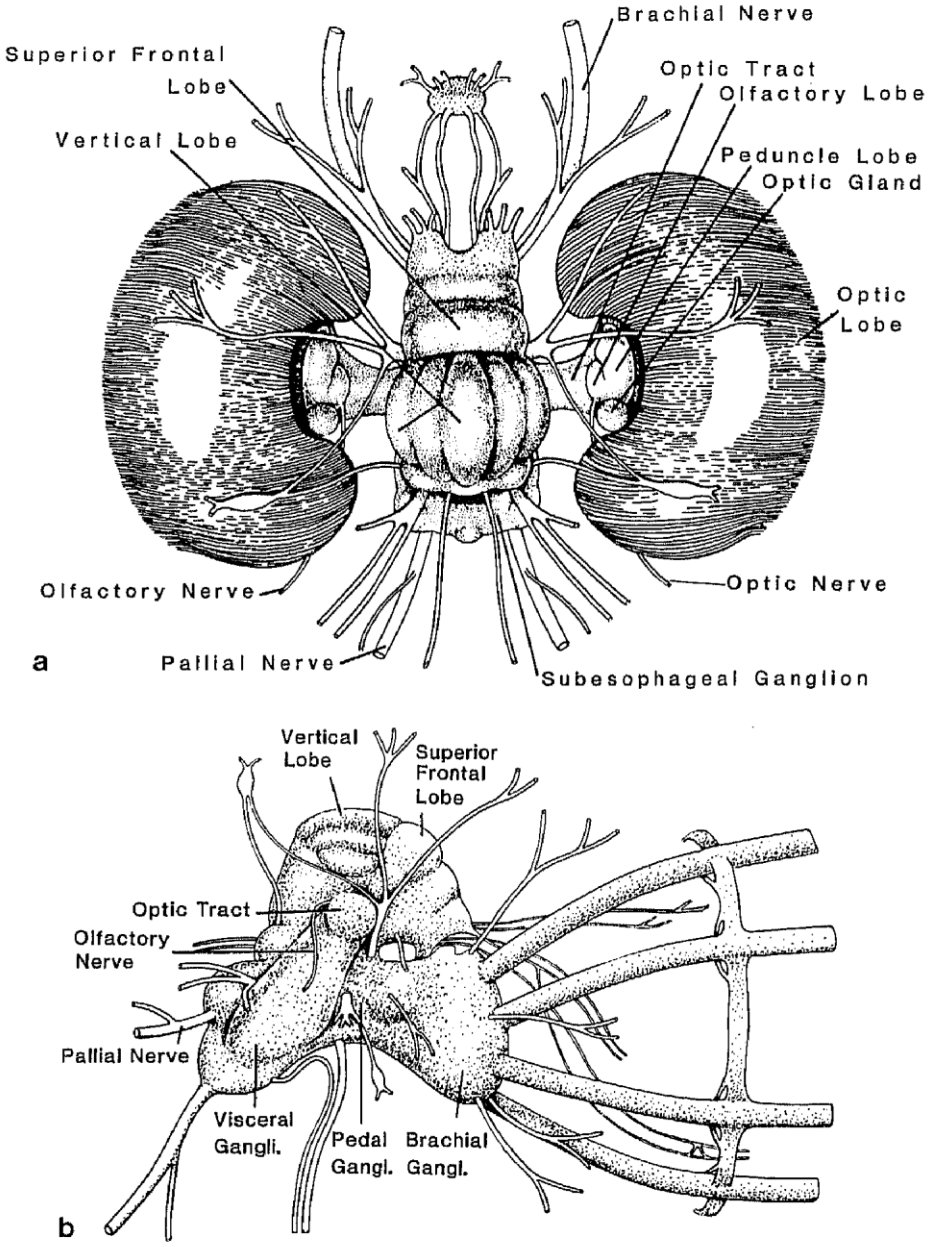

Fig. 1. a and b: dorsal and lateral (right side) views of the brain of *Octopus vulgaris* from Young[249]. Subdivisions of the superior frontal lobe are not apparent in the dorsal view.

One of the first segmental neuropils to be identified was the ventral association center (VAC) of locust and cockroach ganglia174. This neuropil receives most of the incoming sensory afferents and in some animals is subdivided by sensory modality. Also, fields of sensory receptors are known to be somatotopically, represented within this neuropil[6,7,31,32,104,126,155,158,159,161,173]. The segregation of sensory afferents to a specific region in the ventral part of the ganglion is characteristic of insects[36,174] and possibly of all arthropods. A homologous neuropil occurs in crayfish ganglia[122-124,211] Recent data suggest that within this neuropil sensory afferents are also organized somatotopically[121]. Comparative studies of ganglionic organization from more groups are needed to determine if this is a general arthropod characteristic.

Extensive lateral and dorsal areas of neuropil also occur in insect and crustacean ganglia[36,125,174,211,234], although the boundaries of these regions are less obvious in the insects. Nonetheless, electrophysiological and anatomical studies on the neurons that branch in these regions have shown that the dorsal and lateral neuropils are concerned with different behavioral activities. In locusts, the lateral areas contain mostly arborizations of neurons active in the control of leg movements[38,39,206,207,209,237], while neurons or parts of neurons that are

involved in the control and production of flight motor patterns branch in the dorsal neuropil[5,16,50,233.] In crayfish abdominal ganglia the lateral neuropil regions are histologically distinctive and are homologous in function to those of locust thoracic ganglia[94,124,167.] Thus, each area has a distinct functional role and can be considered a module, even in the absence of obvious morphological boundaries. Cells that coordinate several functions branch in several areas'. For example, in locusts some neurons concerned with motor output also collect sensory information from their branches in the VAC[39,40,208]. Locust ganglia are fairly large, about 500 μm high, 1000-1300 μm long and 1000-1200 μm wide, but this segregation of motor functions even holds true for the small, fused thoracic neuromeres (elemental ganglia) of *Drosophila melanogaster,* each of which is about 200 μm in diameter[50].

A comparison of insect thoracic and crustacean abdominal ganglionic architecture does not always allow generalizations. The dorsal neuropil in crayfish abdominal ganglia contains arborizations from 4 sets of motor neurons that are active in both rapid tailflip and slow positioning movements of the abdomen[122,123,245]. No clear functional segregation of neuronal branching pat-terns has been discovered. It also has no obvious histological borders that support the notion of this area being a module. In contrast, in the thoracic ganglia of orthopteran insects the dorsal neuropil is densely invaded by branches of flight neurons and can be considered a specific neuropil. Because flight musculature probably evolved from ambulatory limb muscles[140], the flight motor neurons are most likely not homologous with those in the same region of crayfish or even moth abdominal ganglia. In abdominal ganglia of lepidopteran moths such as *Manduca sexta,* the dorsal neuropil, like the crayfish counterpart, is replete with branches of motor neurons that innervate the intersegmental muscles[127].

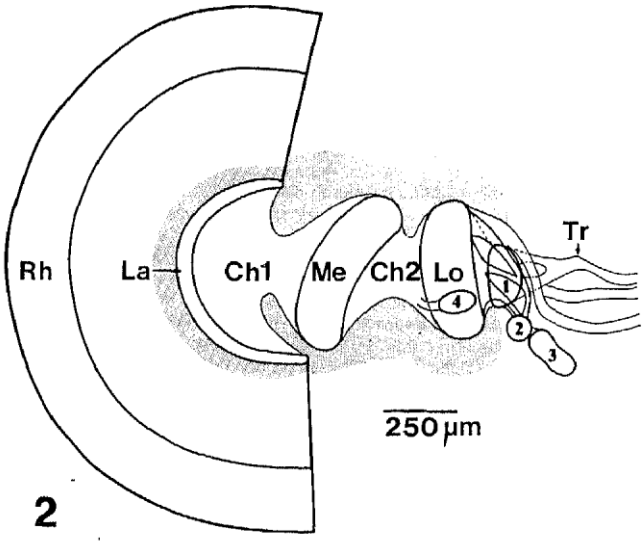

Fig. 2. Diagram of the crayfish retina and optic lobes in the eyestalk, drawn in horizontal cross-section, from Stausfeld and Nässel[219]. The 3 columnar neuropils are the lamina (LA), medulla (ME) and lobula (Lo). Ch1 and Ch2 are the optic chiasmata. Four discrete neuropil regions (Nos. 1–4) receive axons from the columnar neuropils. Rh, rhabdoms; Tr, centrally projecting tracts of axons.

The architectonic organizations of some insect and crayfish ganglia are known in great detail[36,91,174,211,234], but by comparison, relatively less is known about molluscan and annelid ganglia[36,60]. The internal organization of several polychaete brains has been studied[24,36,92] but of the annelid segmental ganglia, only those in leeches have been described in any detail.

Asexual leech ganglia regulate several behaviors, including heartbeat, bodily shortening, walking, swimming and twisting[26,43]. These ganglia are smaller than insect and crayfish ganglia and at first glance the neuropil appears undivided[71]. However, it is not spatially homogeneous. Fernandez" speculates that the ventral neuropil receives sensory information and it does contain dense areas that resemble glomeruli, at least by optical microscopy. Many neurons in these ganglia have been identified physiologically, but their precise neuropilar locations are undescribed. Primary sensory afferents are known to branch mostly ipsilaterally, while motor neurons branch dorsally on both sides of the ganglion, information that tantalizingly suggests some type of ganglionic

partitioning[151-153,163,248.] At this time, I consider each ganglion to be one module; the motor neurons on each side of the ganglion are coupled and are presumed to act in concert[118,164,222]; and the ganglion lacks any obvious internal neuropilar segregation'.

Considering the amount of neurophysiological research that has been performed on gastropod ganglia, it is surprising that we know so little about their internal organization[36,60]. However, information is available about some bivalve and cephalopod ganglia, particularly the parietovisceral ganglion of scallops[56,213] and the stellate and arm ganglia of various cephalopods[90,251]. The architecture of these two cephalopod ganglia, discussed briefly below, illustrates that molluscan ganglia also contain localized neuropils, but offers us no other major generalities about their functional organization.

Cephalopod stellate ganglia control the mantle musculature that moves during both respiration and locomotion. Stellate ganglia also receive afferent terminals from epidermal receptor cells and mantle proprioceptors[251]. The ganglionic core is composed of two neuropils and presumably, two modules (Table III), each of which has a distinctive appearance after silver impregnation. From degeneration studies, Young[251] learned that the ventral neuropil receives input from the CNS while the dorsal neuropil receives peripheral afferent terminals and sends efferents to the mantle musculature. There are interactive pathways between the two areas and some overlap in the inputs they receive. Young[251] presumes that the ventral neuropil is responsible for respiration and that the dorsal one controls locomotion, but he also admits that critical experiments are needed.

Each arm of *Octopus vulgaris* contains several nerve cords. The central cord innervates the muscles of the sucker and the arm itself. This cord consists of a series of ganglia, each with a large neuropilar core (Table III). This central neuropil is divided into 6-8 smaller spherical units[90] that may be large glomeruli. Each putative macroglomerulus is about 120 μm in diameter. The occurrence of these large subunits suggests that they, like the moth macroglomeruli discussed in the next section and not the entire neuropil, are the modules of neural tissue. But again, how or if functions are segregated within these ganglia is unknown.

Other well-known invertebrate ganglia also display no evidence of morphological partitioning that relates to function, even though their neurons may be physiologically segregated. An example is the stomatogastric ganglion of lobsters (Table III), in which one circuit drives the teeth of the gastric mill while the other drives the muscles of the pyloric sac[202]. The center of this ganglion does have some internal structure: a dense synaptic neuropil surrounds a core of larger processes[115,116]. However, the lack of any functional correlations with this ganglionic substructure[115,116] suggests that the entire ganglion is one module. When stained with antibodies to any of several neuromodulatory substances, these ganglia again display no obvious compartmentalization[22,44].

Similar use of antibodies to other modulatory sub-stances has revealed immunoreactivity throughout the lateral neuropils of crayfish[210], suggesting that many neurons within the neuropil are affected simultaneously. This again points toward the possibility that neuropilar partitioning may serve a neuromodulatory function, as mentioned earlier. Still, without experimental evidence that identifies the target neurons for modulation or that differentiates neuropil from the surrounding tissue on the basis of a unique morphological feature or some physiological activity or gradient that can be correlated with neuromodulatory activities, this aspect of modular function remains speculative.

4. NEUROPIL SUBSTRUCTURE

Within invertebrate neuropils, a few types of micro-architecture are common, including radial columnar organization and synaptic glomeruli. As in vertebrate cortical modules, internal structure is likely to be critical to the ability of a module to simultaneously C011SCINC modality and topographic representation[148].

4.1. Columnar organization

Neuropils in the optic lobes of arthropods and cephalopods are similarly organized into radially arranged columns[36,219,252], a system which allows for both hierarchical and parallel analysis in signal processing as well as the retention of the retinotopic representations of the visual field. However, such radial architecture is not

characteristic of all optic neuropils. For example, in crayfish optic lobes (Fig, 2), only the first 3 of 7 neuropils have columnar architecture[219].

In squid, the outer part of the optic lobe neuropil is arranged in concentric layers while the large inner mass of the lobe is organized into alternating columns of neuropil and axon tracts. These columns are narrow and most numerous distally, but larger and fewer proximally. These columns grade from about 25 μm to about 150 μm in diameter[252] and, intriguingly, this size is reminiscent of the single orientation minicolumns found in mammalian visual cortex137. Although there are even similarities in cell type and function[252], the cephalopod circuits have not been analyzed in the detail known for vertebrate cortical columns[30].

4.2. Synaptic glomeruli

A different type of architectonic structure is found within the neuropils of many invertebrate sensory systems. Glomeruli are spherical clusters of complex synapses, recognizable both by light and electron microscopy, as they are often set off from the surrounding tissue by distinctive glial capsules[225], These structures, usually 15-50 μm in diameter and occasionally reaching 100 μm across, occur in large numbers in the olfactory and accessory lobes of many arthropod brain[27,28,47,67,117,142,196,197]. These lobes process chemoreceptive information received by the antennal sensory receptors (Fig, 3). Spherical glomeruli may be the most efficient way to package 3-dimensional neural tissue when many afferents converge onto relatively fewer interneurons[28] and when afferent responses are transformed by the actions of several interneurons. For instance, in cockroach brains, some 260,000 sensory afferents project into 125 giomeruli of the deutocerebral olfactory lobe. The numerous local interneurons in this lobe each contact several glomeruli and receive most of the terminations of the Efferent axons, while projection interneurons convey information to higher-order processing centers (Fig. 3). Each projection interneuron receives information from only one glomerulus, generating an afferent to projection interneuron convergence of about 2080:1. The local interneurons appear to act in 'horizontal' fashion, interconnecting different glomeruli and vastly improving the signal-to-noise ratio at the level of the projection interneurons[28]. The projection interneurons are thus far more responsive to small amounts of odorants than are individual afferents and are all probably preferentially sensitive to specific mixtures of odorantsu.

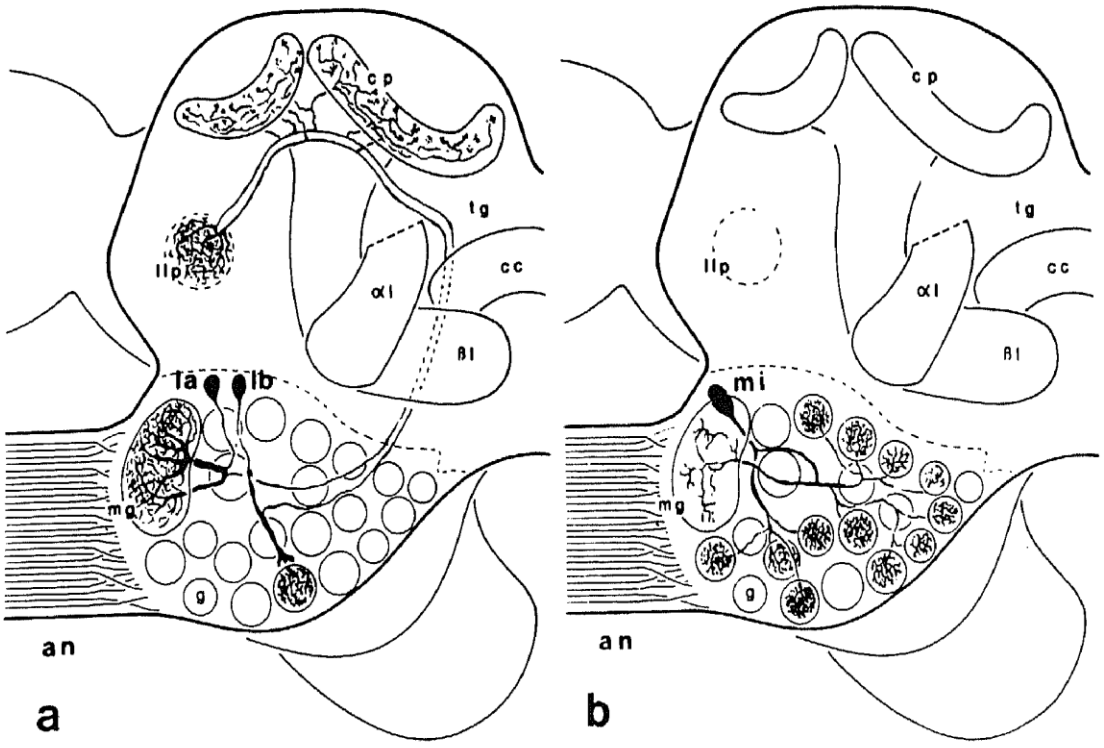

Fig. 3. Diagram of right half of brain of the cockroach *Periplaneta americana* from Ernst and Boeckh[66]. a: Camera lucida drawings of two projection interneurons. 1a responds to female sexual pheromone and innervates the macroglomerulus (mg). 1b also innervates one glomerulus (g) but responds to other odours. Both project to the calyces of the corpora pedunculata (cp) through the olfactorio-globular tract (tg). Collaterals of both interneurons reach the lateral lobes of the protocerbrum (llp). b: Camera lucida drawing of a local interneuron (mi) that innervates many glomeruli and has no axon. an, antennal nerve, α1, β1, lobes of corpus pedunculatum, cc, central body.

Glomeruli in vertebrate brains have been described in the cerebellum, the medial and lateral geniculate bodies and in other thalamic nuclei[180,204,205,226]. The cockroach glomeruli described ,above also have many features that are analogous to glomeruli mammalian olfactory buibs[204,205]. As Shepherd[204,205] mentions, in rabbits, about 50 million unmyelinated afferents enter one olfactory bulb and innervate about 2000 large glomeruli. The afferents terminate upon two types of projection inter-neurons and upon local interneurons. In this case, the convergence is about 25 000:1, greater than in cockroach brains by an order of magnitude. The rabbit glomeruli are also larger, being 100-200 μm in diameter (0.00052— 0.0042 mm^3 in volume). However, in male moths, the so-called `macroglomerulus' reaches 200-300 pm in diameter2"" (0.0042-0.014 mm3 in volume) and each one receives about 86 000 afferents that select strongly for female sex pheromones (Fig. 3). Thus, glomerular size is correlated with the number of afferents converging into it. The complexity of local interneuronal synaptic interactions must also play a role in determining glomerular size. Shepherd[205] compares the complexity of rabbit olfactory bulb glomeruli to that of the somatosensory barrels of the neocortex, implying that one can consider olfactory bulb glomeruli and hence cockroach macroglomeruli to be individual modules. Although the synaptic details may differ, the basic arrangement of synapses within these glomeruli allow for both vertical and horizontal processing. Vertebrate glomeruli are usually, but not solely associated with brain structures that process sensory information. They may also contribute to an increase in the safety factors associated with signal transmission among 3 or more synaptic element[148].

Glomeruli also occur in at variety of other invertebrate neuropils, in annelid mid- and hindbrains[24,92], in the lateral lobes of the parietovisceral ganglia of scallops[56,213] and in the horseshoe neuropil of crayfish abdominal ganglia[123,211,212]. Again, as in vertebrate nervous systems, invertebrate glomeruli appear to be overwhelmingly a product of sensory systems and tend to be found in conjunction with well developed sensory organs[36]. For the tissues mentioned above, polychaete midbrains and hindbrains process information from the antennae, eyespots and nuchal organs[36]; the lateral lobes in scallop parietovisceral ganglia receive afferents from the mantle eyes[56,213]; and the horseshoe neuropil of crayfish collects afferent information from exoskeleton sensory hairs[123].

4.3. Somatotopic order

Topographic representations of the body or external receptive fields are common and well documented in mammalian cortical sensory areas[68,69,98-100,110,112,144,145,147,148.232,240,247], prefrontal regions[77,149], cortical motor areas[12-14,72,110,148,193] and subcortical nuclei[2,55] and have been the subjects of several extensive reviews[77,144,148,227]. Many of these areas display multiple representations of the body or receptive fields[144,149,227]. These repetitive representations are not redundancy, but result from the complexity of information that is derived from and processed within each subregion.

Somatotopic mapping of sensory afferent projections has been found more recently in several invertebrate neuropils, particularly in the insects (Fig. 4). Neurons from the eyes project retinotopically into the brain in numerous species[215,219]. The central projections of auditory afferents in crickets are also arranged tonotopically in the thoracic sensory neuropils[190,191,146]. Likewise, mechanoreceptive afferents from hairs on the cerci, wings, thorax and legs of crickets are organized somatotopically[108,154,160,173], as are hairs on the abdomen and prolegs of larval moths[126,172].Within these sensory neuropils, afferent projections can also be spatially segregated by specific modalities (Fig. 4)[15]. Unlike the representations in vertebrate brains, neuropils display only a single body map.

Somatotopic organization of the central projections of motor neurons is less well known, but has been found in both moths and locusts[127,233]. Topographical mapping within neuropils in animals of other phyla is less well documented. However, somata of mechanosensory neurons in ganglia of the mollusc *Aplysia* are organized somatotopically[23,236] which suggests that these ganglia may be the ones to explore for a similar organization of the neuropil.

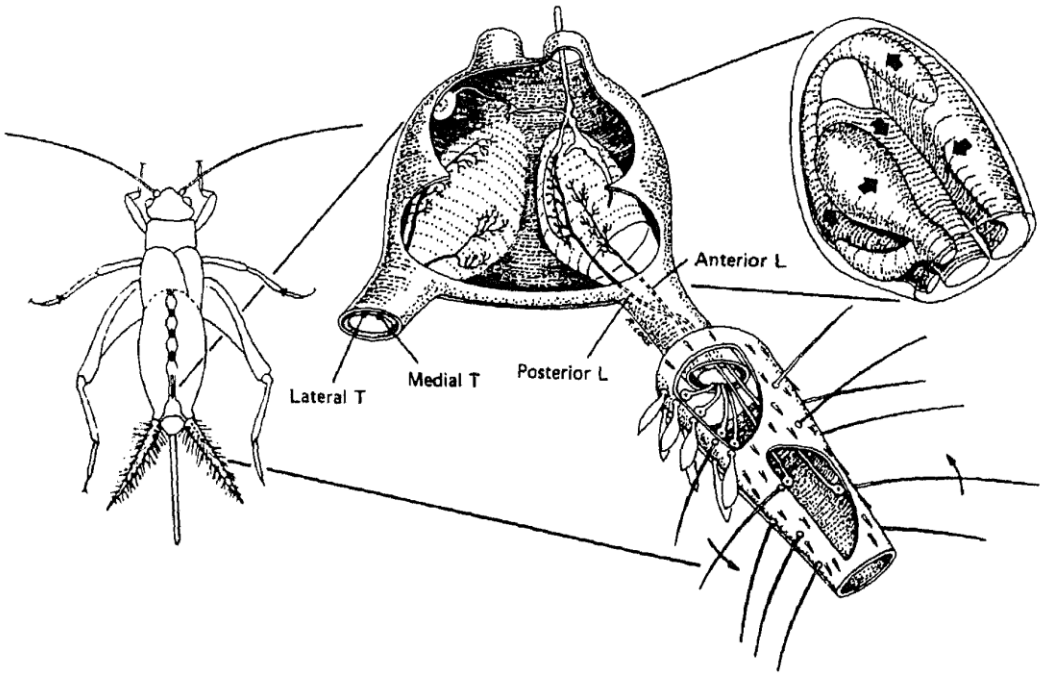

Fig. 4. Diagram of the cercal-to-giant axon system in the cricket from Bacon and Murphey[15]. The central panel shows location of the cercal glomeruli with 4 types of afferent projections. The right panel shows directional sensitivity to wind displayed by afferents in each neuropil subregion.

5. MODULE SIZE

The diverse neural modules discussed in this review are more similar in size than a study of their parent nervous systems might suggest. The organisms mentioned here vary over several orders of magnitude in volume or weight, as do their nervous systems. However, their nervous systems scale allometrically with body size, so that brain weight (y) increases with increasing body size (x), usually by more than a two-thirds power of the ratio of the body weights ($y = kx^{0.7}$). The exact ratio depends upon the taxonomic group examined[96]. The proportionality constant (k) also varies from group to group[1,96]. This equation can also be used to describe the relationship between brain volume and various cortical measurements, such as cortical surface areas, thickness or volume[96]. However, when animals of very different sizes are compared, certain anatomical features of homologous brain regions increase less than would be suggested by this equation. For example, neocortical thickness varies by a factor of 3 from mouse to elephant, whereas their brain weights differ by 4 orders of magnitude[37]. Within a given taxon, larger animals tend to have larger brains, which has been explained as the need to service and control larger organs[96]. Still, most of the increase in brain weight (or volume) relates to the addition of modules, which in mammals corresponds to an expansion and convolution of the cortical surface[96].

The amount of variability found in module size depends upon the measurement taken. Most modules are between 150 and 1000 μm wide, with only a few reaching 1500 μm or more. In length, modules vary over an order of magnitude, from about 250 to over 3500 μm (Tables 1—III). In volume, modules can differ even more, over 3 orders of magnitude. Modules perform diverse functions, from the integration of sensory information through higher-order associations to motor pattern generation. The processing of sensory information often includes the convergence of input from thousands of afferents[49] whereas motor pattern generation can require input from relatively fewer neurons and in some cases can be produced by less than 20 neurons[202]. Thus, even within a single individual, the nervous system should contain modules of different sizes. Nonetheless, the general restriction of module size, especially in width, to less than 1 mm crosses phyletic boundaries and suggests a common underlying causality that is addressed in the next two Sections.

5.1. Cellular basis for modules

The question of how a module's size relates to its neuronal constituents and to its electrophysiological activities has perhaps been more perplexing for neuroscientists working on vertebrate systems than on invertebrate ones. Only recently has a general, although not unanimous, concensus been reached about the structural basis for compartments in mammalian cortical sensory areas. A simplified version of this model is presented below,

concentrating on the major cell types and their most likely functions. Columns in other areas are likely to have somewhat different circuits[111]. Because earlier reviews already treat this subject[48,74,137,148,227], the intricacies added to columnar circuitry by the laminar origins of the cells involved will not be discussed in detail.

A typical cortical column (Fig. 5) centers upon a bundle of thalamic afferents that terminate mostly upon spiny stellate interneurons but also directly onto pyramidal cells of the central layers[70,109,111,148,227]. Spiny stellate cells make excitatory synapses onto the apical dendrites of pyramidal cells in all layers and probably ensure that the pyramidal cells are activated in concert. The narrow branching patterns (100-200 μm wide) of the spiny stellate cells tend to restrict afferent input to a limited field of pyramidal cells and may also help to maintain any topographic order of afferent input. Many spiny stellate cells are involved in the circuit of a single column. Columnar width, which is usually 500-1000 μm, is thought to correspond to the width of the terminal field of the afferent axons[70,109,111,148], overlapping with the extent of the dendritic fields of the pyramidal and spiny stellate cells[137].

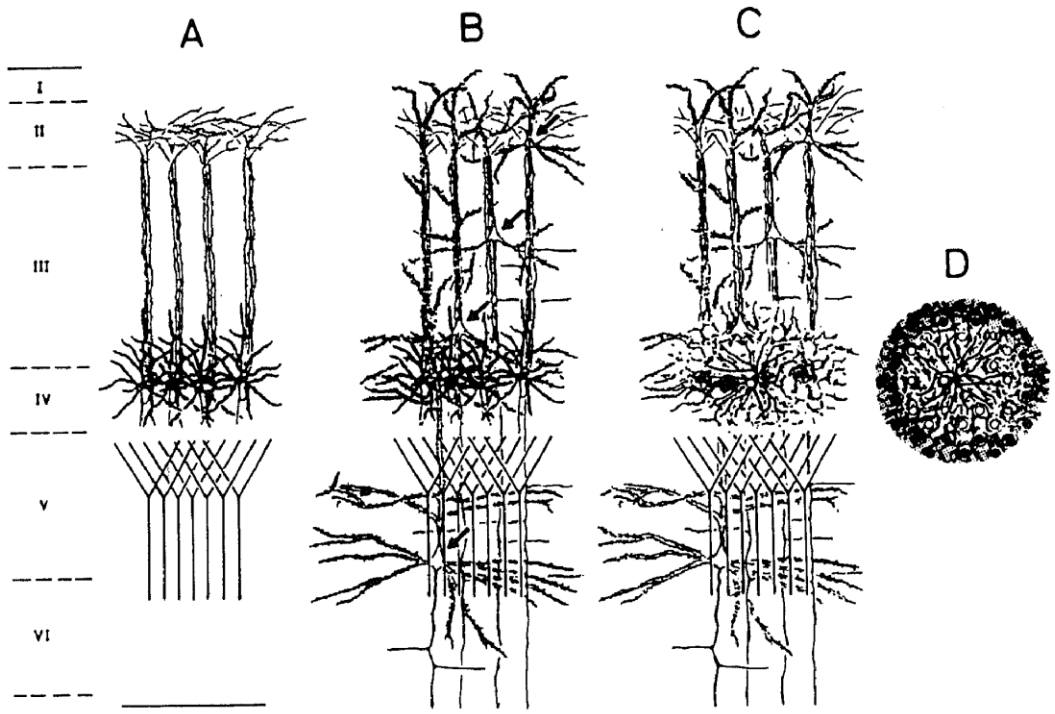

Fig. 5. Diagram of mammalian cortical layers showing postulated input–output columns based upon thalamocortical fiber bundles, from Jones[111]. Small spiny cells with vertical axons in (A) receive thalamocortical synapses. Vertical axons synapse on pyramidal cells of all layers (B). Pericolumnar inhibition is thought to be mediated by Golgi type II Cells (C), which serve to inhibit weakly excited small spiny cells at the perimeter of the column (black and stippling in D). These synaptic relationships do not exclude termination of thalamic axons on other types of interneurons or on pyramidal cells directly.

Many other types of interneurons are active components in these cortical compartments, but are not thought to delimit their borders. For example, local interneurons, such as the small basket cells and chandelier cells can also receive thalamic afferent terminals and provide inhibitory influences to an activated bundle of pyramidal Cells[137,225,227]. Large basket cells, local interneurons with broad horizontal dendritic arborizations and axons often several millimeters long, make inhibitory synapses onto pyramidal cell somata. These basket cells are presumed to mediate some type of pericolumnar inhibition[109,148], thereby isolating active from inactive columns. They may thus link adjacent active columns into slabs of tissue. Extrinsic neurons in the column give off collaterals that may also add to the intercolumnar inhibitory network[111,148].

Columnar output arises from pyramidal cell axons and from a few stellate cell axons that project to columns in the same or different cortical areas and to other subcortical sites. Pyramidal cell axon collaterals that contact neighboring pyramidal cells could also act EIS a positive feedback system[225], serving to link adjacent active columns into stripes of tissue.

Columnar structure is not static; sets of pyramidal cells are probably components of different columns over time or during differently modulated states of nervous activity. Also, the amount of overlapping input to adjacent columns is unknown[111]. Furthermore, in at least the somatosensory areas, corticocortical connections exhibit an analogous plan of organization, so that neurons in any given column should receive input not only from a particular bundle of thalamic afferents but also from a bundle of corticoccirtical fibers[68,69,110]. Obviously, a great number of excitatory and inhibitory connections are possible, so that while all cortical columns may have the same basic components, their electrophysiological circuits can be quite various.

The cellular components of compartments in the basal ganglia are less well understood. Dopamine islands in the caudate nucleus correspond to striosomes late in embryonic development and Graybiel[84] makes several suggestions about the neuronal populations that determine the 200-500 μm diameter size of these patches. Terminals from a bundle of axons arising from the rostral frontal cortex may span each striosome, at least in the dorsal part of the caudate nucleus. Other afferent systems may terminate in the more ventral striosomes[84]. The dendritic spread of the intrinsic postsynaptic neurons — the medium spiny neurons — could also determine the size of these compartments. The average medium spiny neuron arborization field lies between 350 and 500 μm in diameter in the adult cat[84]. Medium spiny neurons expressing different neuropeptide immunoreactivity also occur in clusters that match the extent of the dopamine islands in some areas.

The identification of the neurons that comprise and delimit invertebrate modules has been more straightforward. In many cases, specific areas of neuropil could he identified from histological characteristics without a knowledge of individual neuronal shapes. Such areas include neuropils in annelid and cephalopod brains[24,29,92,239,249-252], bivalve ganglia[56,213] and insect and crustacean nervous systems[48,91,174,196,234]. For many of these neuropils, later studies of individually identified neurons would confirm the neuropilar functional roles. In all of these regions, neuropil or module size is governed by the combined arborizations of extrinsic and intrinsic neurons subserving a particular behavioral, associative or perceptual activity.

Other neuropils were only recognized as such when various ganglionic regions were found to contain a cluster of whole neurons or particular branches that subserve a distinct motor, sensory or associative function. Examples of this include the dorsal flight neuropil in orthopteran insects, in which all or parts of the branches of the interneurons, sensory neurons and motor neurons involved in flight production overlap[5,16,50,233] and the lateral or intermediate neuropils in locust thoracic ganglia where leg movements are coordinated[38,39,40,168,206,208,209,237]. Neurons involved in the coordination of the basic neuropilar functions will of course branch in several modules4. For example, spiking interneurons in locust metathoracic ganglia function in local leg reflexes. These neurons branch dorsally in the neuropil that coordinates leg movements and collect sensory information directly from afferents in the Ventral Association Center (VAC)[39,209].

Studies of the anatomy and physiology of single cells located in previously described neuropils have often yielded further information about neuropilar organization and interactions. For instance, the VAC that integrates information from sensory afferents in orthopteran insect ganglia[174] was shown to contain subdivisions, each of which includes terminals from sensory afferents located on a particular bodily region. Thus, the VAC of locust thoracic ganglia has been divided into two regions, the VAC and the ventralmost VAC (vVAC)[108]. The more dorsal VAC receives afferents from bristles on the dorsal thorax and wings, while the vVAC receives similar afferents from bristles on the ventral thorax and legs. In a detailed study of cricket cereal hairs that respond differentially to wind direction, Bacon and Murphey[15] found that each cereal glomerulus, the large neuropils in the last abdominal ganglion in which these afferents branch, had 4 subregions, each with branches from afferents sensitive to a particular wind direction (Fig. 4).

5.2. Module size depends upon membrane electrotonic structure

Why are modules generally less than 1 mm across in at least two of their 3 dimensions? Module size appears to be determined by the extent of the component neuronal arborizations, but what restricts their sizes? The most reasonable answer is a combination of passive cable properties, branching patterns and synapse distribution. An examination of the cable properties of the important intrinsic neurons in several vertebrate and invertebrate

modules is necessary to test this hypothesis. Nonetheless, by inference from studies on other neurons, it becomes apparent that neuronal arborizations have a maximum size limitation of about 1 mm diameter.

Dendritic membranes of most neurons do not support action potentials[35]. Thus, the distance over which passively conducted potentials can provide useful information may ultimately limit module size. Decremental signals can be transmitted over long (1-2 cm) distances to perform useful functions[41,42,58,146,166,189,203], but in these situations, the electrotonic membrane is usually that of an unbranched axon cylinder with a relatively high specific membrane resistance[41,203], often near 1 $M\Omega \cdot cm^2$.

Many types of neurons throughout the animal kingdom have large dendritic trees which will allow for the multiplicity of synaptic contacts necessary to ensure faithful transmission. Nonetheless, if dendrites are too long, distal synaptic information will not be useful at the spike initiating locus. Most vertebrate neurons have dendritic trees that are at most two length constants from the soma[185] so that an incoming postsynaptic potential is reduced to about 40% of its original value. The arborizations of many invertebrate neurons are also electrically compact. However, in cells with complex dendritic trees, synaptic potentials may be further decremented. Voltage may spread well in the proximal to distal direction, but can be sharply attenuated centripetally, especially if branch diameters differ greatly[81]. As an example, after analyzing the electrical properties of neurons from the mollusc *Aplysia*, Graubard and Calvin[81] calculated that a voltage applied distally on a 2 μm diameter branch fell to 3% of its original value some 1000 μm from the application site. This fall in voltage occurs because the branch terminates at a large axon, not because of the cell's length constant which they calculate to be 5.6 mm. Voltage applied at the soma would drop to 95% of its original value at the branch point and little more attenuation occurs along the narrow branch. Thus, complex branching patterns, typical of many neurons, can decrease the apparent space constant, affecting the relative weights of synaptic inputs and outputs and drastically reducing the distance over which passively conducted potentials are significant changes in membrane potential[81].

The electrical properties of cerebellar Purkinje cells have been explored in several vertebrates and modeled in detail[131-134,169-171]. Again, I use this case to illustrate how one cell type has overcome the spatial limitations imposed on its conduction capabilities by its complex branching pattern.

Purkinje cells have planar dendritic trees about 400 × 400 × 10 μm (ref. 204) and transmit electrical information by both passive and active. means. The Purkinje cell is the sole cerebellar output neuron (Fig. 6) and each one can receive excitatory input from as many as 400 000 parallel fibers. The dendrites of each Purkinje cell also receive 200-300 excitatory synapses from one climbing fiber[169]. Inhibitory input from several types of local interneurons are superimposed onto this circuit[169, 204].

The membrane response properties of alligator and frog Purkinje cells have been studied and modeled for both types of orthodromic activation (via parallel and climbing fibers) and for antidromic activation via the Purkinje axons[132,169-171]. As mentioned, the dendritic trees of these cells are capable of generating action potentials in response to orthrodromic activation, although the entire dendritic membrane cannot produce regenerative responses. Specific regions produce calcium action potentials[132,134]; these 'booster' sites most likely occur at dendritic branch points. Unlike the responses of the neurons modeled by Graubard and Calvin[81], a spike in the Purkinje cell soma decrements to 16% of its original voltage some 300 μm distal in the dendrites[169,170]. The incorporation of regenerative responses into their Purkinje cell model shows an apparent increase in the membrane length constant; an orthodromic spike would decrement to 66% of its original value when measured at the same point, a far more significant change in dendritic membrane potential. The possibility that other cells with complex arborizations in the larger mammalian, molluscan and arthropod modules might use similar mechanisms needs to be explored experimentally.

6. DEVELOPMENTAL SIGNIFICANCE

The development of any nervous system incorporates a bewildering array of cellular and molecular interactions. The literature in this field is enormous, but several books[106,165,175,176,214] and review articles[9,20,34,59,63,129,

[157,184,195,238] can provide entry into or review of specific issues. In the next two sections, I review recent developments in those topics particularly germane to the formation of neural compartments.

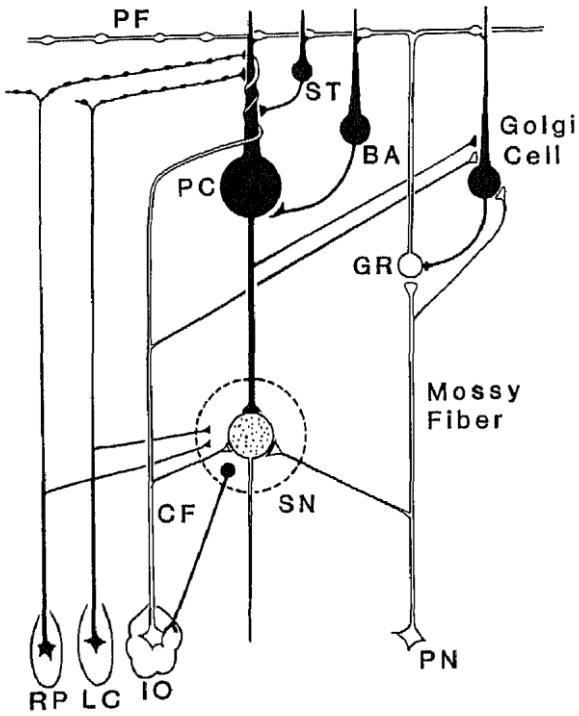

Fig. 6. Basic neuronal circuitry in the cerebellum from Ito[103]. BA, basket cell; CF, climbing fiber; GR, granule cell; IO inferior olive; LC, locus coeruleus; PC, Purkinje cell; PF, parallel fiber; PN, precerebellar neuron that extends mossy fiber; RP, Raphe nuclei; SN, vestibular or cerebellar nuclear cell; ST, stellate cell. Inhibitory neurons and synapses are in black, excitatory ones are unfilled. New inhibitory connection from IO to SN, also from Ito (personal communication).

In many systems, especially invertebrate ones with relatively fewer modules, module integrity appears to be invariant with time. This is not always the case. Regeneration of afferents can change modular properties and boundaries in both vertebrates and invertebrates[101,156,157,179] and as mentioned earlier, neurohormonal modulation may significantly alter module activity. Compartment patterns can also change during development, as they do in the mammalian basal ganglia. Two sets of compartments, i.e. patches of dopaminergic and cholinergic neurons, change their organization over the cat's fetal and early postnatal development. In early fetal stages, dopamine islands and acetylcholinesterase-rich (AChase-rich) patches are in register[84]. As development proceeds, AChase staining becomes diffuse until AChase-poor patches co-localize with dopamine-rich areas. In adults, dopamine patches as revealed by tyrosine hydroxylase immunohistochemistry disappear[84], although they are visable with more sensitive methods. Thus, the AChase-rich patches appear to be the forerunners of the AChase-poor patches (striosomes). Changes in striosomal make-up most likely reflect differential expression of neurotransmitter-related com-pounds; Graybiel suggests that the changing dopamine expression may be important to the development of synaptic specificity.

6.1. Axon outgrowth and guidance

Developing nervous systems exploit numerous mechanisms, such as cellular migration, generation, differentiation, loss, synapse formation and elimination, neurite extension, etc., that cross broad phyletic boundaries[59,157]. In both vertebrates and invertebrates, large areas of the brain develop simultaneously[9,20,34,45,177,183,184,238] necessitating the action of guidance mechanisms to ensure that young neurons reach their appropriate targets[45,59,177,184]. Several types of interactions have been implicated in this path-finding predicament. Neuronal inter-actions, such as the selective affinities displayed by insect afferent neurons for each other[23,53,228], the migration of neurons over glial scaffolds in arthropod[105] and mammalian[59,128,177,184] nervous systems and the migration of arthropod[51,52] and possibly teleost65 neurons over the extracellular matrix, may all be mediated by several classes of cell-surface markers, usually glycosylated molecules and matrix

compounds[59,63,80,120,188,195]. The outcomes of such interactions while genetically predetermined in part, are highly plastic events that can depend upon both the animal's internal milieu and upon its interactions with environmental stimuli.

Some of these same cell-surface markers are thought to specify compartment boundaries[54,95,184,229] although the relative importance of glial vs neuronal components is unclear. Compartment boundaries may also be specified by components of the extracellular matrix. These boundaries are undoubtedly significant for the retention of topographic order and target specificity in a growing field of axons.

Several systems have been important in molding our ideas about neuronal guidance cues. As an example, in mammals, neurons bound for the cortex proliferate around the cerebral ventricle. The ventricular zone is divided into columns of stem cells whose progeny migrate to their final positions in the cortex[128,138,177,178,184,201]. The neurons navigate through the various developing brain regions by following a scaffolding of radial glial cells[177] that is in position before neuronal migration begins. The glial arrays allow the developing neural fields to retain the correct spatial and temporal organization. Presumably, some family of cell surface markers is responsible for each glial unit[63,129,184]. Each glial unit produces columns with 80-120 neurons and most likely corresponds to a cortical minicolumn[148], such as the single orientation columns in the visual cortex[128,148,225]. Recent work on the clonal relationships of migrating neurons within the developing cortex suggests that members of individual clones may all finally reside within a single cortical column[138].

In the insects, 3 classes of glial cells in the central nervous system (CNS) develop early in embryogenesis and like their mammalian cortical counterparts, act a substrate for the migration of pioneer neurons[105]. The pioneer neurons, which include interneurons, motor neurons and sensory neurons[8], are the first neurons to grow over this scaffolding[17,105,186,228]. The roots of one set of peripheral nerves, the intersegmental nerves, have similar glial foundations[105]. Successive generations of neurons will selectively fasciculate with particular pioneer axons or bundles of axons[93,187]. Insect pioneer neurons also have their mammalian counterparts; axons from subplate neurons migrate into the thalamus, establishing the route for axons that will become the adult subcortical projections[143].

In the periphery, pioneer neurons migrate towards the CNS between the limb epithelium and its basal lamina, creating by their paths, the major nerve trunks[52]. Here, the pioneer neurons are dependent upon the presence of the basal lamina for axon elongation[51,52]. The limb basal lamina displays distinct structural variations, both spatially and temporally, that may be critical to its guidance functions[11]. Central and peripheral pioneer growth cones make specific turns that require the presence of guidepost neurons, usually other immature neurons, for normal pathfinding[10,51-53,186,187.] In some cases, specific turns depend upon glial cells[186,187]. In all cases, specific cell-to-cell or cell-to-basal lamina contact mediates neuronal path choice[18,19,53,61].

As in vertebrates, glycoptroteins are important cell surface molecules[8,93] that mediate some of these interactions. Treatment of embryonic grasshopper limbs with proteolytic enzymes results in retraction of pioneer growth cones, indicating that interactions with basal lamina components are critical for axon outgrowth[52]. The importance of specific molecules for neuron guidance warrants further study.

In the arthropods, some neuropils, such as the insect VAC and crayfish HN and LNs, Eire bounded partially or wholly by specific tracts[174,211,212,234] and/or t thickened extracellular matrix[212]. As yet, no studies of the development of these neuropils has been undertaken to ascertain the role these tracts or matrix plays in their formation. Studies on the growth of moth olfactory lobes (as described in the next section) may illuminate this subject.

Regenerating adult neurons also appear to use cell-surface markers to determine compartment boundaries, although whether or not embryonic anti regenerating axons use the same markers is unknown. Epidermal sensory neurons of the locust head and cricket legs and cerci can be transplanted to foreign body regions where they will regenerate their central projections[7,158,159]. Ectopic axons will grow into the appropriate neuropils

within their foreign segmental ganglia and retain their spatial organization. However, such axons usually do not connect with their normal target interneurons in those neuropils[7].

6.2. Sensory input

Neuronal activity is crucial to module development in both vertebrates and invertebrates. In the monkey cortex, ocular dominance columns belonging to an eye that is removed or sutured closed at birth are narrower than those of the surviving eye[101,179]. Ocular dominance columns fail to develop in layer IV if one eye is enucleated during a critical period before birth[181,182]. This latter result occurs before visual input would normally commence. The competition between the growing axons may depend upon spontaneous electrical activity in the retina[220]. Similarly, in the rat barrel cortex, vibrissae removal and follicle cauterization results in the developmental loss of the corresponding row of cortical barrels[235]. Cricket sensory axons display comparable plasticity in the growth of their central projections[156,157]. Afferents from cricket cerci that branch in specific neuropils on both sides of the last abdominal ganglion increase their contralateral arborizations when that side is deprived of its normal ipsilateral input[156,157,162]. De privation also decreases the responsiveness of the sensory interneurons141. The area of increased afferent arborization occurs only within the normal neuronal target region. Thus, new dendritic growth is activity-dependent and spatially restricted by the same positional information that specifies their original locations[157,162].

The mechanisms underlying such changes are not always known, but research into some systems has yielded useful information. Afferent input affects the emergence of glial compartment boundaries in the moth olfactory system[229] and in the barrel fields of rodent somatosensory cortex[54,107]. In moths, the growth of sensory axons into the olfactory lobe initiates a sequence of changes in the neuropil-associated glia, so that they come to define glomerular borders[229]. Deafferented moths produce no glomeruli and display afferent synapses in abnormal positions within the neuropil. Moths with normally afferented lobes but with experimentally depleted glial populations show similar results. However, the few remaining glia behave normally and migrate into areas where glia would have demarcated glomerular boundaries. Glia-deficient lobes also display abnormal afferent dendritic branching patterns. Tolbert and Oland[229] suggest that glia play a direct role in normal morphogenesis of glomerular neurons. How afferents activate glia and how glia in turn exert their effects is still under investigation[229]. One possibility is that glia actually induce considerable neuritic branching in olfactory lobe neurons. Mudge[150] has demonstrated that Schwann cells induce a mature type of branching pattern in cultured dorsal root ganglion cells. Other researchers have found that dense neuritic branching of cultured neurons is induced by culturing them with homotopic but not heterotopic glial cells[46,57]. It would be most interesting to know if glia play a general role in the induction of afferent branching in invertebrate sensory neuropils.

Lest generalizations be too tempting, Tolbert's and Oland's[229] results do not indicate that *all* compartments depend on the presence of glial cells. The large MGC develops properly even in the face of reduced glial cell number. This module has no distinctive glial boundary and its development must be governed by different processes.

7. PERSPECTIVES

Building on Mountcastle's[148] definition of a module as the elemental unit of brain tissue, one can list the following characteristics.

(1) Modules are local networks of cells containing one or more electrically compact circuits[73] active in a particular behavioral function.

(2) Modules can occur in any region of a complex nervous system.

(3) Modules range in diameter from about 150-1000 μm.

(4) Repetitive arrays of modules in a given neural region contain homologous sets of cells.

(5) Modules can retain topographical order of connections, either within individual modules or across an array of many modules.

(6) Modules are anatomically differentiable from the surrounding tissue.

(7) Modules can have identifiable substructure, such as layers or glomeruli.

These characteristics can also be used in a predictive fashion, as an aid to interpreting the roles of newly recognized neural tissue regions.

Small tissue compartments, such as the macroglomerular complex (MGC) of male moths[27,28,49,117] (also called the macroglomerulus), will be somewhat problematic, as they have characteristics of both modules and glomeruli. Because the MGC in some species contains several distinct lobes or glomeruli[49,117], because topographic ordering of afferents is generally maintained[117] and because activation occurs only in response to female pheromones[49], the MGC is more easily considered to be a small module than a synaptic glomerulus.

Evidence from the Chordata, Mollusca, Arthropoda and Annelida supports the view that nervous systems have been enlarged by the addition of more modules rather than by the expansion of these individual components. Several testable hypotheses emerge from this theory. Firstly, non-spiking interactions[206] should be limited in their spread to individual modules or to linkage of adjacent modules. Secondly, in terms of the usage-dependency of modules, any change in module size should be correlated with changes in the arborizations of their key constituent neurons. Thirdly, within a taxon, animals displaying less behavioral and metabolic complexity should have fewer modules. An examination of the reptilian general cortex, the first extant and recognizable phylogenetic occurrence of primordial neocortex[198], for columnar architecture should also yielt1 fresh insights into the evolution of the complicated overlapping columnar fields in the mammalian neocortex.

Discrete modules are identifiable in annelid brains and the nervous systems of large, free-living flatworms need to be examined with this idea in mind. Modules probably made their first appearances in cephalic ganglia as processing units for information arising from particular sensory modalities. The developmental constraints that regulate the growth of module-bearing nervous systems, in addition to their functional success in adults, undoubtedly accounts for the widespread occurrence of discrete neuropils within invertebrate nervous systems. These same constraints, operating in the brain of vertebrates and the larger invertebrates, have promoted the evolution of multiple compartment systems.

Clearly, the ability of a field of growing neurons to find their paths to and through particular modules based on cell-surface landmarks is an essential feature without which neural development cannot occur. The answer to the question of how modules first arose may lie in the comparative study of neural development in animals with few modules.

In addition to any developmental benefits, modules may serve to keep interactive neurons grouped together, yielding ecomony in length and number of interconnections[98]. Graybiel[83] suggests that neuronal compartments may also serve to localize modulatory influences. Systems in which one would expect the most dramatic results would be those showing differential function dependent upon the animal's activity state. Connective tissue or glial wrappings around such modules may be indicative of such functions.

Several caveats should also be emphasized. Module size obviously correlates with the branching patterns of certain important intrinsic neurons. However, we do not know that the electrotonic capabilities of these arborizations actually govern module size. A knowledge of module size also does not necessarily indicate the length constants of the intrinsic neuronal arborizations, although it may point towards reasonable hypotheses. A hazardous implication of this idea is that electrotonic length of neurons within modules in vertebrates and invertebrates is similar. Where this is true, any similarity can result from entirely different physiological

mechanisms. Furthermore, complex neuronal arborizations and the variety of functions performed both within and between modules would seriously limit any such generalization.

The physiological circuits within the numerous modules I have mentioned perform a wide array of tasks. Nonetheless, in qualitative terms they are the basic parallel processing units, much like microprocessors in modern computers, that are the foundations for complex animal behaviors.

8. SUMMARY

The modular construction of brain tissue is not solely a feature of vertebrate nervous tissue, but is characteristic of many invertebrate nervous systems as well. Modern vertebrate and invertebrate modules vary over several orders of magnitude in volume but vary less in diameter. Although the physiological and anatomical differences between the modules discussed herein are overpowering, their importance to nervous system functions are similar. Modules are the serial and parallel processing units that have allowed large-brained animals to evolve.

Many invertebrate modules are discrete, hemispherical lobes, visible on the :surface of the brain or nerve cord, whereas most mammalian modules are columnar or ellipsoidal tissue compartments that can only be visualized with specific anatomical methods. Lobes from the largest invertebrates can be more voluminous than any neocortical compartments, but these large lobes are usually not single modules. Large invertebrate lobes contain internal compartments that are single modules and of similar size to their vertebrate analogs. However, vertebrate cortical modules or columns, are far more numerous than the compartments in invertebrate brains and in several cases are known to be adjoined laterally into slabs of tissue that extend for several millimeters.

Physiological data support the idea that neural modules are not just anatomical entities, but are active local circuits. The specific activities within each type of module will depend upon its neuronal components, both intrinsic and extrinsic, its functional roles and phylogenetic history.

Many cellular and intercellular phenomena common to vertebrates and invertebrates underlie the development of modules. Neuronal and glial interactions and their interplay with the extracellular environment depend upon families of molecules with broad phyletic occurrences. The commonalities of growth mechanisms may to a large degree account for the widespread incidence of neuronal processing units.

The strategy of enlarging a nervous system through the replication of the basic units is thought to be advantageous for several reasons. This plan allows nervous systems to economize on the branch sizes and lengths needed for interconnections, to ensure that appropriate targets are reached during development and to modulate specific circuits within El larger network.

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