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Evolution and ontogeny of neural circuits

Sven O. E. Ebbesson
Department of Anatomy, Louisiana State University School of Medicine, Shreveport, La. 71130

Abstract: Recent studies on neural pathways in a broad spectrum of vertebrates suggest that, in addition to migration and an increase in the number of certain select neurons, a significant aspect of neural evolution is a "parcellation" (segregation–isolation) process that involves the loss of selected connections by the new aggregates. A similar process occurs during ontogenetic development. These findings suggest that in many neuronal systems axons do not invade unknown territories during evolutionary or ontogenetic development but follow in their ancestors' paths to their ancestral targets; if the connection is later lost, it reflects the specialization of the circuitry.

The pattern of interspecific variability suggests (1) that overlap of circuits is a more common feature in primitive (generalized) than in specialized brain organizations and (2) that most projections, such as the retinal, thalamotelencephalic, corticotectal, and tectal efferent ones, were bilateral in the primitive condition. Specialization of these systems in some vertebrate groups has involved the selective loss of connections, resulting in greater isolation of functions. The parcellation process may also play an important role in cell diversification.

The parcellation process as described here is thought to be one of several underlying mechanisms of evolutionary and ontogenetic differentiation.

Keywords: commissures; development; evolution; lateralization; learning; neocortex; neural circuits; olfactory system; ontogeny; plasticity; somatosensory pathways; superior colliculus; thalamus; visual pathways

Introduction

An understanding of the evolutionary history of brain structures and functions should be no less important to the neurobiologist than the evolutionary history of galaxies is to the astronomer. Yet today there is no comparison in the amount of effort in the two fields. The trend is away from studies on evolution of vertebrate brain organization; and whereas earlier brain scientists, such as Sigmund Freud and Paul Broca, were fascinated by comparative neurology, hardly a neurobiologist today, 100 years after Darwin, appears to think much about the evolution of the system or process being studied. This is particularly disconcerting at a time when the comparative data are starting to make sense, especially as they relate to ontogenetic development.

The fundamental problem of obtaining insights into brain evolution is that there are no fossil records of microscopic brain structures. Hence, we have to extract information from the study of extant vertebrates. This approach is now beginning to yield conceptual insights into how neural systems evolve. One of these insights is the recently described *parcellation process,* which involves increased neuronal migration, increase in the number of certain select neurons, and the segregation–isolation of circuits by selective loss of neurons or axonal branches. This idea and its basis are described here as an example of what is happening in the field, and because the idea appears to elucidate some aspects of the following questions confronting contemporary neurobiologists:

1. What is homologous to what in various species?
2. How are new structures added on in the evolution of more complex brains?
3. Why do axons grow in some directions and not in others during their development?
4. Why do some cells or collateral axons die during ontogenetic development?
5. What is the significance of so-called inappropriate connections during ontogenesis?
6. Why is there overlap of systems in some species and not in others?
7. Why are some pathways crossed in one species and uncrossed in another?
8. Why are there commissural connections between some areas of cortex and not betweeen others?
9. Why does a given cortical area in one species have commissural connections while the same cortical area in another species lacks such connections?

The time has not yet arrived when we can answer these questions completely, but hints of answers are emerging from recent data on interspecific variability of connections.

The Nauta revolution

During the last few years it has become clear to some of us that an understanding of the evolution of circuits is an essential requirement for understanding many aspects of brain structure and function and, as we shall see, normal

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and abnormal ontogenetic development. Meaningful data about distant neural connections originated with Nauta, whose contributions have revolutionized the study of brain organization. His method (Nauta 1950; 1975) led not only to a vast number of new insights into brain structure and function but also the development of a whole array of new neuronanatomical techniques for studying connectivity of the brain (Cowan et al. 1972; Fink & Heimer 1967; Kuypers et al. 1977; LaVail & LaVail 1972). Comparative studies on nonmammalian vertebrates have benefited especially from these new research tools, and many old concepts of brain organization in such vertebrates have been replaced in the last 15 years (Finger 1974; Hall & Ebner 1970; Ito et al. 1980a; Karten et al. 1973; Northcutt 1982).

A major consequence of the Nauta approach was the discovery of well-defined interspecific differences in connections. One of the first was Mehler's (1969) finding that direct spino-olivary projections are lacking in chimpanzee and man. His findings stimulated me to engage in a long-range study of interspecific variability of connections in vertebrate brains.

There have been two main approaches in comparative neurology: to study many neural systems in one species, as Herrick (1948) did with the tiger salamander, or to do what I have been doing, namely, approach the enormous diversity of brain organization in vertebrates by examining a given neural system in as many different vertebrates as possible. I began this study with the hope that the range of variation and the pattern of interspecific variability would provide clues about the underlying evolutionary strategies.

The rationale for my approach was based on several considerations. It was clear, for example, that one cannot get an accurate picture of all systems from the study of one species, since neural systems have obviously evolved at different rates in a given lineage. The choice of species is also not obvious, since the paleontological evidence of lineages is not always clear and is difficult to relate to the evolution of specific neural structures and behaviors. It was abundantly clear that one must look at all the arrangements of a given system before one could identify and describe (1) the progressive and regressive evolution of the system, (2) the evolutionary history of a species, (3) the known adaptations, and (4) the functions related to the system.

In order to get a general picture of brain evolution, I have concentrated my studies on six basic systems in a broad spectrum of vertebrates ranging from cyclostomes to primates. The systems studied are olfactory tract projections, retinal projections, ascending spinal projections, tectal projections, thalamic projections, and telencephalic projections. Some of the studies are not yet completed, but together with the information published from other laboratories, they form a promising, cohesive picture of some evolutionary mechanisms (Ebbesson 1972b; 1980b).

The parcellation theory

The principal preliminary conclusion from this work is that basic brain organization is, in some respects, much more similar in the various groups of animals than previously believed. The data suggest that diffuse, relatively undifferentiated systems existed at the beginning of vertebrate evolution and that during the evolution of complex behaviors and the analytical capacities related to these behaviors a range of patterns of neural systems evolved that subserve these functions. One principle underlying the growth, differentiation, and diversification of neural systems appears to be a process of "parcellation" that involves the selective loss of connections in daughter systems and cellular aggregates as a result of selective pressures. The result is an isolation of functions as new circuits and neuronal aggregates are formed with connections and character different from the ancestral organization (Fig. 1–2). These concepts have recently been assembled in what I have called the parcellation theory (Ebbesson 1980b; 1981). Since those publications, it has become clear that what was described as a hard rule probably should have been expressed as a trend and that other variables should also be included. Hence the present paper.

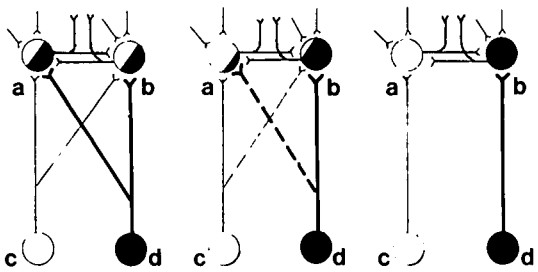

Figure 1. The parcellation process is thought to involve the loss of one or more inputs to a cell, or an aggregate of cells, as new subcircuits evolve. This diagram shows how two identical neurons (a and b) in a hypothetical aggregate become less and less influenced by a given input, with the eventual outcome that cell (a) loses input (d) and cell (b) input (c). Further parcellation of such clusters can occur by some cells' losing other inputs or outputs. Collaterals or the main axon may degenerate in response to various selective pressures. The evolutionary and ontogenetic development of monocular laminae in the lateral geniculate nucleus and ocular dominance columns is apparently achieved by such a parcellation process.

The findings in support of the theory can be listed as follows: (1) The basic systems appear to be present in all vertebrates, and these basic systems are often more extensive in primitive species than in advanced species. Neural systems apparently do not appear *de novo*, nor do they usually invade others to form new aggregates. (2)

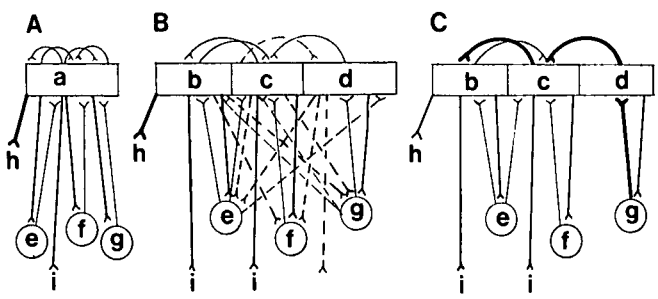

Figure 2. Schematic diagrams of a hypothetical cell aggregate (a) undergoing parcellation with the eventual production of three cell groups (b–d), each aggregate containing neurons with more restricted connections than in the hypothetical ancestral cell group (a). The principal functional output (h) would in this case differ in "quality" after the parcellation. Interrupted lines represent lost connections.

The pattern of interspecific variability of a given system points to a primitive condition of overlap of circuits and an increased parcellation with the progressive development of a system. (3) Some neural systems in birds and mammals show the same organization transiently during ontogeny that primitive vertebrates show as adults. (4) Experimentally induced sprouting can result in the selective sprouting of connections with cell aggregates which appear to have such connections in primitive vertebrates. (5) Sensory deprivation can apparently produce features of primitive organization. These five categories of evidence in support of the parcellation theory will be elaborated here.

Do neural systems invade one another during evolution?

One concept that has been with us for a long time is that neural systems can invade one another in evolution to make new circuits. Diamond and Hall (1969), for example, mentioned the then prevailing view that retinal axons invade thalamic targets in evolution to generate a retino-geniculo-cortical pathway. The key findings against this invasion hypothesis came from three related discoveries: (1) the discovery of a direct retino-geniculo-telencephalic pathway and other visual pathways in anamniotes (Ebbesson 1980a; Ebbesson & Schroeder 1971; Graeber et al. 1973; Ito et al. 1980); (2) the related discovery that the telencephalon of anamniotes is not entirely olfactory, but that this modality has a very limited territory (Ebbesson 1972a; Ebbesson & Heimer 1970; Scalia & Ebbesson 1970); and (3) the identification of a neothalamus in poikilothermic vertebrates by the finding, in a variety of species, of direct spinothalamic projections (Ebbesson 1967; 1969; 1976a; 1978; Ebbesson & Goodman 1981; Ebbesson & Hodde 1981; Ebbesson, Jane & Schroeder 1972; Fig. 3) that had not been thought to exist in more primitive forms, but had been thought to invade the diencephalon in more advanced forms (Goldby & Robinson 1962). The resultant evidence for the presence of *neocortical equivalents* in a variety of structural arrangements in the telencephalon of anamniotes was also supported by discoveries of descending projections to thalamus, red nucleus, mesencephalic tectum, reticular formation, and spinal cord, similar to mammalian neocortical projections (Ebbesson 1972a; 1980b; Ebbesson & Schroeder 1971; Kokoros & Northcutt 1977).

If progressive evolution of the nervous system entails the invasion of axonal branches of one system into another (presumably unrelated) system, one would expect to see evidence of invasion in the most highly differentiated systems. We have found only one apparent example of this (the pyramidal system); the bulk of the literature suggests that the opposite occurs, namely, that some inputs and/or outputs are lost in cases of greater development and differentiation. It is unfortunate that at this time we do not have enough systematic data on the pyramidal system to present it as a solid example of "invasion," which after all is not incompatible with the concept of parcellation. Invasion may indeed occur, although it does not appear to happen on the sensory side of brain organization.

There is also considerable evidence for the existence of

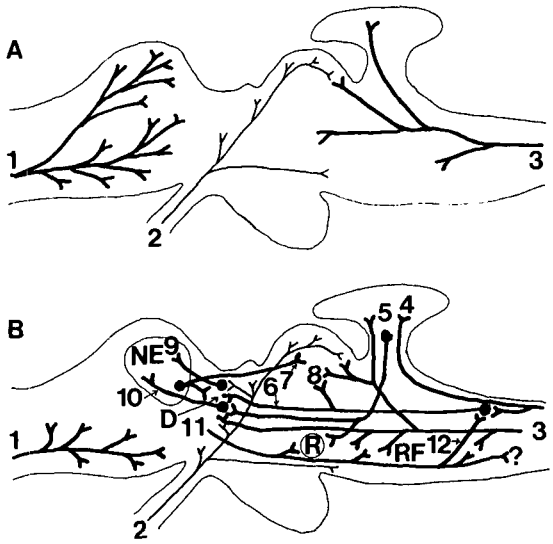

Figure 3. Schematic representation of some assumed connections in cold-blooded vertebrates prior to Nauta studies (A) and some mammalianlike connections in poikilotherms discovered in my laboratory (B) that led to the view that neocortical equivalents (NE) exist in primitive vertebrates and that most neural circuits evolve by a "parcellation process" as opposed to neural systems invading one another to form more complex brains. The reduced olfactory tract projections (1) were first seen in sharks and teleosts (Ebbesson & Heimer 1970; Scalia & Ebbesson 1970). More extensive retinal projections (2) were then found in teleosts and sharks (Ebbesson 1968; 1970b). Direct spinothalamic projections (3) were first seen in a lizard (Ebbesson 1967). The discovery of NE was based on the finding that visual (9) and somatosensory (10) thalamotelencephalic pathways projected to it (Cohen et al. 1973; Ebbesson 1980a; Ebbesson & Hodde 1981; Ebbesson & Schroeder 1971; Smeets 1982) and that NE projects to the thalamus and optic tectum (7) (Ebbesson & Schroeder 1971). Spinocerebellar fibers (4) from the dorsal funiculus were first seen in a lizard (Ebbesson 1967). Cerebellar projections (5) to the red nucleus (R) and dorsal thalamus (D) were discovered in the shark (Ebbesson & Campbell 1973). The medial lemniscus (6) projections to nucleus intercollicularis (8) and dorsal thalamus (D) were seen in a lizard (Ebbesson 1978). Telencephalic projections (11) to R, the reticular formation (RF), the dorsal column nuclei (12), and spinal cord were discovered in a shark (Ebbesson & Schroeder 1971).

more extensive connections in primitive circuits than in more advanced ones (Fig. 4). In some adult teleosts, for example, the olfactory bulb projects to the contralateral bulb (Finger 1974; Scalia & Ebbesson 1971) and directly to the hypothalamus (Ebbesson et al. 1981; Finger 1974). Such connections are not known in higher vertebrates. Interhemispheric connections between the primary telencephalic visual areas appear to be more extensive in the opossum than in the rhesus monkey (Ebner 1969). Direct telencephalocerebellar connections are known in sharks (personal observation), the tiger salamander (Kokoros & Northcutt 1977; personal observation) and in the neonate rabbit (Distel & Hollander 1980), but not in adult higher vertebrates. The following projections have been seen in some adult lower vertebrates but seldom in adult mammals: multiple retinopetal systems (Ebbesson & Meyer 1981), tectohypothalamic systems (Ebbesson 1970b, 1981; Fiebig et al. 1982), an ipsilateral posterior accessary optic root (Fritzsch 1980; Toth et al. 1980), direct retino-oculomotor connections (Fritzsch 1980), di-

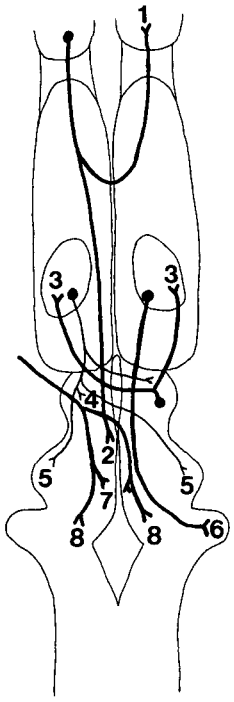

Figure 4. Examples of projection systems in some cold-blooded vertebrates that, with few exceptions, have not been seen in adult mammals: (1) commissural olfactory bulb projections (Scalia & Ebbesson 1970); (2) direct olfactory bulb projections to hypothalamus (Finger 1974); (3) bilateral visual thalamotelencephalic projections (Ebbesson & Schroeder 1971); (4) bilateral telencephalothalamic projections (Ebbesson & Schroeder 1971); (5) bilateral telencephalotectal projections (Ebbesson & Schroeder 1971); (6) direct telencephalocerebellar projections (Kokoros & Northcutt 1977); (7) retino-oculomotor projections (Fritzsch 1980); (8) retinorhombencephalic projections (Toth et al. 1980).

rect cerebellotectal connections (Scheich & Ebbesson 1983; Smeets 1982), bilateral thalamotelencephalic (Ebbesson & Schroeder 1971; Schroeder & Ebbesson 1974) and bilateral telencephalotectal projections (Ebbesson & Schroeder 1971; Kokoros & Northcutt 1977; Smeets 1982).

The pattern of interspecific variability

A spectrum of connectional arrangements was found in various vertebrates where either one system overlapped with another in the primitive condition or there was no, or only limited, overlap of systems in the more highly developed species. The variety of connections encountered in the visual system can serve as an example of the highly variable patterns seen in neural systems (Fig. 5).

In the presumed primitive model (Fig. 5A, found in some sharks, amphibians, and reptiles) retinal and tectal afferents to the thalamus overlap diffusely and extensively (Ebbesson et al. 1972). The thalamotelencephalic projection in this case is single, whereas in highly differentiated visual systems (as in some birds and mammals; Diamond & Hall 1969, Fig. 5C; Karten et al. 1973), two completely separate projection systems are found, reflecting the parcellation of retinothalamic and tectothalamic systems. Between these two extremes, a variety of intermediate arrangements have evolved. This

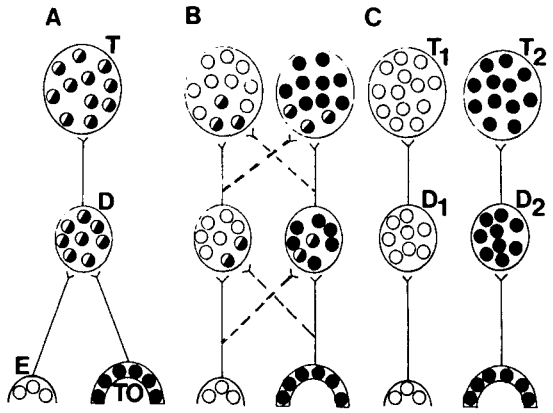

Figure 5. Schematic diagram of the parcellation of a portion of the visual system as envisioned by the parcellation theory. In the ancestral condition (A), inputs to the thalamus (D) from the eye (E) and the optic tectum (TO) overlap diffusely, whereas in the completely parcellated condition (C), the retina and optic tectum project to different thalamic nuclei (D_1, D_2), which in turn project to different telencephalic aggregates (T_1, T_2). Interrupted lines in (B) indicate inconstant connections encountered in various vertebrates and during ontogeny in some. These connections are thought to reflect the presumed ancestral connections seen in (A).

variability coincides with the theoretical predictions of variability, if one assumes that neural systems evolve by a parcellation process (i.e., the selective loss of connections in the daughter circuits, for the purpose of isolating given functions). Examples of this are the projection of the dorsal nucleus of the lateral geniculate body to peristriate cortex in the cat and the projection of the lateral posterior nucleus to the striate cortex in the opossum, hamster, mouse, and monkey.

The evidence for ontogenetic parcellation of the two visual systems is scarce. Perry and Cowey (1982) have recently described a transient retinal projection to the nucleus lateralis posterior in the developing rat, and I have observed that there is a transient direct retinorotundal projection in newly hatched ducks (unpublished), while in the adult duck there is only a direct retinal projection to another thalamic nucleus (dorsolateralis anterior). Other examples are likely to appear as we look for them.

Somatosensory and motor systems

A spectrum of arrangements is also found in other systems; for example, the somatosensory and motor cortex in the opossum are completely overlapping, while in the rat only the areas concerned with the hind limbs are overlapping (Fig. 6; Donoghue et al. 1979). Since motor and somatosensory cortices are completely parcellated in primates, it is concluded that the two systems were completely overlapping in the primitive condition and that the isolation of the two areas in evolution was accomplished by the parcellation process.

The only studies on the ontogeny of somatosensory and motor systems I am aware of that reflect the parcellation process are the recent exciting studies by D'Amato and Hicks (1978) and Stanfield et al. (1982) that show that almost the entire rat neocortex projects to the spinal cord during the first postnatal week and that large areas lose

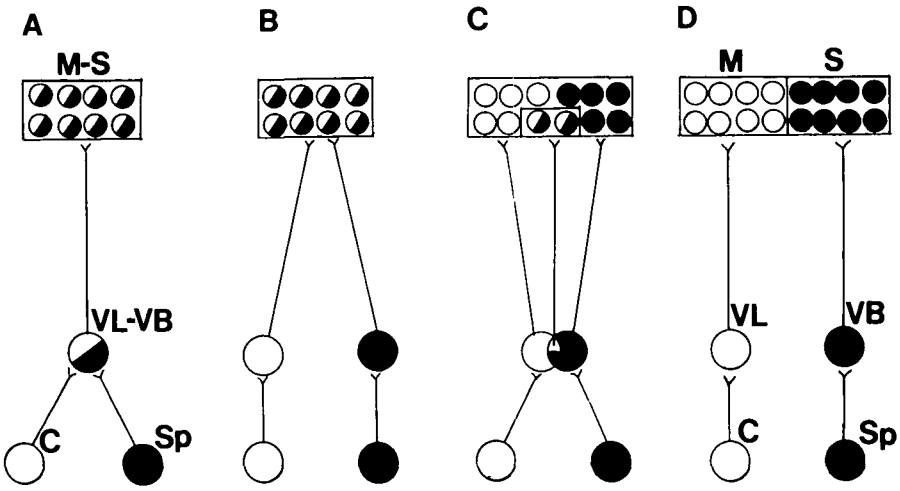

Figure 6. Schematic representation of cerebellar and spinal projections to the ventral tier of the thalamus (the ventrolateral nucleus, VL, and the ventrobasal complex, VB) and the thalamic projections to motor (M) and somatosensory (S) cortex in the rat (C), the opossum (B), and the monkey (D). The hypothetical ancestral condition seen in A, with complete overlap of these systems, has not been observed in extant forms. Note the range of overlap at thalamic and cortical levels in (B) and (C). After Donoghue et al. 1979; Ebbesson 1980b; reprinted with the permission of the publisher.

such projections during the following weeks. Data also exist that ontogenetic parcellation occurs in the ontogenesis of cortical barrels. In this case electrophysiological studies have shown that during certain developmental stages a given cortical barrel responds to the stimulation of several whiskers but that eventually the barrel responds only to one whisker (Van der Loos, personal communication). This presumably reflects the loss of some connections in the sytem during ontogenetic development. Such a decrease in receptive field size may in turn reflect an evolutionary reduction in receptive field size.

Retinopetal systems

Retinopetal systems have been best known in birds, where the isthmo-optic nucleus (ION) projects in the adult chick to the contralateral eye (Cowan et al. 1961). During ontogenetic development additional cells ventral to the ION also project to the eye, as do the same cell groups on the side ipsilateral to the eye. This bilateral projection to the eye is reduced at later stages of development, and the projection from the ipsilateral ION disappears completely (Cowan & Clarke 1976; Hayes & Webster 1981). Cowan and Clarke (1976) have referred to the transient connections as "aberrant" and the cells outside the isthmo-optic nucleus as "ectopic," preprogrammed to die during development. Clarke and Cowan (1976) view this developmental phenomenon as the "occurrence and correction of developmental errors in the location and connections of isthmo-optic neurons," and Cowan (1973) concludes that the observed neuronal death in this case serves "as a regulative mechanism in the control of cell number in the nervous system."

For a long time birds were thought to be unique in having an ION, but since exactly such bilateral retinopetal systems have now been identified in the adult lamprey (Vesselkin et al. 1980), the bichir (Meyer et al. 1982), and the caiman (Ferguson et al. 1978), it seems likely that the ontogenetic process Cowan and Clarke observed in developing birds reflects an evolutionary history involving parcellation (Fig. 7). This example of evolutionary processes may serve to challenge the current view that every pathway or event in the brain serves a particular functional need of the organism. It also raises the question about the possible existence, in the adult of any species, of ancestral connections that serve no particular function but have not been lost because they are not "in the way." No data about such connections are known, but it seems prudent not to discount the possibility of such "useless" phylogenetic remnants that may represent evolutionary markers as well as evolutionary potential.

The evolution of retinopetal systems is, however, more complex than described above, since a variable number of such systems have been seen in various vertebrates (Ebbesson & Meyer 1981; Münz & Claas 1981). The conclusion one can draw for these data is that, in general, more retinopetal systems exist in primitive vertebrates than in mammals; thus far only one from the pretectum has been described in rats (Itaya 1980). Whether this apparent reduction in retinopetal systems in evolution reflects "isolation" (i.e., parcellation) or regression is not known.

It is important to know in this context that afferents to the retina in the triggerfish are activated by visual, vestibular, vibratory, and tactile stimuli (Sandeman &

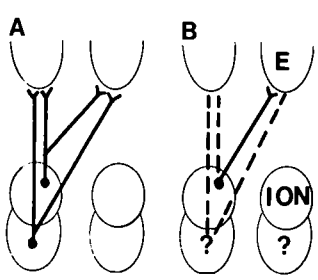

Figure 7. Projection of the isthmo-optic nucleus (ION) to the retina (E) are bilateral in the lamprey, bichir, and caiman (A) and during ontogenetic development in birds. Some of the connections in the bird disappear (interrupted lines) at later stages of development (B).

Rosenthal 1974) and that the terminations within the retina in some teleosts and elasmobranchs are on amacrine and bipolar cells (Witkovsky 1971), whereas in birds the connections are limited to amacrine cells. This suggests that in the ancestral condition retinopetal fibers also had a more extensive innervation of the retina.

Bilaterality of retinal projections and development of monocular parcellation

Bilaterality of retinal projections to all targets seems likely to be an ancestral condition since such projections are seen in many primitive species (Fig. 8). Bilaterality is a fairly constant feature of most vertebrate groups, including at least some cyclostomes (Ebbesson & Northcutt 1975; Vesselkin et al. 1980), teleosts (Ebbesson & Ito 1980), amphibians (Ebbesson 1970b; Lazar 1978; Riss et al. 1963; Toth et al. 1980), reptiles (Butler 1974; Ebbesson 1970b; Ebbesson & Karten 1981), and most mammals (Campbell et al. 1967; Kaas et al. 1978). On the other end of the organizational spectrum, there is complete absence of input from the ipsilateral eye (as in birds and most teleosts). There is also complete segregation of inputs from the two eyes within the dorsal lateral geniculate of mammals, but not in other vertebrates with bilateral retinothalamic projections. This pattern of variability points to a presumed ancestral condition in which the retina projected bilaterally in a diffuse and overlapping manner to several targets, and the absence of ipsilateral connections to one or more of these presumably reflects the parcellation process.

This evolutionary process is only partly repeated during the ontogenesis of the system (Fig. 9). Rakic (1976; 1977) and So et al. (1977; 1978) were first to show that retinal afferents to the geniculate nuclei in the neonate

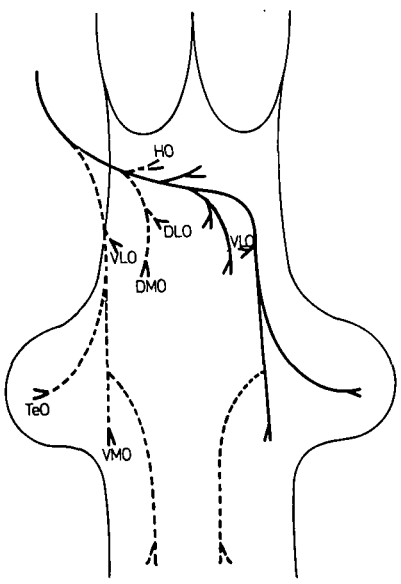

Figure 8. The ancestral retinal projections in vertebrates are thought to have been bilateral, and specialization of visual functions appears to have involved the loss of one or more connections (interrupted lines) in various vertebrate groups: HO, hypothalamic optic nucleus (suprachiasmatic nucleus of mammals); DLO, dorsolateral optic nucleus (dorsal nucleus of LGB of mammals); DMO, dorsomedial optic nucleus (olivary pretectal nucleus of mammals); VMO, ventromedial optic nucleus (medial terminal nucleus of mammals; see also Ebbesson 1972b).

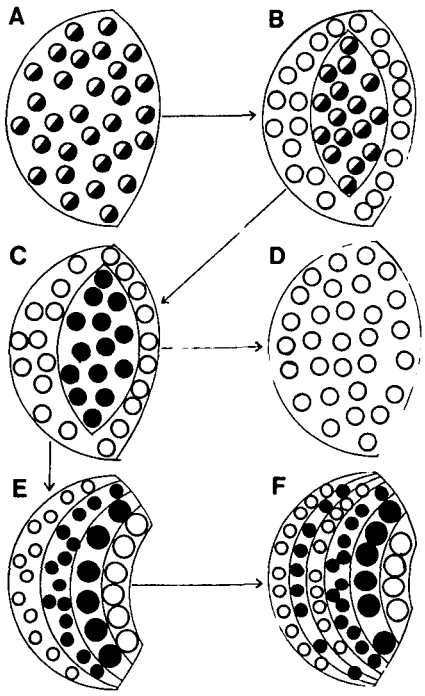

Figure 9. The ancestral retinal projections to the dorsal thalamus are thought to have been bilateral, with overlap from the two eyes on the same cells (A, half-filled circles). This condition is best seen in some amphibians. B. In reptiles many neurons appear to have a monocular input from the contralateral eye. C. In primitive mammals (e.g., hedgehogs) only monocular layers are found. D. Birds have only an input from the contralateral eye. E. Some primates have four monocular layers in the lateral geniculate. F. Adult rhesus monkeys have six monocular layers, but during ontogenetic stages both eyes appear to project to the same cells as in the presumed ancestral condition seen in (A).

monkey and the hamster occupy the entire geniculate nuclei bilaterally for an extended period of time between their first arrival and the eventual parcellation into monocular layers. This transient overlap of connections has also been observed in the opossum (Cavalcante & Rocha-Miranda 1978), the cat (Shatz & DiBernadino 1980; Williams & Chalupa 1982), the rat (Maxwell & Land 1981), the ferret (Linden et al. 1981), and the gray squirrel (Cusick & Kaas 1982). It should be pointed out that it has not been confirmed by electron microscopy that actual synapses are formed. In addition to the more extensive retinogeniculate projections in mammalian neonates, more extensive bilaterally overlapping, retinocollicular connections were also seen with apparent degeneration of fibers to certain loci during ontogenetic development (Cusick & Kaas 1982; Frost et al. 1979; Laemle & Labriola 1982; Rakic 1977). Bilateral overlap of retinotectal terminations are also seen in some adult cyclostomes and amphibians.

The thalamotelencephalic projections

The thalamotelencephalic projections show considerable variability in terms of laterality of distribution. In mammals and teleosts so far examined, thalamocortical projections are typically ipsilateral, whereas in other vertebrates various degrees of bilaterality are found (Fig. 10). If the ancestral projections were bilateral, as the parcella-

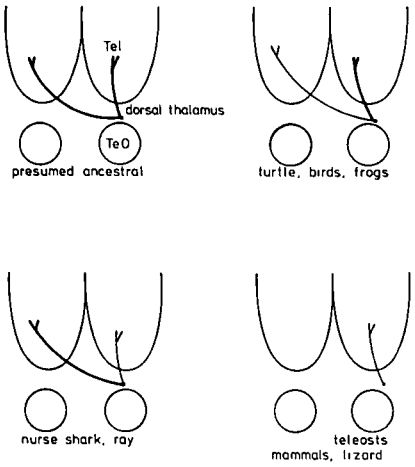

Figure 10. Visual thalamotelencephalic projections show a great deal of variability in terms of laterality. The presumed ancestral condition is thought to be bilateral.

tion theory would predict on the basis of the pattern of interspecific variability, some connections to one or the other hemisphere have been lost in the evolutionary process. To my knowledge there are as yet no data from ontogenetic studies that support this hypothesis.

Evolution of ocular dominance columns

The evolutionary and ontogenetic parcellation of monocular geniculate layers in mammals can be seen as the first step in the parcellation process of this system. In the primitive condition binocular convergence occurs in layer IV of the primary visual cortex, but further evolutionary development involves the parcellation of monocular (ocular dominance) columns in visual cortex. Such a columnar organization has apparently evolved several times independently due to some yet unknown selective pressure. Columns have been found, however, only in mammals with highly developed binocular vision, though not in all such species. They have been found in the cat (LeVay & Gilbert 1976), the prosimian galago (Glendenning et al. 1976), the cercopithecid monkeys (Hendrickson et al. 1978; Hubel & Wiesel 1968), the chimpanzee (Tigges & Tigges 1980), and the New World monkey *Ateles* (Florence & Casagrande 1978) but not in other New World monkeys (Hendrickson et al. 1978; Spatz 1979).

The late evolutionary development (parcellation) of ocular dominance columns is apparently comparable to the ontogenesis of such columns in the rhesus monkey (Hubel et al. 1977; Rakic 1976; 1977). During the late developmental stages ocular dominance columns in the visual cortex do not exist, but they appear in layer IV as the cells lose the input from one geniculate layer but not another. These ontogenetic data support the concept that ocular dominance columns evolved from an organization that lacked such columns. The significance of progressive parcellation (i.e., from the periphery toward "association cortical" areas) in evolution is not clear, but the result is probably a "different quality" of the image.

The commissural connections of neocortex

Neocortical commissural systems provide yet another example of a greater degree of parcellation being associated with the absence of some connections of the most developed regions (Ebner & Meyers 1965). Whereas commissural connections are found to all areas of neocortex in the primitive opossum, large areas lack such connections in primary visual, auditory, and somatosensory cortex in adult carnivores and primates (Fig. 11). These data suggest that all of the primitive mammalian cortex had extensive commissural connections, but with the progressive development (parcellation) of certain systems interhemispheric connections were lost in most parts of the specialized regions having the primary thalamic input. The ontogenetic data provided by Innocenti (1979) appear comparable to such an evolutionary sequence of development; he has shown that during certain stages of ontogenetic development of the cat the commissural connections are to the entire visual cortex and that most of those between areas 17 are lost during further development.

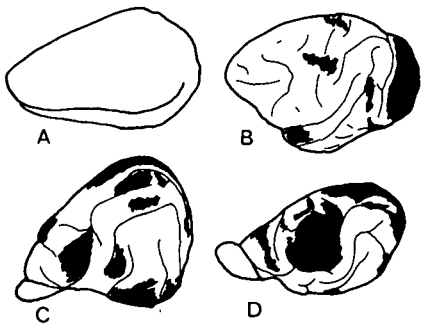

Figure 11. A–D. Schematic representation of the corticocortical connections in the opossum (A), the monkey (B), the cat (C), and the raccoon (D). Note the absence (black areas) of callosal projections to the most developed sensory areas in B, C, and D. The entire neocortex of the opossum displays commissural connections. Adapted from Ebner 1969; Ebbesson 1980b; reprinted with the permission of the publisher.

Telencephalotectal projections

Telencephalotectal projections vary greatly among vertebrates in terms of their unilateral and bilateral distribution. Bilateral projections were first noticed in the nurse shark (Ebbesson 1972a; Ebbesson & Schroeder

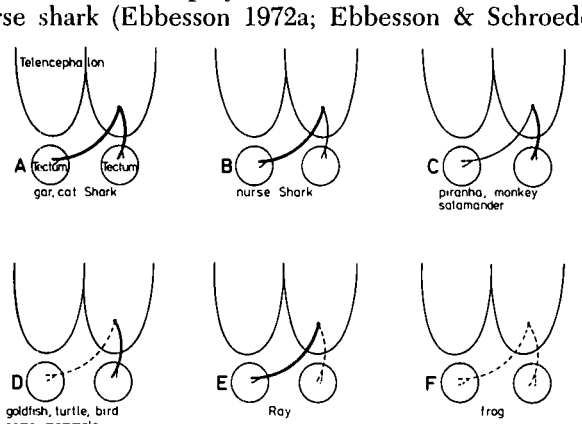

Figure 12. Telencephalotectal projections are highly variable. The ancestral condition is thought to be bilateral as in the gar (Northcutt 1982), the nurse shark (Ebbesson & Schroeder 1971), and the cat shark (Smeets 1982). In the frog the connections are completely lacking (Wilczynski & Northcutt 1977). The variability encountered here exemplifies the problems one encounters with the lack of strict correlation between the degree of parcellation and phylogenetic position.

1971; Ebbesson et al. 1975) and have since been seen to various degrees in other vertebrates (Kokoros & Northcutt 1977; Smeets 1982; Fig. 12). In anurans telencephalotectal connections are totally lacking (Wilczynski & Northcutt 1977), indicating a specialization of the anuran tectum. The pathway in urodeles and mammals is known to be related, at least partly, to directional selectivity of neurons (Grusser, personal communication; Sterling & Wickelgren 1970), but the absence or bilaterality of the system is poorly understood. There are to my knowledge no data available on the normal ontogenesis of the system, but it is known that extensive sprouting of cortical efferents to the contralateral tectum can be induced under certain circumstances (Lund 1978; Rhoades 1981).

Corticocerebellar projections

Direct cerebellar afferents from cortex are not known in any adult mammal but are present for a short time during the ontogenetic development of the rabbit (Distel & Hollander 1980). This transient connection is reminiscent of a telencephalocerebellar projection in adult salamanders (Kokoros & Northcutt 1977; personal observation) and sharks (personal observation). The corticocerebellar connection is therefore thought to be primitive and has for some unknown reason been lost in mammals (Fig. 13).

Tectoisthmal connections

The connections between the optic tectum and the nucleus isthmi, called the parabigeminal nucleus in mammals, are reciprocal. The parabigeminotectal connections are bilateral in the frog (Gruberg & Udin 1978; Wang et al. 1981), the tiger salamander (Ebbesson and Jane, personal observation), the opossum (Mendez-Otero et al. 1980), the rat (Watanabe & Kawana 1979) and the cat (Sherk 1979), but ipsilateral in the piranha (Fiebig et al. 1982), the teleost *Navodon modestus* (Ito et al. 1981; 1982), and the pigeon (Hunt & Kunzle 1976). The bilateral connections probably represent the ancestral projections (Fig. 14), indicating that some mammals have retained a primitive character while some lower vertebrates

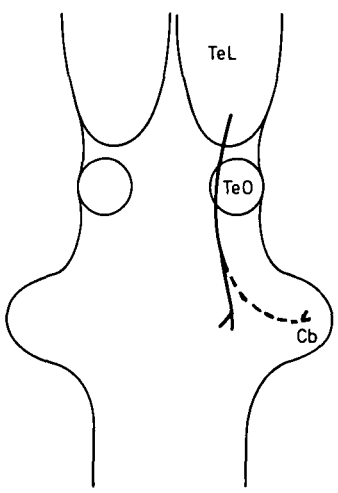

Figure 13. The direct corticocerebellar projection is seen in the adult shark and salamander. It is also present in the neonate rabbit but not in the adult (Distel & Hollander 1980).

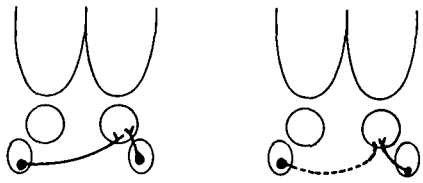

Figure 14. Connections between the nucleus isthmi and the optic tectum are bilateral in the frog, salamander, opossum, rat, and cat (left figure), but only ipsilateral in teleosts and birds. Although widely separated phylogenetically, frogs and opossums appear to share the presumed primitive bilateral projections whereas animals with apparently greater differentiation (parcellation) lack the contralateral projections.

with highly differentiated tecta have lost the contralateral parabigeminotectal projection.

Although nothing is known about the normal ontogeny of these connections, it has been shown that contralateral isthmogeniculate connections can be induced to sprout by the early removal of both eyes (Stevenson & Lund 1982). This may indicate that isthmogeniculate projections existed in some ancestral forms.

Lateralization

Lateralization of function is recognized as an isolation of a given function to one side of the brain. This phenomenon has intrigued neurobiologists for a long time, but precisely what the changes are in the neural substrates underlying such specialization eludes us. Although it is known that certain cortical regions, such as auditory association cortex, are larger in the dominant hemisphere, differences in circuitry between the two hemispheres have not been shown. The elegant studies by Nottebohm and his group on vocalization in birds, however, for the first time provide evidence that such specialization may involve a parcellation process, that is, the loss of certain connections. They have found that in the canary the left hemisphere controls vocalization and the connection from the telencephalic nucleus robustus archistriatalis (RA) is unilateral (ipsilateral) to the syringeal motor nucleus, which in turn innervates the syrinx unilaterally (Fig. 15B; Nottebohm et al. 1976). In the budgerigar, on the other hand, the projections from RA to the syringeal nucleus are bilateral and the innervation of the

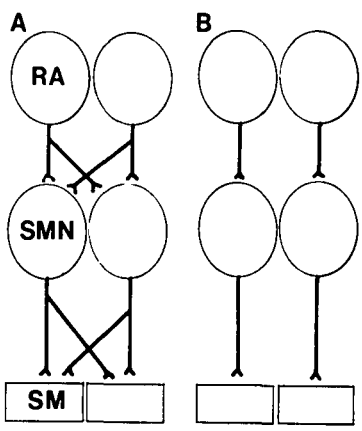

Figure 15. The connections related to vocalization (B) are ipsilateral in the canary (Nottebohm et al. 1976) but bilateral in the budgerigar (Paton et al. 1981). RA, telencephalic RA nucleus; SM, syringeal muscles; SMN, syringeal motor nucleus.

syrinx is also bilateral (Paton et al. 1981). We have recently found that the innervation of the syringeal muscles in the guinea fowl is also bilateral (Bock, Scheich & Ebbesson, unpublished). It is tempting to suggest that the primitive organization of the system is bilateral and that the evolution of species-specific vocalization in the canary has involved the parcellation process. The data therefore suggest the possibility that behavior-specific circuits exist and are at least partly formed by evolutionary changes involving the parcellation process. Since the evolutionary parcellation of this system is probably a relatively recent event, it would not be surprising if the parcellation process could be observed during the ontogeny of the canary, but such data are still lacking.

Ontogenetic parcellation

In addition to the evidence for the ontogenetic parcellation process mentioned above, it is worth noting that the meager data available suggest that most, if not all, systems go through phases of diffuse projections that later become more restricted, presumably by the degeneration of selected axonal branches or the loss of selected neurons. Wolff (1981 and personal communications) has recently demonstrated systematic degeneration of fibers and terminals during the ontogenesis of bird brains. Using a method for the selective silver impregnation of degeneration products, he and his coworkers have shown interspecific variability in the site and timing of appearance of degeneration, which may reflect the parcellation of species (perhaps behavior) specific circuits. I propose as a possibility that the degeneration products observed by Wolff and his coworkers represent the actual residues from ontogenetic parcellation and that the connections that are lost during ontogenesis represent ancestral connections.

Recent studies on the ontogenetic differentiation of the telencephalic auditory field L in the guinea fowl (Scheich et al. 1982) with the 2-deoxyglucose method also reveal developmental stages when large regions respond in a diffuse manner to a given stimulus. Later developmental stages reveal smaller sites with stronger responsiveness to the same stimulus, suggesting a reduction in the local axonal distribution. Other mechanisms such as increased selective inhibition may contribute to this apparent reduction of target area.

It is now also known that at the cellular level at least some neurons go through developmental stages involving extensive dendritic formation followed by retraction (Jhaveri & Morest 1982) while other neurons go through a developmental phase with a larger number of dendritic spines (presumably with synapses) followed by a distinct reduction of the spines, presumably reflecting ontogenetic parcellation. Rausch and Scheich (1982) have shown such a model in the telencephalic HVc nucleus of the mynah bird during the period of development of vocalization, and Garey and Saini (1981) have shown a similar process in lateral geniculate neurons in the monkey during the first month postpartum that may correlate with the development of visual acuity. Whether these processes reflect evolution of the systems is not clear, but it is possible that in a previous ancestral phase the homologous neurons had more spines in the adult stage, before the circuits changed in relation to specific functional requirements. On the other hand, the transient phase of increased spines may result from an initial low excitability of the neuron or disproportional inhibitory inputs to the neuron, as Wolff (1981) has suggested. This suggestion is not in opposition to ontogenetic parcellation as a reflection of evolution.

Cytodiversification

The parcellation theory explains, to a certain extent, the possible evolutionary course of cytodiversification, in that specialization of neuronal cell types in certain cases appears to be related to a restriction of inputs to a given neuron (Ebbesson 1980b; Ebbesson et al. 1975; Fig. 16). This explanation is in agreement with the conclusions of Ramon-Moliner (1962) and Ramon-Moliner and Nauta (1966), who concluded that specialization of dendritic trees reflects "a high degree of homogeneity of input" whereas generalized or isodendritic types of neurons prevail in brain regions characterized by afferent connections of heterogeneous origin. An example of the latter is the isodendritic neurons in the reticular formation, which are known to have diverse inputs.

The optic tectum of vertebrates provides a good model for studying cytodiversification, because cytoarchitecture and dendritic structure are enormously variable (Ebbesson et al. 1975). A comparison of interspecific variability in tectal organization of adult vertebrates reveals that each vertebrate group has its own range of predictable variation. Although the tecta of all vertebrates have

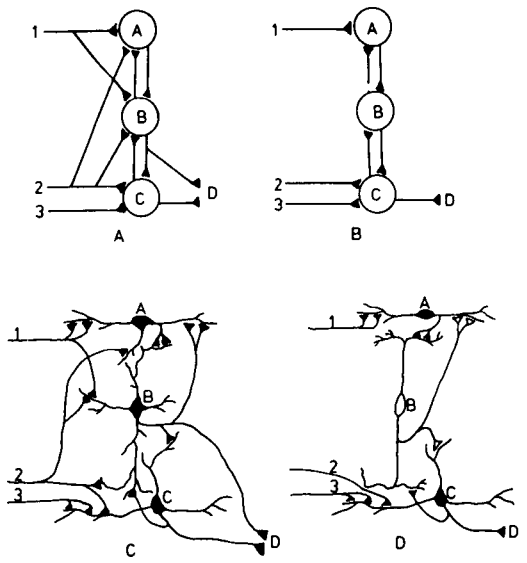

Figure 16. A–D. Vertical parcellation (lamination) in the cortex and the optic tectum is associated with segregation of inputs and specialization of cell types. The increase in differentiation and parcellation is always associated with more restriction of inputs, indicating a loss of inputs to some cells (Fig. 1). Such parcellation can hypothetically take place in the manner indicated here where the end result (B and D) is the production of an internuncial neuron (neuron B) and one neuron (neuron A) losing one input. Note that the selective loss of an input to the "lateral" dendrites of neuron B would hypothetically result in the loss of those dendrites with the result that a new neuronal type would have evolved. The evolution of complex circuitry in a laminar structure would result in greater morphological diversity of the neurons, which is in fact what one observes (Fig. 17).

basically the same afferent and efferent connections (Ebbesson 1970b; 1980b), intratectal organization is extremely variable. There are species in each class with poorly developed tecta and other species with more "differentiated" tectal organization. Indeed a whole spectrum of arrangement is usually found within a class. Higher differentiation of the optic tectum is associated with (1) better separation layering of inputs, (2) greater diversity of cell types, and (3) regional specialization of the tectum (Butler & Ebbesson 1975; Ebbesson & Goodman 1981; Ebbesson et al. 1975; Peterson 1980; Schroeder & Ebbesson 1975; Schroeder et al. 1980). This interspecific variability can be explained by the parcellation theory, which proposes that the evolution of such variable organizations is accomplished by mechanisms of vertical and horizontal parcellation, presumably resulting in new subcircuits (Figs. 16, 17). It is presumed that these subcircuits, although still an integral part of the system as a whole, achieve the functional isolation necessary for the processing of some parameter not possible without such isolation.

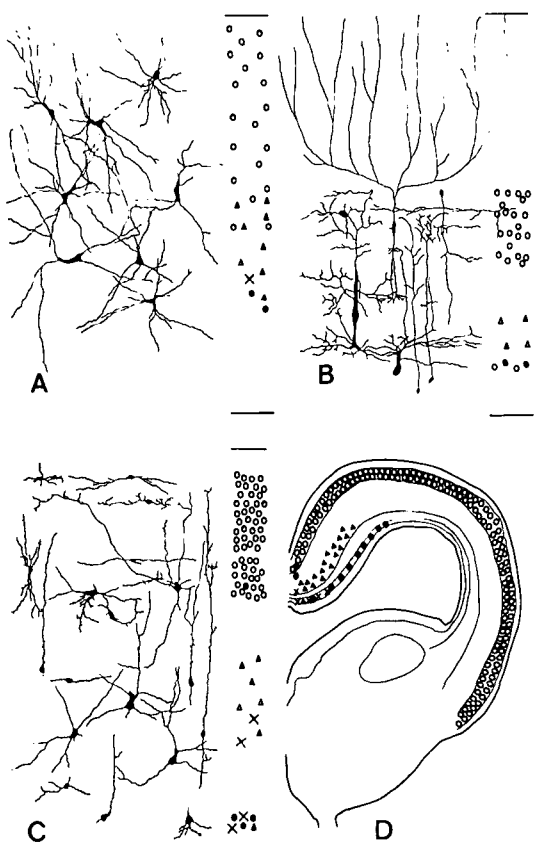

Figure 17. A–D. The optic tectum of the nurse shark (A), the squirrel fish (B), and the Tegu lizard (C and D) show considerable variability in cell types and stratification of inputs from the retina (open circles), opposite tectum (closed circles), ipsilateral telencephalon (open triangles), contralateral telencephalon (closed triangles), and spinal cord (X). The spinal input to the optic tectum in teleosts is not known. The drawing of some of the inputs to the lizard tectum indicates that direct nonretinal inputs are restricted to the medial third of the tectum. Since this is not the case in some snakes (Ebbesson 1969) and the caiman (Ebbesson & Goodman 1981), it is suggested that in some species certain tectal areas lose their direct nonretinal inputs concomitant with elaboration (parcellation) of the visual functions. This appears comparable to parcellation of cortical areas in mammals. From Ebbesson 1980b; reprinted with the permission of the publisher.

Evidence from sprouting experiments

The sprouting that results from experimentally induced damage is very selective in that sprouts do not make synapses with just any structure. One interpretation is that some axons make connections with cell aggregates with which they presumably had connections earlier in evolution. This interpretation is based on several findings, including the massive sprouting of retinal fibers to the lateral posterior nucleus following tectal lesions in the neonate hamster (Schneider 1973). This may reflect sprouting to a nucleus that once in evolution is postulated to have had a considerable retinal input (Ebbesson 1972; 1980b). The sprouting of fibers from one eye into all layers of the mammalian dorsal nucleus of the lateral geniculate body following unilateral eye enucleation also appears to mimic the presumed ancestral arrangement seen in adult specimens of poikilothermic species as well as the developing retinogeniculate projection of mammals.

The classic study of Liu and Chambers (1958) revealed that the dorsal root distribution to the spinal cord could be expanded from three to six segments by cutting the pyramidal tract. That these expansions are to segments innervated earlier in evolution is likely since such broad innervations are seen in adult amphibians (Joseph & Whitlock 1968). The sprouting of corticotectal fibers to the contralateral tectum in the rat (Lund 1978) perhaps reflects the organization in sharks (Ebbesson & Schroeder 1971) and amphibians (Kokoros & Northcutt 1977) where bilateral telencephalotectal fibers are found.

If "abnormally" sprouting fibers have an affinity for ancestral connectional sites, it could be possible to use this plasticity not only to learn about ancestral brain organization but to manipulate sprouting for specific needs in a predictable fashion.

The evidence from deprivation experiments

There are no clear-cut experiments to date showing how deprivation experiments may provide clues about primitive organization and function. However, since deprivation may, in essence, block the normal development of a system at a transitional stage, such a stage may reflect a more ancestral condition of the organization. It is clear from a number of experiments (Pettigrew 1974) that cortical units, following ocular deprivation, show either very little orientation and directional selectivity or somewhat more broadly tuned selective responses. From an evolutionary point of view that is, of course, what one would expect; that is, broadly tuned responses must have preceded finely tuned responses. The contention, then, is that the evolutionary and ontogenetic development of specifically responsive cells involves a rewiring, guided by the parcellation process, that is, by the loss of selective connections within or to the circuit.

Genetic control of parcellation

If the parcellation process is as universal as the available data suggest, one would predict that it is, like cell proliferation, partially controlled by genes. It should be possible to determine to what extent genetic coding or experience determines the parcellation processes in such specialization of circuits as is required for the visual thalamocortical connections.

An examination of the neural connections in certain mutants sometimes reveals distinct differences from the normal that can be considered related to parcellation. For example, congenitally anophthalmic mice show a greater projection from LP to area 17 than normal mice (Kaiserman-Abramof et al. 1980), similar to what one would expect in a more primitive condition. It is not known, however, to what extent this reflects gene expression, since it is possible that this condition is produced by visual deprivation.

The parcellation theory provides yet another view on brain development and may be of relevance in explaining such phenomena as human individual differences in cognitive functions or certain abnormalities of brain function. If the parcellation process, as defined here, is controlled by genes, one would expect to find abnormalities in which a given parcellation process is not complete, but such data are meager. It could be that the suggested larger number of callosal fibers in some schizophrenic patients may reflect such an abnormality (Randall 1980).

Conclusion

To what degree the conclusions drawn here from our work and that of others are correct remains to be seen. The parcellation theory has been reviewed here only as one example of ongoing work and thought on evolutionary aspects of brain development. It is a working hypothesis that is far from demonstrated and will require extensive testing and modification. As with most biological phenomena, there are exceptions to the rule, and they must be listed as they appear. The evidence for the theory comes from studies on distant connections of neurons and not from examination of nearby connections such as intratectal or intracortical relationships of neurons. We must therefore not exclude the possibility that the parcellation process, as defined here, competes with other, yet undefined, evolutionary processes. This includes the possibility of invasion in evolution, as appears likely in the case of the evolution of the pyramidal tract. It is also clear that the degree of parcellation is often correlated with (1) the degree of migration of neurons, (2) the relative size of regions, and (3) the number of given neurons.

The emerging picture of the evolutionary and ontogenetic development (specialization) of circuits seems to involve an inherent capacity for overproduction of neurons (Clarke 1981; Finlay & Slattery 1983) out of which new ("specialized") subcircuits are formed, on the one hand by an increase of connections from some sources and on the other hand by the selective loss of connections either by select neuronal death or select loss of "collateral" axonal branches. The end product must be the correct balance between excitatory, inhibitory, and temporal components to fulfill its function.

The remarkable interspecific diversity of brain organization appears to tell us of evolutionary strategies, but the study of such strategies is marred by the difficulty in selecting species for study and by the difficulty in interpretation. It is generally true that brains of species considered primitive by paleontologists have more primitive brain characters than the more specialized species, but given a specific neural system, that is not necessarily true, since some "primitive" species may have several specializations. As we review the evidence for parcellation, as presented here, we note that some features presumed to be "primitive" (like extensive bilateral retinal projections) have been retained in some advanced lineages. On the other hand, some "primitive" features have been lost in "primitive" species. The variability in the degree of parcellation of a given system appears more related to the "dominance," and hence the degree of development, of a given neural system. But even this correlation does not always explain the variability encountered, and we must therefore await information about what selective pressures account for any given rewiring.

It is possible to speculate, on the basis of available information, that increased isolation of a circuit results in a "finer tuning" of a given function as extraneous inputs are reduced. One possible result of parcellation, on the sensory end of circuits, is the addition of "discrimination filters" (selectivity filters) between the sensory input and the output of the CNS. If so, one would predict that a larger number of better-quality filters would result in more appropriate behavior in response to a given stimulus. On the motor end, the result of parcellation is more selective motor control, as one observes during ontogenetic development and in species-specific vocalization. One cannot help speculating that parcellation of selected neural circuits might be necessary in the development of such fine motor skills as are needed by a concert pianist, and that the learning of any skill might involve plasticity of circuits and rewiring via a mechanism of parcellation, that is, the increase of selectivity in the interaction of circuits. If learning involved the opposite, that is, less selectivity in circuits, one would expect to find more diffuse circuitry after such learning.

The major purpose of this article has been to stimulate those who usually do not think about the evolutionary past. Surely every brain structure today is a reflection of its ancestry, and every process is determined, at least partly, by ancestral processes. The guiding hand of evolution touches every aspect of neurobiology, from molecular biology to psychiatry. It should be unnecessary to say that evolutionary processes can be considered in whatever we do, and that the search for evolutionary strategies can be rewarding in its relevance to a number of current problems in neuroscience.

ACKNOWLEDGMENTS

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A return to the *Bauplan*

Pere Alberch

Museum of Comparative Zoology, Harvard University, Cambridge, Mass. 02138

The concept of the *Bauplan* or archetype, introduced by European morphologists during the nineteenth century, was the cornerstone of a unified theory of form. The German morphologists of the *Naturphilosophie* school and the French Transcendentalists were trying to construct a theory of morphology based on the basic premise of a fundamental structural plan present throughout the natural world. The goal of their research was to elucidate some general principles of organization and transformation underlying the diversity of forms observed in the natural world. The method was a holistic one based on the study of regularities in spatial arrangements and of patterns of interconnection among elements. In general, it was concluded that primitive vertebrates were segmented organisms composed of many repeated, and unspecialized, parts. An increase in complexity characterized the organization of life, and that complexity was achieved not by invention of new parts but by divergent specialization of the components initially present and increased dissociation among parts. Furthermore, there was a parallel between the increase in complexity that characterizes ontogenetic transformations and the change in structural plans with adults (see Russell 1916 and Gould 1977 for more comprehensive historical reviews of the ninteenth-century morphologists).

This morphological approach preceded the advent of the Darwinian theory of evolution; however, it was not difficult to translate its postulates from a metaphysical to an evolutionary level, a task in which Haeckel played a protagonist role. The basic unity in design was not the result of God's plan but the result of inheritance from a common ancestor. However, the approach was a static one and was slowly abandoned to be replaced by a more mechanistic and reductionist approach integrating Mendelian genetics and population biology.

Ebbesson's target article represents a return to the basic axioms of the archetype. He replaces the metaphysical belief in a basic archetype with the empirical assumption that "basic brain organization is, in some respects, much more similar in the various groups of animals than previously believed." Then, by comparative analysis of the neural circuits in the brain in vertebrates, he postulates the following general principles: (1) The brain is compartmentalized into well-defined regions. The topographic arrangement of these regions has been preserved throughout evolution. (2) Phylogenetic changes have generated increased local differentiation, specialization, and complexity; and (3) this has been achieved via selective loss of connections which have allowed the emergence of new circuits.

I find this article extremely valuable for its general implications concerning the problem of evolution of complex integrated systems. With the abandonment of the holistic theory of morphology espoused by the proponents of the archetype, evolutionary morphology has been unable to deal with problems concerning transformations of complex systems. It has basically restricted itself to the analysis of changes in metric traits, such as cusp height in teeth, or very simple meristic traits, such as number of spots on butterfly wings.

An evolutionary analysis of complex systems will entail the development of new analytical approaches and borrowing from some of the perspectives offered by the *Naturphilosophen* and Transcendentalists of the nineteenth century. It is for this reason that I am very sympathetic to Ebbesson's approach, since it shifts the emphasis from adaptive explanations to a thorough analysis of the internal organization of the systems as well as a characterization of the internal principles of transformation.

Ebbesson's conclusions about parcellation of the vertebrate brain are not simply an "atavistic" return to obsolete theories; they are consonant with current experimental work on the segmentation of the head. Meier and Tam (1982), Meier and Jacobson (1982), and Packard and Meier (1983) have recently shown that the vertebrate skull shows signs of segmentation since the very early stages of development. This view, emerging in developmental biology, that there is a mosaic of cell populations with fates determined since early development also has a connection with the work on compartmentalization and homoeotic mutants in insects. Perhaps Goethe was right after all in his theories about the segmentation of the vertebrate skull (see Jarvik 1980 for an updated, and minority, view).

Ebbesson's analysis suffers, however, from a problem similar to that of the classical morphologists. It is a static view. This is not a criticism of the evidence presented. The work outlined by Ebbesson is a necessary first step, which generates testable postulates and highlights the patterns to be explained. The next stage is to understand the mechanisms that control change in these neural circuits. Is the change gradual or discontinuous? What kind of variation is found within groups upon which selection can operate? How can "fine-tuning" integration be explained? The problem of how complex systems with many interacting component parts can evolve is a major challenge in evolutionary biology. I have argued elsewhere (Alberch 1982a) that such a system can in general be transformed only discontinuously and that we need to invoke second-order developmental interactions that are regulative in nature. Katz (1983) and Katz et al. (1981) have postulated some of these integrative mechanisms for the nervous system. To have a comprehensive theory of the evolution of complex systems, a comparative analysis of patterns such as the one presented here by Ebbesson must be coupled with developmental models about the controls of the genesis of the system (see discussion on this issue in Alberch 1982b; Goodwin 1982; Oster & Alberch 1982). These dynamic models of development can provide the mechanistic justification for the regularities or "principles" outlined by Ebbesson.

Parcellation: An explanation of the arrangement of apples and oranges on a severely pruned phylogenetic tree?

Mark R. Braford, Jr.

Department of Anatomy, Schools of Medicine and Dentistry, Georgetown University, Washington, D.C. 20007

Ebbesson suggests that the pattern of interspecific variation in neural circuits among living vertebrates is significantly, if not primarily, the result of the selective loss of connections which transforms primitive conditions of overlap into specialized conditions of segregation. Few neurobiologists would, I think, deny the theoretical possibility that the "parcellation process" might have occurred in one or more instances, although I can think of no unambiguous case to cite as an example at the present time. Likewise, few evolutionary neurobiologists would, I think, accept that parcellation is likely to be an important process in the evolution of neural circuitry. Its premise – the presence of overlap as a general primitive condition – is not well supported. As presented by Ebbesson, parcellation remains a process in search of a pattern to explain, for Ebbesson's interpretation of

the pattern of interspecific variation in neural circuitry among vertebrates is neither logical nor biological.

Statements concerning the evolution of brains must, as Ebbesson notes, consist largely of inferences based on observations of living forms. However, all living vertebrates are contemporaries; one is not ancestral to another; each has had its own evolutionary history up to the present day. From this and our current understanding of vertebrate phylogeny, several corollaries concerning rules of inference and constraints on comparisons follow. For example, the relationship of the brains of living amphibia to those of living mammals is at best a quasi-evolutionary one, for we cannot assume that the neural circuitry has remained unchanged in the amphibian lineage for the past 400 million years (Hodos 1970). In addition, we cannot expect to find a neural circuit in the brain of a teleost fish that has evolved (by whatever process) into a neural circuit in the brain of a mammal, because these two groups of vertebrates originated from separate ancestral populations at about the same time some 170 million years ago.

Statements about the evolutionary relationships between neural characters in various living vertebrates depend upon both the degree of *similarity* between the characters and the *distribution* of the characters among vertebrates.

In his analysis Ebbesson has been quick to hold up neural characters as similar (homologous) without critically examining or defining the similarities. Why are the retino-thalamo-telencephalic pathways of a shark and a teleost called the retino-*geniculo*-telencephalic pathway? Why are they homologized to the pathway of the same name in mammals? Are apples being compared with oranges? Is there evidence for fundamental similarities in these pathways? Alternatively, might such pathways have been independently evolved, perhaps several times? Similarly, why are all of the telencephalotectal connections considered to be of the same character? How similar are they? Do they originate from similar cell populations or is the similarity between the cell populations limited to the fact that they project to the tectum? With respect to the variation in telencephalotectal projections, Ebbesson states that the "variability encountered here exemplifies the problems one encounters with the lack of strict correlation between the degree of parcellation and phylogenetic position." If the living vertebrates are truly understood to represent multiple parallel radiations and are not regarded – even in some tacit manner – as forming a phylogenetic scale, then no strict correlation between "degree of parcellation" (or any other neural character) and phylogenetic position would be expected. The lack of such a correlation would present no "problem."

Ebbesson makes a number of statements about the distribution of neural characters among vertebrates, but a systematic phylogenetic presentation is not offered for the distribution of a single one of these characters. Various trends are mentioned that appear to require that various vertebrate groups play a game of musical chairs with their interrelationships. This impression may be more apparent than real, but it derives from Ebbesson's failure to define or use carefully such terms as *primitive*, *specialized*, *advanced*, and *higher*. Teleosts are primitive compared to mammals with respect to olfactory bulb projections but, like mammals and lizards, are advanced compared to elasmobranchs, frogs, turtles, and birds with respect to visual thalamotelencephalic projections. Such statements may well be true for characters, but it is often unclear whether Ebbesson is referring to a character or a vertebrate group. That the interhemispheric connections between primary telencephalic visual areas are more extensive in the opossum than in the rhesus monkey is offered as support for the parcellation process, with the implication that opossums are ancestral to monkeys. This is not so. Data on the laterality of innervation (unilateral or bilateral) of the syringeal muscles in *three* birds are presented. Ebbesson states that it is "tempting to suggest that the primitive organization of the system is bilateral and that the evolution of species-specific vocalization in the canary has involved the parcellation process." There are scientific methods for determining the polarity of a character (e.g., Eldredge & Cracraft 1980) that lead us not into temptation.

Ebbesson's analysis of the distribution of neural characters among vertebrates is hampered by his selective use of the available data from the literature. He has omitted many papers containing data that must be considered in any theory of vertebrate brain evolution. Likewise, several papers that bear directly on the assumptions underlying the parcellation theory, that offer alternate interpretations of existing data, or that analyze the variation of neural characters in a biological context have been ignored. These include Kaas (1980; 1982), Kuypers (1981), Luiten (1980a; 1980b), McCormick (1982), and Northcutt (1981).

The field of comparative neurobiology appears to be reaching the point at which it may have a data base sufficient for the formulation of meaningful hypotheses concerning the evolution of brain characters. Neural characters, like all other characters, must be sorted critically and manipulated in a biological context if the theories generated are to bear fruit.

A milestone in comparative neurology: A specific hypothesis claims rules for conservative connectivity

Theodore H. Bullock

Neurobiology Unit, Scripps Institution of Oceanography and Department of Neurosciences, University of California, San Diego, Calif. 92093

What is so rare as a phylogenetic hypothesis in neuroscience? The first thing to be said about Ebbesson's parcellation idea is that it is historic. No doubt the first of its kind in *BBS*, it may well be one of the first proposals for a broadly applicable phylogenetic principle of the evolution of the nervous system (beyond gross statements such as encephalization). It asserts more specifically than previous generalizations one of the ways in which the nervous system is conservative. Animal phylogeny in general, despite its plethora of particular guesses about the sequence of events in evolutionary trees or cladograms, is strikingly deficient in principles applicable to complex systems. Here is a hypothesis making assertions about restrictions and preferred mutations in the development of a system vastly more complex than the skeletal, muscular, or any other.

Second, Ebbesson's proposal has heuristic value: Many commentators will have quite disparate reactions to it, in agreement, in disagreement, or expressing cautions; most of these will dictate new research. More than most phylogenetic hypotheses, the parcellation hypothesis is subject to test after test – within the same species as well as among any number of taxa – putting it in a different category from classical proposals about neurobiotaxis, heterogony, size of brain and brain parts, derivatives of head segments, neural crest, cranial nerve nuclear columns and components of the autonomic system.

It is likewise noteworthy that Ebbesson's article appears in the peer commentary format, putting into print the considered reactions of a wide sample of experts, allowing us an unprecedented acceleration of the normally glacial process of responding to a new idea in phylogeny.

None of this bears on the question of how correct or general or in need of qualification Ebbesson's hypothesis might be. In the two years since its first announcement (Ebbesson 1980b) I have heard leading anatomists cheer, cite examples in agreement, pronounce "Yes, but . . .", express caution, and disagree: signs of a useful proposition. I leave it to more competent anatomists to comment specifically on these matters; I merely point out some healthy consequences of Ebbesson's proposal.

The proposal necessitates a careful differentiation, for each

instance of structures compared in two or more taxa, between the possibilities of common origin (homology) and of resemblance not due to common ancestry, whether based on convergence or on other mechanisms (homoplasy). It calls for a particularly close examination of a nucleus before claiming that it is in fact undivided and connected diffusely to several inputs, without order. It calls for distinguishing the well-known differences between smaller taxa, such as families of the same order, from those between taxa of older separation, such as classes; this means eschewing the single species as representative of a class. It necessitates a consideration of the possibility that sometimes, when a direct connection seems to be lost, nature has simply inserted a synapse and a relay into the pathway; the principal methods of hodology used by anatomists are rarely able to follow pathways across synapses.

Although Ebbesson's hypothesis will surely require further work and time to assess the significance of the claims that all connections were present in the primitive condition, that advanced taxa parcellate without invasion, and that this is a major tendency in vertebrate evolution, I find it refreshing and an important service to our science to have such a target to aim at. As the "harder" branches of biology have elegantly shown, the value of theory can be either in leading to a new and confirmable induction or stimulating new observations that put it to the test. One hardly expects such a pioneering claim to go for long without reformulation, but the process involved will generate a corpus of new findings.

Precision timing requirements suggest wider brain connections, not more restricted ones

William H. Calvin

Department of Neurological Surgery, University of Washington, Seattle Wash. 98195

I can think of one evolutionary reason that the brain might wish to expand connections, in a manner opposite to that suggested by Ebbesson's parcellation hypothesis but perhaps utilizing it.

Hominid evolution involved the acquisition of precision throwing skills for hunting; their neural machinery may have promoted the threefold encephalization. When one lets go of the rock or spear requires submillisecond timing precision; to double throwing distance requires hitting an eightfold narrower launch window (Calvin 1983a; 1983b; 1984). The law of large numbers permits this precision to be achieved with 64 times as many timing neurons as sufficed for the shorter throw. Triple the throwing distance, and 729 times the number of timing neurons are required, as the N required ascends as the sixth power of throwing distance (depth perception also requires extraordinary accuracy; there, the number of cells required ascends as the fourth power of distance).

There are at least two ways in which such numbers can be achieved. In evolutionary time, bigger brain variants would be promoted by natural selection for Ice Age hunting skills. But, at any stage of encephalization, a second method is always available, just as it is available to us today: borrow the timing neurons from other regions of the brain, temporarily creating a parallel circuit of many hundreds of elementary timing circuits. This presumably occurs as we "get set" to throw. A brain better at such temporary reorganization would be a better brain for throwing. This suggests a series of widespread connections between timing-specialized areas (such as the inferior frontal lobe or anterior temporal lobe) and other association cortex, connections that can be ignored in nonthrowing situations but utilized on throwing occasions when we "concentrate" on the target.

Neoteny (Gould 1977) is likely mechanism for the bigger brain variants on which natural selection operates; slowed developmental rates create an adult brain that retains formerly juvenile features such as a bigger brain/body size ratio. On Ebbesson's parcellation theory, a throwback to an earlier stage with wider connectivity seems a possible concomitant of the juvenilization of hominids, providing not only a bigger brain but one with an ancestrally wider connectivity to allow the temporarily paralleled timing circuits.

Parcellation theory: New wine in old wineskins

C. B. G. Campbell

Division of Neuropsychiatry, Walter Reed Army Institute of Research, Washington, D.C. 20307

Ebbesson has been a major contributor to the information revolution in comparative neurobiology that began in the 1960s. In both his original paper on this subject (Ebbesson 1980b) and the present one, he has attempted to present generalizations based to a large extent on his data. Unfortunately, I believe that all these new data have been interpreted using old, discredited concepts: new wine has been poured into old wineskins. The general statement presented is usually described as a "theory," occasionally as a "process," and only rarely as what it is: a "working hypothesis." Working hypotheses are not ordinarily published in journals; therefore, it is advantageous to call it a theory. The technical definition of a theory as found in the literature of the philosophy of science varies somewhat from author to author (see Bergmann 1958; Popper 1959). Norman Campbell (1952), for example, states that a theory must satisfy these conditions: (1) it must be such that the laws which it is devised to explain can be deduced from it; (2) it must explain those laws in the sense of introducing ideas which are more familiar or, in some other way, more acceptable than those of the laws; (3) it must predict new laws, and they must turn out to be true. Ebbesson's generalization has neither the form nor the scope of a theory. His putative theory of brain evolution resembles most others in that it does not really describe evolutionary mechanisms. The mechanisms of evolution are the same for all structures as parts of organisms. What he is really talking about is a postulated course of brain structural change.

Ebbesson indicates that his studies of six brain "systems" suggest that "diffuse, relatively undifferentiated systems existed at the beginning of vertebrate evolution and that during the evolution of complex behaviors and the analytical capacities related to these behaviors a range of patterns of neural systems evolved that subserve these functions." This idea is not original with him but is derived from Herrick (1926; 1948) and others. Interestingly, his own work, as well as that of many others, has shown this to be untrue, yet he claims to believe it still. What this work has made clear is that what may appear to be undifferentiated in Nissl-stained material is composed of organized pathways with discrete terminal zones when examined with the new experimental methods.

Ebbesson divides the evidence in support of his conjecture into five categories. The first is that the basic systems of the brain and spinal cord appear to be present in all vertebrates and that neural systems do not appear in phylogeny *de novo* or invade others to form new aggregates. He never explains what is meant by *de novo* appearance, but he is presumably denying a role for gene and chromosome mutations. If so, this is a remarkable assertion, especially since he never presents any evidence against such a role. He assumes that merely because the fundamental circuitry of several systems is similar in anamniotes and mammals, all are similar; and that all circuits were present at the beginning of vertebrate history. This is simply not a valid conclusion based on such evidence.

Ebbesson's second category of evidence is that the patterns of

interspecific variability of a given system point to a primitive condition of overlap of circuits and an increased parcellation with the development of the system. This is not evidence in itself, but merely a restatement of his conjecture. Under this category he presents a series of samples of data from his "basic systems" which he contends support parcellation. In his discussion of the visual system evidence he states that there is a presumed primitive model found in some sharks, amphibians, and reptiles. In this model retinal and tectal afferents to the thalamus overlap in a single target nucleus diffusely and extensively. The evidence relied upon (Ebbesson 1980b and the target article) consists of his own work, primarily on the nurse shark *Ginglymostoma*, and Ulinski's (1977) work on the snake *Natrix sipedon*. Ebbesson does not mention that his work was repeated by Luiten (1981a; 1981b) and found to be in error. The tectum and retina do have separate thalamic targets. Ulinski (1977) failed to recognize in his material the separate thalamic tectal target equivalent to nucleus rotundus, but has since clearly demonstrated its presence (Dacey & Ulinski 1983; Ulinski 1983). Ebbesson's evidence as presented is not valid.

Ebbesson's evidence from the somatosensory and motor system consists of a comparison of the motor and sensory cortical areas of the opossum, the rat, and primates (rather briefly presented), from which he infers a phylogenetic sequence. This practice of making historical inferences from comparisons of two or three widely divergent species is the oldest error committed by neuroanatomists, and it has been repeatedly criticized by evolutionary biologists (McKenna 1976; Radinsky 1976). The evidence cited from retinopetal systems is equivocal, as Ebbesson concludes that he is uncertain whether it represents "regression" or parcellation. Space does not permit examination of all of his evidence here. Much of it represents inaccuracies, appeals to faith that parcellation is the only explanation for the data because alternate explanations are not considered, a failure to consider homoplasy as a source of similarities, and in spite of the rare mention of the term "regression," the general adherence to a unidirectional course of evolution (orthogenesis, another discredited concept). Ebbesson's ontogenetic arguments represent Haeckelian reasoning based on no real evidence.

It should be noted that he gives the impression that the new concepts of forebrain organization in nonmammalian vertebrates – the idea that there are neocortical equivalents in nonmammals which are not necessarily organized in cortical formations – originated in Ebbesson's laboratory. This concept was introduced by Karten and his coworkers, and the evidence for it was provided by studies of the visual and auditory pathways in birds (Karten 1965; 1967; 1968; 1969; 1971; Karten & Hodos 1970; Karten & Revzin 1966; Karten et al. 1973). Ebbesson extended similar observations to anamniotes. Furthermore, he gives the impression that the discovery that the telencephalon of anamniotes is not entirely olfactory also came from his laboratory alone, failing to mention Scalia et al. (1968).

The last two decades have seen vast changes in the field of comparative neurology. Many of the new workers in this area are biologically sophisticated and bring to bear both the newer techniques for studying the nervous system and a knowledge of current concepts of the relationships of organisms and modern methods of phylogenetic inference. It is unfortunate that Ebbesson, a pioneer of the application of the new experimental neurohistological techniques to the study of anamniotes, has chosen to interpret much of the new information with the concepts of the 1920s, 1930s, and 1940s.

NOTE

This material has been reviewed by the Walter Reed Army Institute of Research, and there is no objection to its presentation or publication. The opinions or assertions contained therein are the private views of the author and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Parcellation: A hard theory to test

P. G. H. Clarke

Institute of Anatomy, University of Lausanne, 1011 Lausanne, Switzerland

Dr. Ebbesson supports his parcellation theory with an impressive array of evidence, much of which was obtained in his own pioneering experiments. My main objection is that the theory is weak in the sense of being very hard to test (Popper 1959), particularly in the present version, which is characterized as describing a "trend" rather than a "hard rule." Data that match the predictions of the theory are taken to support it, but contrary data can always be accommodated. This objection applies to the entire paper, but I will illustrate it by comments on the retinopetal systems, which Ebbesson discusses in some detail.

As various authors including Ebbesson have shown, retinopetal neurons are not restricted to the isthmic region, but occur in several telencephalic, diencephalic, pretectal, and tectal regions in three species of salamander (Fritzsch & Himstedt 1981), in various teleosts (Ebbesson & Meyer 1981; Münz & Claas 1981; Uchiyama, Sakamoto & Ito 1981), in two species of snake (Hoogland & Welker 1981; Repérant, Peyrichoux, Weidner, Miceli & Rio 1980) and even, it would seem, in one mammal, the rat (Itaya 1980). The parcellation theory implies that the earliest vertebrates should have had most or all of these connections, but the only retinopetal connection found in *Lampetra fluviatilis*, one of the most primitive extant vertebrates, is from the isthmic region (Vesselkin, Ermakova, Repérant, Kosareva & Kenigfest 1980). Moreover, there is no evidence in any vertebrate species of any transitory retinopetal projections during development, except in the restricted sense of lost bilaterality. Examples of such projections would probably have been discovered had they existed, since retrograde tracers have been injected into the eyes of many different species during development and most of the appropriate brain regions have been studied, although the telencephalon has been neglected. These studies have been done on various pre- and post-natal mammals (e.g., Shatz 1983; Bunt, Lund & Land 1983), chicks at all ages above five embryonic days (e.g., Clarke & Cowan 1976; O'Leary & Cowan 1982; O'Leary, Gerfen & Cowan 1983), and *Xenopus* tadpoles at various stages (Steedman, Stirling & Gaze 1979).

Ebbesson has not expressed much concern about these difficulties, for which parallels exist in other systems. He could, of course, explain them all away on the grounds that modern lampreys may differ considerably from the earliest vertebrates, and ontogeny does not perfectly reflect phylogeny. But in that case it would be interesting to know what conceivable data he would consider capable of falsifying his theory.

Can parcellation account for the evolution of behavioral plasticity associated with large brains?

Leo S. Demski

School of Biological Sciences, University of Kentucky, Lexington, Ky. 40506

Before considering the main theme of the target article (the parcellation process), I would like to comment on the introduction. Ebbesson's goal of making neuroscientists aware of the value of comparative studies is highly commendable; however, the statement of need in this regard is misleading. While it may be true that many individuals working on standard laboratory species are not thinking in evolutionary terms, it is incorrect to suggest that there is a lack of interest in comparative vertebrate neuroscience. Several examples clearly illustrate the point: (1) a NATO conference that convened 58 scientists working in verte-

brate neuroethology was recently held in Kassel, West Germany (Ewert et al. 1983); (2) a symposium with 11 speakers entitled "Evolution of Neural Systems in the Vertebrates: Functional-Anatomical Approaches" was held at the American Society of Zoologists meeting in Louisville, Kentucky, USA, in December 1982 (edited by L. Demski for the *American Zoologist*); (3) the J. B. Johnston Club (organized by R. G. Northcutt) meets at the Society for Neuroscience Annual Meeting for a day-long session of papers in vertebrate comparative neurobiology. Thus, although the community of workers in this field is not large relative to some other areas of neuroscience, it is certainly an active group worthy of recognition.

"Parcellation" is described in the target article as an important mechanism for development of new circuitry from existing neuronal patterns. The documentation of the process in both historical and ontogenetic terms is certainly credible. Many species appear to sharpen pathways by the loss of preexisting connections, and, from the accounts presented, the process seems more widespread than previously thought. Ebbesson's descriptions of ontogenetic recapitulation are especially interesting and should stimulate an increased search for possible "windows in time" within the brains of extant species. The concept of outmoded brain circuits that no longer subserve useful functions or at least their original ones is also of great importance. To what extent parcellation is the major factor determining the creation of such circuits remains to be studied. Even simple loss of a peripheral sensory or motor structure could accomplish pathway isolation. How such remnants may be reused is also unknown. Perhaps, as the parcellation theory suggests, the loss of part of the system triggers a reversion to earlier developmental stages that encompass more diversity of neural connections out of which new and useful pathways can be molded.

Throughout the paper, various living species are used to illustrate primitive versus advanced traits. Ebbesson states, "It is generally true that brains of species considered primitive by paleontologists have more primitive brain characters than the more specialized species." The determination of primitive brain characters essentially by their presence in one or more so-called primitive species represents a circular process since the primitive species are defined as those with primitive characters. The trait itself must be analyzed using criteria established by evolutionary morphologists (see Bock 1981). The definition of various vertebrate groups as primitive versus advanced is not even always consistent in the paper. For instance, teleosts are used to illustrate both primitive and advanced CNS features. These examples indicate the need for individual character analysis. Thus, the extent to which various examples cited represent true evolutionary lineages must be viewed with caution. The cases where a system is similar in most of the cold-blooded species and different in birds or mammals probably do represent specializations in the latter groups. A thorough analysis of the traits in living reptiles is necessary, however, to determine the likelihood that any similar putatively derived trait in birds and mammals is due to common inheritance rather than the product of parallel or convergent evolution.

Taken to the extreme, the parcellation theory dictates that all or most systems are present in vertebrate ancestors and that systems in living forms develop by elimination of many connections within the ancestral type. How do large brains evolve, then? Where do all the new cells come from? Do they follow old connections related to their cell lineage or do they form new ones? Perhaps Ebbesson's definition of systems (i.e., visual, etc.) is too broad. In his terms all brains are reduced to very basic sensorimotor pathways that may indeed have been present in ancestral species, even with more diffuse connections; but where do we classify the various functional "subsystems" that are present in the sophisticated brains of many living species? Surely there are more cells in the cerebellum of the cat than in that of the frog, and more interneurons in the visual cortex of mammals than in its presumed neocortical equivalent in the nurse shark. How does parcellation deal with these differences? There must be other important factors involved, such as cellular proliferation and new circuit formation. One case in point is where direct connections between two structures have been lost in evolution, presumably by a parcellation process (e.g., direct telencephalocerebellar connection or olfactory bulb connections to hypothalamus), and the statement is made that "there is also considerable evidence for the existence of more extensive connections in primitive circuits than in more advanced ones." As an alternative, it can be suggested that new systems have evolved by interposition of interneurons in the original simpler pathways. For the olfactory input to the hypothalamus, the interneurons are in various medial telencephalic areas; for the corticocerebellar system, the interneurons are in the pons. These "new" systems must be more complex, since the addition of interneurons can provide substrates for increased plasticity in input–output relationships, such as integration. Loss of connections (for example, the direct bulbar projection to the hypothalamus) may indeed be part of the evolution of the system, but it is certainly not the whole process.

In summary, Ebbesson's theory is provocative. It will stand as a useful model to stimulate research and new ideas. It seems clear that parcellation is an important process; however, its contribution must be considered in the context of other mechanisms such as *de novo* cellular development and system invasion. In addition, a thorough character analysis must accompany any claims for primitive versus advanced (derived) traits.

How do the lateral geniculate and pulvinar evolve?

I. T. Diamond

Department of Psychology, Program of Neurobiology, Duke University, Durham, N.C. 27710

This is the first paper since Bishop's review in 1959 that attempts to collate a wide range of data under a general scheme of brain evolution. It is worth underscoring that the new evidence requiring a modification of Bishop's ideas comes largely from Ebbesson's own research.

Bishop had devoted most of his career to the study of the relation between fiber size and modality in the framework established by Erlanger and Gasser: The first principle was that the large-fiber dorsal column system mediates touch and kinesthesis whereas the small-fiber lateral column system mediates pain. Then Bishop discovered three different fiber sizes in the optic tract, each with a different target: the smallest fibers terminating in the superior colliculus and the largest terminating in the lateral geniculate nucleus where the impulses are relayed to cortex. Since there are no submodalities in the visual system comparable to pain and temperature and touch in the somatic system, Bishop began to doubt that submodality held the key to accounting for parallel pathways. For his next step Bishop relied on Herrick's analysis of the various spinal cord pathways. Herrick distinguished five pathways which he related to phyletic origin: The newest path travels up the dorsal column to the medial lemniscus and terminates in the ventral posterior nucleus. The oldest and most primitive pathway reaches the reticular formation where several more synapses are made before reaching some diencephalic target – perhaps something akin to the intralaminar nuclei. Bishop argued that, in general, the significance of fiber size lies in the evolution of the vertebrate brain. New pathways consist of larger fibers and bypass the older and more primitive targets in the reticular formation. When we discovered a tectothalamic pathway in *Tupaia* we immediately saw a parallel between our results and Bishop's scheme. We argued that the projections to the tectum con-

stitute the oldest pathway that continues into the precursor to the dorsal thalamus; a new pathway with larger fibers bypasses the tectum and terminates directly in the thalamus. In this way the lateral geniculate nucleus evolved.

When the Nauta methods opened up new opportunities for studying connections Ebbesson chose a comparative approach. He discovered that, in general, there are more nonolfactory fibers terminating in the telencephalon and diencephalon of the fish than was believed to be the case by Herrick and Bishop. In particular, the optic tract of the shark projects both to the diencephalon and the tectum. This work has not received the attention it deserves, perhaps in part because of the preoccupation with humans and their diseases. It is good to be reminded that without a base in comparative anatomy of vertebrates, there would not and could not be a neural science of primates. Can you imagine what we would think of the ventral lateral geniculate nucleus, for example, if we had only the adult monkey to look at?

Turning to Ebbesson's theory, we are specially interested in the answer to a question we asked in the 1960s (Diamond & Hall 1969): How do the lateral geniculate and pulvinar nuclei evolve? Our view was that the lateral geniculate evolved at that stage in vertebrate evolution when the optic tract began to send collaterals to the thalamus. Since the optic tract has a thalamic target in the shark, we can no longer maintain that a direct projection from eye to thalamus evolved with mammals. (For the present we will not get into the question of whether the diencephalon target of the optic tract in lower vertebrates is the ventral thalamus and not the thalamus proper. Suffice it to say that the ventral lateral geniculate nucleus in mammals has only descending projections whereas the target of the optic tract in fish projects into the telencephalon.) Ebbesson argues that these nuclei differentiated because the retinal and superior colliculus projections are segregated. He calls this "parcellation." This appears a reasonable interpretation. Our only reservation concerns the large role given to a *loss* of fibers. It could not be the case that the retina at first projected to the pulvinar and then lost these fibers since there was no pulvinar nucleus when the optic tract and tectum each projected to an undifferentiated "precursor" to the pulvinar and lateral geniculate nuclei.

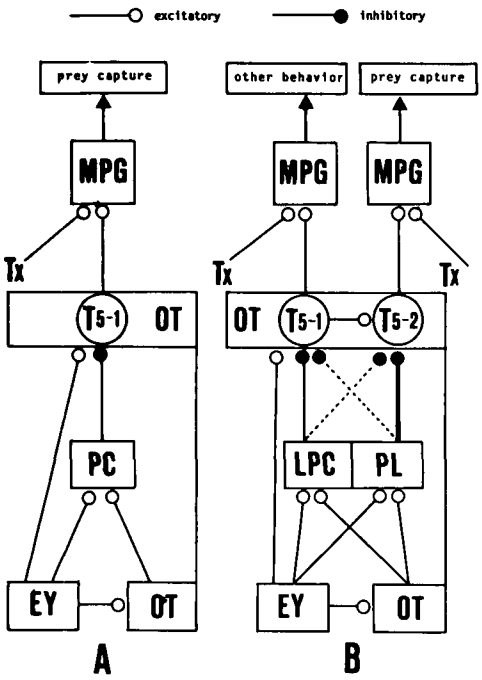

Figure 1. Schematic diagram explaining evolutionary aspects of configurational prey selection in amphibians by Ebbesson's parcellation theory. A: In the ancestral condition, as seen in urodeles (e.g., *S. salamandra*), input to the caudal dorsal thalamus (lateral posterocentral nucleus, PC) from the eye (EY) and the optic tectum (OT) overlap diffusely; the property of prey-sensitive class T5(1) neurons of the optic tectum is determined by inhibitory inputs from PC; class T5(1) neurons and other neurons (Tx) activate the motor pattern generator (MPG) for prey capture. B: In the parcellated condition, as seen in anurans (e.g., *B. bufo*), the retina and the optic tectum innervate different caudal dorsal thalamic nuclei (posterolateral nucleus, PL, and lateral posterocentral nucleus, LPC), which in turn determine the property of configurationally sensitive tectal T5(1) and configurationally selective T5(2) neurons by selective inhibition. Class T5(1) and T5(2) neurons may, in conjunction with inputs from other classes of neurons (Tx), activate motor pattern generators for different types of behavior. In anurans, (A) and (B) resemble stages of ontogenetic development.

Behavioral selectivity based on thalamotectal interactions: Ontogenetic and phylogenetic aspects in amphibians

J.-P. Ewert

Neuroethology and Biocybernetics Laboratories, University of Kassel, D-3500 Kassel, Federal Republic of Germany

Ebbesson's "parcellation theory" predicts that parcellation of brain nuclei may result in finer tuning of a given function. Regarding sensory neuronal circuits this would mean that "discrimination filters" are added between sensory input and motor output, that is, that more and better quality filters would result in a more appropriate behavior in response to a given stimulus. Our neuroethological investigations of the thalamotectal circuitry that controls visual prey-selection behavior in amphibians may provide evidence for this assumption.

In anuran amphibians (toads and frogs), the caudal thalamic-pretectal regions consists of the posterocentral nucleus PC, the posterolateral nucleus PL, and the large celled pretectal nucleus P, all being bidirectionally connected with the optic tectum and receiving retinal input via the pretectal neuropil (Weerasuriya & Ewert 1983; Wilczynski & Northcutt 1977). It could be shown that cutting the connections between PL and the optic tectum abolishes the selectivity of prey-sensitive tectal class T5(1) and prey-selective class T5(2) neurons, a phenomenon which resembles that of prey-catching behavior during recording in the freely moving lesioned animal (Ewert 1984). The configurational sensitivity of T5(1) neurons and the configurational selectivity of class T5(2) neurons is determined by inhibitory inputs from PL and lateral PC (LPC) to class T5 (Fig. 1B), as has been demonstrated, for example, by extracellular recordings from tectal neurons during focal caudal thalamic application of the neurotoxin Kainic acid, or by electrical stimulation of the caudal thalamus (for a review see Ewert 1984). Both class T5(1) and class T5(2) neurons send their axons to the bulbar/spinal motor systems, which has been evidenced by antidromic activation of these cells in response to electrical stimulation applied to the tectobulbar/spinal tracts in the caudal medulla (Satou & Ewert 1983; cf. also Ewert 1984). It is interesting to note that axons of T5(1), T5(2), and other classes of tectal neurons – which seem to be connected with different motor pattern generators – travel in the crossed tectospinal *and* the uncrossed tectobulbar pathways although the ipsilateral projection in frogs (*Rana temporaria*) appears to be much heavier than the contralateral one, whereas in toads (*Bufo bufo*) this relationship is reversed (cf. also Weerasuriya & Ewert 1981).

In urodeles, such as the fire salamander, the caudal dorsal thalamus is not differentiated into PC and PL; the latter nucleus is missing. The caudal PC nucleus receives retinal input and is reciprocally connected with the optic tectum (Finkenstädt et al.

1983). Interestingly, from the fire salamander's optic tectum only T5(1)-type neurons have been recorded (Fig. 1A) (Finkenstädt & Ewert 1983a). Lesions to caudal PC abolish the sensitivity of these neurons to configurational moving stimuli, a property which is also exhibited in prey-catching behavior (Finkenstädt & Ewert 1983b). Further quantitative behavioral experiments show that the ability of intact fire salamanders to discriminate between moving configurational visual stimuli is less than seen in the normal toad (or frog).

During ontogeny in anurans the caudal dorsal thalamus undergoes a special parcellation (whereas in urodeles the whole dorsal thalamus consists of this area alone): Shortly before the middle of metamorphosis a cellular migration, beginning from area dorsomedialis, gives rise to a new area dorsolateralis (Clairambault 1976). The differentiation of the caudal dorsal thalamus into PC and PL is completed 6–12 months following metamorphosis. Toads raised from the egg show a remarkable improvement in configurational prey-selection during the first weeks of postmetamorphic land life. This sort of maturation is independent of food experience. The acuity of configurational selectivity, as seen in adults, is reached approximately one year following metamorphosis (Ewert et al. 1983).

In connection with Ebbesson's "parcellation theory," it seems likely that the evolution of configurational prey selection in amphibians is concerned with the parcellation of the caudal dorsal thalamus and a corresponding differentiation (specialization) of its inhibitory connections to the optic tectum. Enhancement of the selectivity of sensory analyzers leads to functional differentiation of tectal neurons for the purpose of specifying motor functions (Fig. 1B). In anurans this process appears to be repeated during ontogeny. The thalamic-pretectal region of frogs and toads exhibits transiently during ontogeny a functional organization similar to the one primitive amphibians such as urodeles show as adults (Fig. 1A).

Implications of the parcellation theory for paleoneurology

Dean Falk

Department of Anatomy/Caribbean Primate Research Center, University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico 00936

Paleoneurologists who study the direct fossil record of brain evolution that is reproduced on endocranial casts (endocasts) that have been prepared from fossilized skulls have long been frustrated by the superficial nature of the evidence that can be gleaned from such specimens. Endocasts yield information about brain size, shape, sulcal pattern (to a greater or lesser degree depending on the species studied), sutures, vessels, and positions of some cranial nerves (Falk 1978; Radinsky 1968). Despite the superficiality of the evidence, paleoneurologists have determined certain trends in brain evolution – for instance, an increase in relative brain size occurred in parallel in many groups of mammals (Jerison 1973; Radinsky 1978), with human brain evolution during the past three million years providing an extreme and unexplained case (Radinsky 1979). Because of the crude nature of the direct evidence from the fossil record, however, neurobiologists have predicted that the *details* of brain evolution will derive more from the field of comparative neurology than from paleoneurology (Armstrong & Falk 1982; Falk 1980c). Ebbesson's important paper affirms that prediction.

Work on endocasts from fossilized primates has led me to believe that cortical sulci are conservative, that is, slow to appear in evolution: the earliest australopithecines from South Africa (Falk 1980a) and Ethiopia (Falk, in preparation) appear apelike in their sulcal patterns although these specimens represent hominids rather than pongids. Similarly, the fossil ape *Proconsul* appears to be monkeylike rather than apelike in its sulcal pattern (Falk 1982a). Until now, one could only note the "lag" in the appearance of diagnostic sulcal patterns in the fossil record and conclude that the eventual appearance of "new" patterns in lineages (e.g., a humanlike frontal lobe does not appear in the hominid fossil record until 2 million years before present [BP]) represents the end result of evolutionary processes that previously occurred below the brains' surfaces. As explained below, the parcellation process may indeed be an underlying mechanism that explains the appearance of new sulcal patterns.

At this point, it is important to clarify what constitutes a "new" or evolutionarily important sulcal pattern as compared to sulci that are simply the result of allometric constraints. Bigger brains have more sulci than smaller brains (Radinsky 1970; 1972), a rule that results from two laws: (1) in spheres, subcortical volume increases as a function of the radius cubed while the surface area increases as a function of the radius squared, and this holds for brain size across groups of mammals (Ariëns Kappers et al. 1960); (2) according to the law of Baillager and Dareste, the ratio of surface area of cortex to volume of the entire cerebrum remains fairly constant throughout ontogenetic development (Falk 1978; 1980c). Cortical folding is therefore the mechanism that allows area of cortex to maintain the proper relationship to brain volume. Because of these laws, paleoneurologists must continually ask whether a given sulcus is the result of mechanistic allometric factors or the result of significant evolutionary processes.

Cortical maps determined by neurophysiologists show that certain sulci and dimples separate functionally discrete areas of cortex in various groups of mammals including numerous primate species (see Falk 1928b for review). Regularly occurring *functionally significant* sulci such as those which delimit tail representations in prehensile-tailed New World monkeys (Falk 1980b; Radinsky 1972) or those which delimit portions of Broca's speech area in left frontal lobes of humans (Falk 1983) may be identified as evolutionarily significant.

How then can the parcellation process explain the appearance of such sulci in the fossil record? As suggested by Welker and Campos (1963), functionally significant sulci may be related to thalamocortical projections that are projected from the thalamus to the ipsilateral cerebral cortex during ontogeny. Receptive regions in the fetal cortex become gyri and are separated by thin zones which do not receive thalamic projections (these become sulci). According to the parcellation process, "new" sulci would result from the loss of certain thalamocortical projections in conjunction with increased isolation, fine tuning, and, one might add, expansion of the proximal functional area(s). (In this context, it is interesting that Broca's speech area is asymmetrically represented and therefore results from loss of certain connections according to the parcellation theory.)

Although Ebbesson's target article covers a broad spectrum of vertebrates, the above remarks apply to mammals, with specific examples taken from the primate order. It is important to note that, contrary to the selective loss of connections emphasized in the parcellation theory, other evolutionary trends that are both additive and elaborative have been suggested by numerous comparative neurological studies: (1) the increase in relative brain size noted above, (2) increase in neuron size, (3) increase in dendritic branching in conjunction with decrease in neuron density, and (4) possible increase in glial/neuron ratio (Holloway 1966; 1967). (See also Diamond et al. 1964 for positive effects of environmental factors on the histology of the cerebral cortex.) However, this observation simply affirms what Ebbesson stated, i.e., the parcellation process is thought to be one of several mechanisms underlying brain evolution. In short, this paper is most welcome and appreciated because it provides an important step toward synthesizing findings from comparative neurology and paleoneurology.

Is parcellation parsimonious?

Thomas E. Finger

Department of Anatomy, University of Colorado School of Medicine, Denver, Colo. 80262

Parcellation as proposed by Ebbesson entails a selective loss of connections and an increase in number of nuclei during evolution of the central nervous system. A corollary of this hypothesis is that more "primitive" vertebrates (i.e., those at a lower grade of organization) will have a more diffuse pattern of connectivity and fewer nuclei than will "higher" vertebrates. My studies on the organization of the central nervous system in fish do not support this generalization. Neuronal systems appear to be just as specialized and segregated (i.e. just as parcellated) in fish as in so-called higher vertebrates.

Is parcellation an evolutionary theory that describes a mechanism consonant with other known evolutionary mechanisms? No. First, it is necessary to recognize clearly that parcellation is not a *mechanism* by which evolution works but at best could be a description of the *result* of cerebral evolution. Second, the implication in the text that ontogeny recapitulates phylogeny is an egregious atavism referring to a long-discredited theory of a previous century. Ontogeny does not proceed through stages of evolutionary development, but does progress along similar lines in all vertebrates. Accordingly, an early-stage mammalian embryo is similar to an early-stage fish embryo. The two embryos, however, diverge in structure as they mature. This divergence occurs earlier for more distantly related species than for closely related species. Thus a rabbit embryo looks like a rat embryo longer than it looks like a fish embryo, but *at no time* does a rabbit embryo resemble an *adult* fish. Evidence drawn from studies on mammalian embryos has no validity in supporting the case for parcellation as an *evolutionary* process. In this regard, it should be noted that a process similar to "parcellation," i.e., retraction of inappropriate connections, may be a common mechanism involved in the development of the vertebrate nervous system (Lichtman 1977; Stanfield et al. 1982).

Do the experimental data support the concept of parcellation as an evolutionary trend in the vertebrate lineage? No. Throughout the target article, examples are given of systems present in *some* "lower" vertebrates but lacking in adult mammals. What are omitted are citations showing that these same systems are often lacking in other nonmammalian species as well. Thus, what is described as being a general pattern of distribution in "lower" vertebrates often turns out to be a spotty distribution among even the limited number of species examined. Such a spotty distribution may be more indicative of convergent evolution than of selective secondary losses of an ancestral trait.

In my own studies, I have found little support for the concept that connections are more diffuse or overlapped in so-called lower or nonmammalian vertebrates. One prediction that would be made on the basis of the parcellation hypothesis is that in "primitive" grades of vertebrates, the thalamus should consist of a few multimodal sensory nuclei that relay inputs to a generalized area of the telencephalon. Such is not the case. In the diencephalon of teleost fish, for example, a number of nuclei can be identified each of which relays sensory information from a *single* modality to a precise telencephalic target. There is no evidence for convergence of multimodal input onto a general-purpose thalamic nucleus.

Ebbesson discusses the olfactory system as a case in which there are more widespread connections in a primitive than in an advanced system: in some teleosts, the olfactory bulb projects to the hypothalamus as well as to the contralateral telencephalon. These connections are not present in mammals. These facts are true. Yet why are we to believe that teleosts represent the primitive condition? Evidence from Ebbesson's own work (Ebbesson & Heimer 1970) indicates that the olfactory bulb connections in some elasmobranchs are identical to the mammalian condition in terms of laterality and extent. It is more parsimonious to assume that the teleostean characteristics evolved but a single time in that lineage or that the "primitive" characters proposed by Ebbesson have disappeared two or more times during evolution?

Visual connections to the thalamus are also offered in support of the parcellation theory. "In the presumed primitive model . . . [as typified by a nurse shark] retinal and tectal afferents to the thalamus overlap diffusely and extensively (Ebbesson et al. 1972)." Yet subsequent work by Luiten (1981a; 1981b) clearly demonstrates a separation of retinal and tectal target nuclei in the same species. Thus one wonders whether much of the overlap of afferent fiber systems reported in the literature might be due less to actual convergence of diffuse systems than to inadequate definition of cytological boundaries, or problems with fibers of passage in experimental studies.

Another prediction of the parcellation theory is that all pathways found in "higher" vertebrates should be identifiable in nonmammalian vertebrates. This too is clearly incorrect. For example, the spinothalamic tracts are well developed in many mammals. According to the parcellation theory, similar spinothalamic tracts should be present in all fish. Yet a spinothalamic tract does not exist in any teleost studied so far (Finger 1981 and unpublished results on catfish; Hayle 1973) or in lampreys (Northcutt & Ebbesson 1980). In fact, ascending spinal pathways in teleosts appear to be organized more like a spinocervical system or a dorsal column system in which a mandatory synapse has been added at the level of entrance of the spinal nerve root. The thalamic target for ascending spinal input is not a diffuse, general-purpose sensory nucleus but a discrete nucleus of the thalamus, just as in mammals.

Based on all the data currently available, the theory of parcellation must be rejected as an explanation of the mechanism by which the brains of vertebrates have evolved. If the process of parcellation occurred at all during chordate evolution, it took place before the establishment of the vertebrate lineage.

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Parcellation or invasion: A case for pluralism

Bernd Fritzsch

Department of Neuroanatomy, Faculty of Biology, University of Bielefeld, 48 Bielefeld 1, Federal Republic of Germany

The parcellation hypothesis presented by Ebbesson rests on the basic assumption that not invasion but parcellation is the major shaping force of the phylogenetic and ontogenetic development of the nervous system. The fact that nerve cells originate from neuroectodermal cells with only short processes casts serious doubts on this assumption. During both ontogeny and phylogeny, the neuroblasts spill out their processes to reach their targets. Some of the numerous examples for possible ontogenetic and phylogenetic invasion of alien nervous and nonnervous structures illustrate this point:

1. The spinal ganglia derive from the neural crest and invade the spinal cord with their axons. In anamniotic vertebrates an earlier sensory cell, the Rohon-Beard cell, is gradually reduced in numbers after the invasion of the spinal ganglion cell axons, which functionally replace the Rohon-Beard cells during ontogeny (Eichler & Porter 1981).

2. During both ontogeny and phylogeny the dendritic and axonal domain of any neuroblast initially increases its realm by developing more and more axon collaterals and dendritic branches. The growth cone of the axon migrates away from the

cell of origin to contact cells in other parts of the nervous system (Jacobson 1978).

3. Motoneurons grow their axons out of the spinal cord and invade the developing muscular tissue to form functional synapses with muscle fibers (Jacobson 1978).

4. Retinal ganglion cells invade the brain with their axons to establish contacts with, for example, the tectal neurons (Rager 1980). Even an eye explanted to the back of a tadpole can successfully invade the alien tissue of the spinal cord, which normally never receives an innervation by these cells (Giorgi & Van der Loos 1978).

Ebbesson provides no evidence as to how his interconnected nervous system may have arisen in the earliest vertebrates. In the light of numerous examples of early ontogenetic and phylogenetic invasion, partly cited above, the basic assumption of the parcellation hypothesis needs to be modified in the following way: After an initial widespread ontogenetic and phylogenetic invasion further development of the nervous system may proceed by parcellation rather than invasion. However, if this should be the real assumption of the parcellation hypothesis, Ebbesson must provide us with unequivocal evidence about the reason for the cessation of invasion during ontogeny and phylogeny.

Denying any further invasion during ontogeny and phylogeny leads to the logical restriction that the most special connections found in any vertebrate brain must, by definition, reflect the ancient conditions lost in all other vertebrates. That is, structures which according to the invasion model would be considered as derived characters turn into primitive characters for the parcellation model:

1. A retinopetal nucleus with its cell bodies in the olfactory bulb has been described in several teleost fishes (Münz et al. 1982). This nucleus may be considered a homologue to the terminalis ganglion (Crapon de Caprona & Fritzsch 1983), which projects to the retina in fishes lacking the other retinopetal nucleus (Springer 1983). According to the parcellation hypothesis the access of terminalis fibers to the retina must be an ancient condition lost in all vertebrates but the otherwise highly "derived" (apomorphic) teleosts. Clearly, the more parsimonious explanation at the present stage of our knowledge is that the terminalis fibers have invaded the optic anlage in teleosts only.

2. Direct retinofugal fibers reaching the inferior colliculus (Itaya & Van Hoesen 1982) or the piriform cortex in mammals (Pickard & Silverman 1981) have never been observed in homologous structures of lower vertebrates. Thus, some retinofugal connections can be more widespread in advanced than in primitive circuits, but, according to the noninvasive parcellation model, these must be considered as primitive.

Although neither example can be taken as solid evidence for invasion, they do to some extent counterbalance the data cited in favor of a noninvasive parcellationlike development. Clearly more information on the early development of both retinofugal and retinopetal systems is necessary before any conclusive answer in favor of one or the other model can be given.

There are, moreover, examples of primary sensory nuclei that make their first appearance in advanced vertebrates. An acoustic nucleus has been described as a distinct cell group only in anuran amphibians and amniotic vertebrates. Urodele amphibians, but not anuran tadpoles, have been shown to be electroreceptive (Fritzsch & Wahnschaffe 1983). The cells of the acoustic nucleus in anurans (which is not found in urodeles) are proposed to derive from two sources: the anlage of the dorsal electroreceptive nucleus and the ventral vestibular nucleus.

Concerning the cells derived from the vestibular nucleus, a parcellationlike process may be involved. The cells derived from the dorsal nucleus, however, have been invaded by acoustic afferents after the phylogenetic loss of the electroreceptive afferents. No overlap of auditory and electroreceptive afferents has been described in any vertebrate and it appears to be highly unlikely since the two nuclei in question are separated by the mechanoreceptive lateral line or intermediate nucleus (Fritzsch et al. 1983). The ontogenetic and phylogenetic data presented by Ebbesson do not at present exclude the possibility that complicated processes occur in which both invasion *and* parcellation may interact in other parts of the nervous system as well.

To conclude, I would like to remark that for parcellation to take place an initial widespread interconnected nervous system is necessary. In other words, the concept of parcellation itself depends on a previous invasion process. Along with invasion, parcellation may also be a major driving force for the development of nervous structures. The acoustic nucleus of anurans shows us that one may even expect complicated interactions between invasion and parcellationlike processes. More clearcut data are now needed to assess the relative importance of invasion and parcellation in the understanding of brain development.

On evolution by loss of exuberancy

G. M. Innocenti

Institute of Anatomy, University of Lausanne, 1011 Lausanne, Switzerland

Until recently I believed in a direct evolutionary line from rat to cat to monkey to man. These species formed (and still do) a substantial proportion of the animals which I could (and still can) identify with certainty and by name.

My belief was shaken when I realized that the existing animal species are rather like the fruits of a tree, a strange tree which produces different fruits on different branches. The problem with evolution seems to be that all the fruits are on the ground and the tree is gone. If we could put the fruits back on a tree, in their original positions, we would be closer to understanding evolution. People do put the existing animal species on phylogenetic trees, however, and, unfortunately, often on different ones, depending on the morphological or, more recently, the chemical characteristics in terms of which the species have been ordered.

One difficulty with Ebbesson's theory is that its falsifiability (Popper 1969) demands a knowledge not only of the phylogenetic ranks and relations of the existing species but also of the organization of the brains of their ancestors. The common ancestor of mice and men could have had a very different brain from either species, thus failing to support the parcellation theory.

An alternative strategy would identify two species that derived phylogenetically from each other with as few "missing links" as possible. If a well-known California-based program of human selective breeding proves successful, human beings may soon constitute such an animal; in that case we should immediately begin the study of the relevant brains using neuroanatomical tracers, while the future ancestors are still around.

Although difficult to falsify, Ebbesson's theory may well be right, and an enlargement in my personal understanding of phylogenesis was, in fact, stimulated by an earlier version of the theory (Ebbesson 1980b). Thus, Ebbesson has achieved his declared goal "to stimulate" one of "those who usually do not think about the evolutionary past." As far as I am concerned, the stimulating effect of Ebbesson's theory was potentiated by another theory which also links the phenomena of structural exuberancy in ontogenesis with evolution (Katz & Lasek 1978).

It appears that one of the earliest discovered and most robust losses of "connections" in the development of the mammalian brain results from the juvenile exuberancy of cortico-cortical and corticofugal projections (Clarke & Innocenti 1983; Distel & Holländer 1980; Innocenti, Fiore & Caminiti 1977; Stanfield, O'Leary & Fricks 1982). I will summarize how I presently

understand some of these phenomena and to what extent they support Ebbesson's thesis.

In newborn kittens, callosal axons originate from the entire tangential extent of each visual area; part of this projection, notably that from most of area 17, is lost during the three months following birth (Innocenti & Caminiti 1980; Innocenti et al. 1977). Callosal projections undergo a similar maturation in other sensory areas and animal species, for example, rabbits and rats (Chow, Brumbach & Lawson 1981; Ivy & Killackey 1981).

The loss of callosal projections seems to consist mainly in the elimination of transitory axons, with no neuronal death (or very little) (Innocenti 1981; Ivy & Killackey 1982; O'Leary, Stanfield & Cowan 1981). It is presently unclear whether the callosal axon is a collateral that dies off, or whether the ipsilateral axons grow after the elimination of the callosal ones. However, if cortical neurons have collaterals before the loss of the callosal axons, these collaterals are very difficult to demonstrate, possibly because they are very selective in their distribution (Innocenti & Clarke 1983).

The loss of callosal axons in the kitten is a sizeable phenomenon. Using quantitative electronmicroscopy, we have recently estimated that 70% of the axons present at birth are lost by adulthood (Koppel & Innocenti 1983). Perhaps one of the ancestors of the cat (say, the saber-toothed tiger) had 3.3 times more callosal axons than the cat, or perhaps 3.3 corpora callosa. I would hate to think that this may be why it became extinct.

Unfortunately, it is not clear whether the loss is greater in more "evolved" brains, such as the cat's, than in more "primitive" ones (e.g., the rat's or rabbit's). One also knows little about the development of commissures in marsupials. That the opossum has commissural connections throughout the neocortex seems to suggest that more "primitive" brains may indeed undergo a less severe loss. This argument is not compelling, however, since there is partial loss of connections in regions of the kitten's neocortex that are not destined to become acallosal (see below). Furthermore, Rogers and Ehrlich (1983) have described conspicuous developmental loss of connections in a forebrain commissure, the supraoptic decussation of the chick, whose brain I suspect to be phylogenetically more "primitive" than that of marsupials. Whether the anterior commissure of marsupials, the corpus callosum of rats and cats, and the supraoptic decussation of birds are equivalent structures I do not know.

In the cat, the developmental elmination of callosal axons achieves two things: (1) It restricts callosal connections to specific portions of the cortical representations of the sensory peripheries, and (2) it contributes to establishing the adult pattern of area-to-area connections. We have in fact found transitory callosal projections from auditory to visual cortex in the kitten (Clarke & Innocenti 1983), in addition to the auditory-to-auditory callosal connections, which are, at least partially, preserved through adulthood (Feng & Brugge 1983). It is noteworthy that there are also transitory ipsilateral projections from auditory to visual cortex, suggesting that association and callosal connections may develop a similar way (Clarke & Innocenti 1983).

From what I have described, one may gain the impression that if Ebbesson is right the ancestor of the cat had a diffusely interconnected neocortex and had severe difficulties in making any use of it. This conclusion does not necessarily follow. First, the kitten's cortico-cortical connections are organized according to a specific pattern, but the rules that this pattern obeys seem different from those governing adult connectivity (Innocenti & Clarke 1984). Second, we do not know whether the transitory projections function, or even whether they form synapses. The little available evidence suggests that they do not (Chow et al. 1981; Innocenti 1981).

Finally, one of Ebbesson's questions is whether parcellation is genetically controlled. The postnatal reduction of visual callosal connections appears to be under the influence of both genes and experience. Connections which would normally be lost can be stabilized by abnormal vision (Innocenti & Frost 1979) and by genetic abnormality (Shatz 1977).

One should resist the temptation of thinking that genes specify in detail what will happen to every single transitory neuron, axon, dendrite, or synapse. We still have no reason to believe in a view very similar to preformationism, that is, that genes contain a detailed *Bauplan* of a brain to be (for discussion see also Van der Loos 1979). Studying transitory structures in brain development may be one way of understanding the roles of genetic and nongenetic factors in brain development, and possibly in evolution.

Possibility of "invasion" in the sensory area

Hironobu Ito

Department of Anatomy, Osaka University Medical School, Nakanoshima 4, Kitaku, Osaka 530, Japan

The "parcellation" hypothesis proposed by Ebbesson seems a reasonable one. We have some supporting evidence from teleost brains.

The corpus glomerulosum pars rotunda of Brickner (1929) shows various developmental degrees of concentric laminar organization associated with specialization of dendritic trees of two kinds of neurons (Ito & Kishida 1975; 1977; Ito, unpublished observation of 125 teleost species), as in the case of the interspecific variability of the optic tectum described in Ebbesson's target article. The corpus glomerulosum receives fibers from the nucleus corticalis and the nucleus intermedius (Sakamoto & Ito 1982); the laminar formation and cell specialization of the corpus glomerulosum, therefore, undoubtedly reflect the developmental level of these two afferent sources. Species that lack the corpus glomerulosum (but probably have scattered precursor cells) have no nucleus corticalis or intermedius. Species that have a poorly organized corpus glomerulosum have a few cells corresponding to those of the nucleus corticalis scattered *in* the optic tectum. In species with a well-organized corpus glomerulosum the nucleus corticalis is clearly formed in the ventromedial part of the optic tectum. Cells in the nucleus extend long dendrites into some layers of the tectum, suggesting that these cells were originally located in the tectum and migrated to the ventromedial margin of the tectum to form an isolated nucleus.

It is well known that some species of Cyprinidae and Siluridae have well-developed gustatory systems (Finger 1978; Morita et al. 1980; 1983). The visceral sensory areas of the cyprinid fish medulla have evolved into prominent features – the facial, glossopharyngeal, and vagal lobes. Ascending pathway patterns from the primary centers to the diencephalon are essentially the same as in mammals. Cells in these lobes, however, show conspicuous specialization in fish. The vagal lobe especially is a well-organized laminar structure composed of highly differentiated neurons. The laminar formation and morphological specialization of neurons (vertical parcellation) in the lobe seem to be closely related with segregation of inputs as well as specialization for outputs.

Teleosts of the Balistidae have a retinopetal nucleus in the preoptic area (Uchiyama & Ito 1983; Uchiyama et al. 1981). The caudally elongated portion of the nucleus tapers and is directed dorsomedially in continuity with a part of the dorsal thalamus. Because several retinopetal neurons are scattered in this part of the thalamus in perciform (see Uchiyama & Ito 1983) and scorpaeniform (Ito, unpublished observation) teleosts, the preoptic retinopetal nucleus in the Balistidae is thought to be derived from the dorsal thalamus.

Auditory systems in teleosts are quite similar to those in other vertebrate groups in terms of bilateral projections to the torus semicircularis from the primary center in the medulla oblon-

gata, with contralateral projections predominating. In addition, Finger (1980) and Finger and Bullock (1982) have identified a lateral line center (mechanoreceptive zone) in the catfish thalamus, which receives fibers from the torus semicircularis and responds to acoustic stimuli as well as lateral line nerve shock. This thalamic center projects to the telencephalon. Our preliminary experiments (Ito et al., in preparation) suggest that the nucleus of the spinal trigeminal tract also projects to the torus semicircularis in *Sebastiscus*. If so, the two leminiscal systems, acousticolateral and trigeminal somatosensory, are not yet "parcellated" in the species.

We have recently identified a cortical equivalent area in the telencephalon of some advanced (or specialized) teleosts such as the scorpaeniforms and tetraodontiforms (Murakami et al. 1983; Ito, unpublished observation). The area projects to the optic tectum and has reciprocal connections with the nucleus prethalamicus of Meader (1934; Ito & Vanegas 1983a). Because tectal neurons previously known to receive retinofugal input project to the nucleus (Ito & Vanegas 1983b), the retino-tecto-prethalamico-telencephalic path corresponds to the so-called extra geniculate visual system.

However, one of the two visual systems, the geniculate visual system, has not yet been demonstrated in any teleost species. In addition, except for the spinocerebellar path (Ito et al. 1982), no long ascending systems (oligosynaptic systems such as the dorsal system and spinothalamic system) have been found. One of the most important problems therefore still remains unsolved by the parcellation theory alone. Why do such oligosynaptic systems disappear in advanced or specialized teleost species? If the lack of long ascending systems is explained in connection with limbs, we have to recognize the possibility of "invasion" on the sensory side of the brain organization, like the pyramidal system on the motor side, because limbs have evolved from paired fins.

Duplication of brain parts in evolution

Jon H. Kaas

Department of Psychology, Vanderbilt University, Nashville, Tenn. 37240

The widely accepted conclusion that the number of subdivisions of the brain has increased in several lines of vertebrate evolution raises the intriguing question of how this increase occurred. Ebbesson attempts to answer this question by speculating that new divisions gradually differentiated from parts of old divisions by selectively losing connections. This "parcellation theory" is a more specific version of the prevailing notion that the evolution from primitive to advanced brains proceeded by the gradual separation and differentiation of originally overlapping fields (see Kaas 1982 for review). While "parcellation" theory seems in many ways reasonable, and it may indeed account for much of brain evolution, the supporting evidence is limited and open to other interpretations. In addition, the selective loss of connections, when it occurs, could be the result rather than the cause of an increase in the number of subdivisions of the brain. Finally, alternative mechanisms for increasing the number of subdivisions deserve more consideration.

In support of his parcellation theory, Ebbesson notes that connections often are widespread in early development and later become more restricted, and that connection patterns can be experimentally altered in development and regeneration. While these observations suggest that connection patterns can be easily modified in the course of evolution, especially by the process of selective loss, they do not necessarily reflect, as Ebbesson suggests, any previous sequence of evolution. For example, if transient and experimentally alterable patterns of connections (Bohn & Stelzner 1979; Constantine-Paton 1981; Constantine-Paton & Capranica 1975) reliably indicated ancestral conditions then we would be forced to conclude that the ancestors of frogs had projections from each eye to the other, ocular dominance columns in the tectum, and retinal projections to the spinal cord.

It also seems to me that the evidence that species differ in certain patterns of connections does not by itself indicate that gradual changes in connections led to the evolution of new subdivisions of the brain. A compelling argument for a "gradual separation" hypothesis, by loss of connections or other means, would come from evidence that intermediate stages of separation exist. Unfortunately, such intermediate stages have sometimes been incorrectly suggested by experimental procedures that failed to reflect actual brain organization accurately. For example, by using relatively large surface recording electrodes on the very small brain of hedgehogs, Lende (1969) incorrectly concluded (see Kaas 1982) that the auditory, visual, somatosensory, and motor cortical fields all partially overlapped; he therefore hypothesized that hedgehogs represent an intermediate stage between an ancestral condition of complete overlap and the advanced condition in most mammals of complete separation.

More recently, Donoghue et al. (1979) have presented evidence that primary motor (M-I) and sensory (S-I) fields partly overlap in the region of the representation of the hindfoot in rats. Since a complete separation of these fields occurs in advanced mammals such as cats and monkeys (see Ebbesson's Figure 6), and it can be argued that M-I and S-I are completely overlapping in the opossum (Lende 1969), a graded series of three stages of separation would seem to exist. However, the "motor-sensory" cortex of opossums is organized in a somatotopic pattern that is characteristic of S-I (Pubols et al. 1976) rather than of motor cortex, and it seems reasonable to conclude that the field is in fact S-I with some motor features and that M-I is absent (see Kaas 1982). By the same reasoning, the overlap region of "M-I" and "S-I" in rats appears to be a part of the somatotopic map of S-I as described by Welker (1971) and may therefore be S-I rather than two combined fields. A separate and complete motor field may exist anterior to S-I. Thus, the evidence for the gradual separation of S-I and M-I is equivocal.

An apparent difficulty for any "gradual separation" hypothesis, at least for large cortical fields and thalamic nuclei, is that the functions of these subdivisions must depend on rather precise patterns of intrinsic organization that seemingly would be disrupted in intermediate stages of separation. Thus, selection should be against intermediate stages. Given the highly ordered sensory representations that are found in the cortex of even "primitive" mammals, it is difficult to see how two or more orderly sensory representations could gradually, over many generations, drift apart within a single orderly parent representation. The problem of gradually creating two differing patterns of organization from a single existing pattern is usually addressed by assuming little or no organization in the parent field. But I am impressed with the evidence for the prevalence of rather precise order in most brain systems. The occasional appearance of disorder may only reflect our failure to understand the bases of organization for a field. One wonders if the proper functioning of any field allows for much disorganization. Because of the problem of disrupted functions, it seems to me that the formation of new brain structures by the gradual loss of connections is most unlikely, except perhaps over short distances at the local level. In forming new layers, modules, or columns, the problem of gradual change may be reduced by less need for an extensive series of intermediate stages.

Even if one accepts the evidence that the gradual loss of connections has been a common occurrence, it is not necessary to conclude that this had any causative role in the formation of new brain structures. The selective loss of connections seem likely to be the result rather than the cause of forming subdivisions. If there are few brain parts, each part is likely to be very general in function and therefore very general in connections. If more parts are created, then parts can specialize and have less

widespread connections. Given this viewpoint, the species differences in interhemispheric connections described by Ebbesson do not seem so puzzling. The opposum, with relatively few cortical subdivisions, must involve most of these subdivisions in the direct transfer of information from one hemisphere to the other. Cats and monkeys, with many more cortical subdivisions, can have subdivisions with few or no callosal connections and still send as much or more interhemispheric information from other subdivisions. For example, the loss of callosal connections from the representation of the hand in Area 3b of somatosensory cortex of monkeys may have been possible because sensory information is relayed ipsilaterally to the hand representation in Area 2, which does have callosal connections (Killackey et al. 1983).

An alternative to the gradual differentiation hypothesis is that the number of brain parts has increased from one generation to the next by the replication of existing parts and connections (Allman & Kaas 1971; Kaas 1982). A single cortical field or thalamic nucleus could duplicate from one generation to the next by genetic mutation, and the two fields could be passed on from generation to generation where they would be subject to selective pressures for gradual changes in connections, intrinsic organization, and function. There is no direct evidence that this has happened in the brain, but it is a common observation that body parts, digits for example, sometimes duplicate, and that this can be a heritable condition. Furthermore, duplication followed by gradual differentiation and specialization has been thought to be a major mechanism in evolution (Gregory 1935). Finally, it may be relevant that it has been possible to induce experimentally the formation of two mirror-image retinotopic maps in the optic tectum where only one normally exists (Chung & Cooke 1975) and that adjoining sensory representations throughout the brain are commonly mirror images of each other (Kaas 1982). Such mirror-image representations may be duplicates of an original representation.

Parcellation: A reflection of the structure of the animal's world

Jan J. Koenderink

Department of Medical and Physiological Physics, Physics Laboratory, State University Utrecht, 3584 CC Utrecht, The Netherlands

Ebbesson's target article is of a rather technical nature and I don't consider myself competent to judge its status in comparative neuroanatomy. Because it addresses issues that are of the highest relevance to brain theory, it tantalizes me that the author presents us with so much phenomenology but refrains from outlining the far-reaching implications of these facts.

The concept of *parcellation* has many obvious parallels in such fields as human motor behavior and sensory, even cognitive capabilities. Thus the development of language shows many instances of progressive articulations reminiscent of parcellation (Cassirer 1955). In early science – white and black magic, astrology, rosicrucian alchemy – we observe the absence of boundaries between astronomy, number theory, inorganic chemistry, physiology, and psychology (e.g., people assumed "causal" connections between the planet Saturn, the metal lead, black bile, the melancholic character, coldness, etc.). In fact, the "sciences" as we know them are the result of a rather recent parcellation process. Parcellation in this sense often represents a true advance in knowledge about the world; for instance, we no longer assume a causal connection between lunar phases and the menstrual cycle, a parcellation from which both astronomy and physiology profit. Parcellation processes in learning to appreciate music are well known, as are similar ones in the development of sensorimotor coordination and many ballistic motor programs (e.g., writing your signature). The ontogeny of human behavior can easily be interpreted as a hierarchical process of progressive parcellation (e.g., Piaget 1977).

In all these examples we observe a gain in quality, meaning, or ability accompanied by a loss in potentiality. You cannot modulate your signature to any great extent or easily forge your neighbour's; if you are an accomplished listener to Western music of some period you will hardly recognize even the superficial structure of Oriental music; if you place astronomy and physical geography in different bins you may ridicule people who seek a causal connection between the lunar phases and the tides (as Galileo ridiculed Kepler). In fact, parcellation is akin to specialization, the tuning to specific tasks to the exclusion of others. Thus it is like the microprogramming of modern central processing units; this makes the machine more "dedicated," that is, useful for some tasks at the expense of general usefulness.

Specialization is useful only in (relatively) stereotyped circumstances. Parcellation *limits* an animal's potentiality and increases its capability to deal efficiently but stereotypically with a more or less well defined world. This can be understood as a *tuning* of the animal to its environment: the parcellation reflects the lawfulness of the environment relative to the animal's goals.

Ebbesson complains about the nonexistence of fossil remains of neural systems, yet in my opinion he then proceeds to deal with existing neural systems as if they *were* fossil remains, that is, as systems that are studied without much relation to the environment in which they have evolved and function!

A comparative study must consider the neural systems as basic and integral entities together with their environments and goals. Ebbesson proposes a kind of Erlangen (Coxeter 1961) program for neurobiology (which has my greatest sympathy), but surely you must then study the invariant features of neural structure over groups of transformations that are specified through *life style and environment rather than species per se.*

Finally, let me comment on some machine theoretical aspects of parcellation. Clearly parcellation saves hardware: consider a machine whose outputs are logical functions of the momentary inputs. Suppose there are n binary inputs. Then the most general machine must have $N=2^{2^n}$ states because this is the number of different logical functions that can be computed on n-bit numbers. A completely parcellated machine that does not discard information obviously has n states, an enormous difference! The most "extremely parcellized" machine would even have just one state, independent of the inputs. Note that in the absence of a homunculus, both extreme cases are trivial: in the richly connected machine "one out of N bulbs lights up" for any input; for the poorly connected one the "single bulb" is either always on or always off. In the former case all states are equivalent without a "local sign" provided by a convenient homunculus; in the latter case there is only one state to begin with (Lotze 1884).

Both the machine in which every connection is present and the machine in which no connection is present are structureless. "Structure" is due to nontrivial constraints, and both the case wherein anything goes and the case wherein nothing goes are trivial. You can *store* selective information in the specifications of the machine. This information can be used, for instance, to code the topological structure of a sensory modality (Koenderink 1984a; 1984b). Obviously the *programming* must take place during active sensorimotor activity. (Thus deprived animals will remain structureless; this may well entail an overrichness of connections, however! The latter circumstance means less constraint, thus less information stored.)

In certain specific cases it is not difficult to appreciate how a progressive loss of wiring may tune the system to the outside world. Take the case of the "focussing" of a neural map of the visual field. Let there be a primal projection that is very diffuse and blurred. Then the map may be focussed or "deblurred" through erosion of the target areas of input fibers. (Note that

"deblurring" has both a spatial and a functional interpretation!) This is feasible under the following constraints: (1) the target areas remain convex, such that all overlap areas remain simply connected; (2) for every pair a,b of cells in the projection you may find a chain of cells $(c_1, c_2, \ldots, c_k)$ such that the pairs $(a,c_1),(c_1,c_2), \ldots, (c_{k-1},c_k),(c_k,b)$ carry pairwise correlated activities. The rules prevent the parcellation from progressing too far (so that the coherence of the map suffers), and it enforces an isomorphism with the topological structure of input activity. For example, in the visual modality this topological structure is in the final instance due to the structure of the world, for it relates to the way geometrical optics maps the environment on the receptor mosaic. Similar reasonings hold for other modalities. Thus the system really incorporates the lawfulness of the world in its parcellation. The limitations of the finally programmed system can be understood as the way the structure of the animal's world is coded into the system. [Cf. Ullman: "Against Direct Perception" *BBS* 3(3) 1980.]

The latter thought makes it likely that only very general information is stored phylogenetically and that the "tuning up" of any new system occurs ontogenetically. The tuning can only be guided through correlations in the system, for example, correlations between afferents, but especially correlations between afferents and efferents (they carry objective information about the causal structure of the world). This concept is reminiscent of the classic perceptron (Minsky & Papert 1969) – in which parcellation occurred through the adjustments of weights – although it is more general and powerful.

A brain theory commensurate with Procrustes' bed

Paul D. MacLean

Laboratory of Brain Evolution and Behavior, National Institute of Mental Health, Bethesda, Md. 20205

Ebbesson begins by remarking that "the evolutionary history of brain structures and functions should be no less important to the neurobiologist than the evolutionary history of galaxies is to the astronomer." Yet, he points out, few neurobiologists appear "to think much about the evolution of the system or process being studied." If such a disinterest exists, it can be partially attributed to the continuing fallout of academic decisions made in the 1930s. Many educators believed that with the dynamic approach provided by the newly available cathode-ray oscilloscope, electrophysiology would replace the dry bones of neuroanatomy and comparative neurology. It was as though in this particular field the automobile had done away with the horse and buggy. Today, departments of cellular biology replace what were once called departments of anatomy.

In a seminal paper written early in his career, C. Judson Herrick (1899) emphasized the value of the comparative approach for investigating the evolution, anatomy, and functions of the central nervous system. In effect, he was stating that there is no experiment that nature has not done for us. Apropos of Ebbesson's target article his references to "atrophic" or "hypertrophic" processes occurring in various conducting tracts would be illustrative. He looked upon such changes as analogous to pathological conditions, with the difference being "that they are spread out in time and extended along the phylogenetic pathway" (ibid., p. 160). This, he maintained, is one of the great powers of the comparative method. Following the lead of Strong (1895), he and others used the Golgi method to reconstruct in beautiful detail the entire peripheral and central nervous systems of small vertebrates. Nature, he said, has "performed for us in fishes a series of experiments" which clearly reveal "what are the primary and secondary anatomical centres for the several systems of sense organs" (ibid.; p. 165).

Ebbesson's provocative concept of parcellation and isolation attests to the heuristic value of the comparative method. By inquiring into the organization of the forebrain in a cartilaginous fish commonly regarded as being quite divergent from the vertebrate line, he has been led to generalizations that may prove quite useful in obtaining a better understanding of the evolution of the mammalian forebrain. One finds the germ of his parcellation theory in a paper published in 1972 in which he noted that the counterpart of the lateral geniculate body in sharks "is interesting because it has the combined connections of the two main, usually separate, visual systems" (see Ebbesson 1980, p. 11). This finding suggested to him that "the dorsal nucleus of the lateral geniculate body and the inferior part of the nucleus lateralis posterior of mammals may have evolved from a single nucleus" (ibid., p. 11).

William K. Gregory, the paleontologist who followed in the footsteps of Cope and Osborn, was fond of saying that every one of the 28 bones of the human skull "has been inherited in an unbroken succession" from the fishes of pre-Devonian times (Gregory 1967, pp. 21–22). Isn't Ebbesson speaking in similar terms when he says that "the data suggest that diffuse, relatively undifferentiated systems existed at the beginning of vertebrate evolution and that during the evolution of complex behaviors . . . a range of patterns of neural systems evolved that subserve these functions"? Some may detect in this expression the echoes of Aristotle's "potential." Others may see it in modern dress: if, as now often viewed through the brain's sticky protoplasm, the universe is alternately expanding and collapsing, has it not all happened before – a "crystallizing" out of various forms of life just as, according to the accident of mix, there have crystallized out many forms of granite?

Given the mysterious "potential," what is the publicly shared evidence that parcellation and isolation constitute an evolutionary process? Ebbesson gives several appealing examples, and if readers were to share their own observations, the list might be quite sizable, especially if one were to include some artificially produced examples. Among projections seen in some adult "lower vertebrates," but seldom in adult mammals, Ebbesson lists the ipsilateral posterior accessory optic root. However, if one removes the eye of a newborn rat, one is surprised to find in the adult animal a respectable ipsilateral root (Harris & MacLean, unpublished). Does this condition reflect a reversion to the "primitive condition," or does the uncrossed projection of axons developing from the remaining eye (Lund et al. 1973) result from mechanical or other factors, as discussed by Cunningham (1976)?

In terms of function the parcellation theory has appeal because it allows one to imagine how such a process might afford a reduction of "noise" and improved discrimination. Elsewhere I have referred to special thalamocortical parcellations as biocones (MacLean 1975). In the evolutionary process the parcellation theory would allow for either a decrease or an increase in the number of "biocones" or for both conditions to happen concurrently.

Perhaps the major difficulty that crops up in connection with the parcellation theory is the one pertaining to homology. In recent years there has been the tendency among some comparative neurologists to regard cerebral structures as homologous if they are similarly connected in different species. In regard to the forebrain this has led to vigorous argument as to whether or not the dorsal ventricular ridge (DVR) of reptilian and avian forms can be regarded as homologous to cortex of mammals. This is somewhat like arguing about whether or not computers of widely different vintages can be considered as homologous because they carry out many of the same kind of operations. Mammalian cortex looks very different from parts of the DVR or, say, the pallium ("covering" in the sense of Reichert) of sharks that Ebbesson compares to neocortex (Ebbesson 1980); it is also "wired" differently. One proponent of DVR/neocortex equivalence has remarked that the hypothesis has "proved sufficiently procrustean to make possible an explanation of each and every set of observations" (Webster 1979). It will be recalled that the word "procrustean" derives from the

name for the mythical robber of Attica, who either stretched his victims or cut off their legs in order to make them conform to the length of his iron bed. Any theory worth its salt will stand up to a good deal of cutting and stretching, and one senses that Ebbesson's theory of parcellation will survive in Procrustes' bed for a long time.

Parcellation: The resurrection of Hartsoeker and Haeckel

R. Glenn Northcutt

Division of Biological Sciences, University of Michigan, Ann Arbor, Mich. 48109

Ebbesson proposes that the variation in the number of cell groups (aggregates) in the brains of living vertebrates, as well as interspecific differences in the pathways connecting these aggregates, arose in phylogeny primarily by the differential loss of selected pathways and the concomitant subdivision of aggregates into more disparate aggregates. He terms this "evolutionary and ontogenetic mechanism" the parcellation process or theory, and he correctly indicates that interpretations of brain phylogeny, whose events are not well documented in the fossil record, must be based primarily on the pattern of interspecific variability exhibited by brains in contemporary species. Thus parcellation is a phylogenetic hypothesis. Like all scientific hypotheses, it cannot be proven, only rejected, or not, in favor of other hypotheses. And, like all hypotheses, it should be testable in at least two ways: it must be logically formulated, and its predictions and corollaries must be supported by descriptive and experimental data.

In an earlier paper, parcellation was held to be the only one of three theoretical mechanisms actually operating in brain evolution (Ebbesson 1980b). As so formulated, this hypothesis is not logical, because it suffers from a problem similar to that of the preformation theorists of embryonic development in the seventeenth and eighteenth centuries. Hartsoeker and other preformationists believed that the vertebrate body was completely preformed in miniature in either the egg or the sperm and only enlarged during development. Given this position, they had also to admit that all future generations were likewise encased, one inside another, like Chinese boxes. Similarly, if parcellation is the only process by which brains change, and if connections can only be lost, then all connections found in modern, complex brains must have existed in earlier vertebrates. Thus a corollary of the parcellation hypothesis is that connections were progressively more extensive earlier in phylogeny, whereas cell aggregates were correspondingly fewer. Taken to its logical conclusion, this thinking leads to an ancestral organism that might have possessed only three cell aggregates (the minimum needed to form a network), but these aggregates had to have all the connections exhibited by modern mammals! Ebbesson proposes such a corollary by stating that "these basic systems are often more extensive [i.e., exhibit more overlap] in primitive species than in advanced species." Yet many examples cited by Ebbesson are those for which data specifically do *not* support this corollary (Kaas 1982; Luiten 1981a; 1981b; Neary & Northcutt 1983; Smeets 1981a; 1981b).

Logically, parcellation cannot be the only process by which brains change. In the present article, Ebbesson has altered his position and states that parcellation is only one of several evolutionary "mechanisms," but he leaves the impression that it is the major one underlying brain evolution. He suggests that the invasion of an aggregate by the axonal branches of another aggregate might be a second "mechanism," but he concludes that this appears to occur only rarely in motor systems and not at all in sensory systems. A very different interpretation has been presented, however (Northcutt 1981; 1983), based on virtually identical data. At this point, it should also be noted that evolution is usually defined as change in the gene pool, i.e., frequency of alleles, of a biological population (cf. Dobzhansky 1951; Futuyma 1979), and the *mechanisms* of evolution are commonly considered to be mutation, natural selection, and geographic isolation. Parcellation, if it occurs, describes a phylogenetic pattern is not itself a mechanism of evolution.

The testing of alternate phylogenetic hypotheses requires that the *pattern* of homologous versus homoplastic traits be established for a large number of species, with sufficient outgroups being represented. The interpretation of a series of characters as homologous leads one to reject a hypothesis of invasion, whereas the interpretation of the same characters as homoplastic results in the rejection of a parcellation hypothesis. Thus many of the brain characters cited by Ebbesson as supporting the hypothesis of parcellation could be used to reject this hypothesis if they are interpreted as cases of homoplasy (Northcutt 1981).

A phylogenetic hypothesis can be evaluated only when terms such as "homology" and "homoplasy" are clearly defined and the criteria for establishing comparisons are stated. Ebbesson has neither defined his phylogenetic descriptors nor provided any insight into his criteria or his analysis of the brain characters used. Equally important, alternate interpretations in the literature are ignored. We are simply asked to accept that the brain characters cited form a particular pattern of variation and that parcellation most probably accounts for the genesis of that pattern. The lack of a rigorous phylogenetic analysis of these brain characters makes it impossible to determine even whether parcellation exists as a process, let alone the extent to which it accounts for brain variation in living vertebrates.

Finally, Ebbesson cites transitory connections observed in various stages of ontogeny as supporting the concept of phylogenetic parcellation and suggests that such transitory connections represent connections that were once present in ancestral species. Interpreted in this context, ontogenetic parcellation is a specific example of Haeckel's biogenetic theory that the ontogeny of an organism recapitulates its phylogenetic history. In turn, Haeckel's theory is essentially an elaboration of the earlier Meckel-Serres theory that the ontogeny of "higher" animals recapitulates the adult structures of animals below them on the scale of beings. These reflections of *scala naturae*, and the hypotheses they generated, were critically analyzed and rejected by von Baer (1828), as well as by most subsequent biologists (cf. Gould 1977; Raff & Kaufman 1983; Wiley 1981). It is obvious that multiple hypotheses regarding transitory connections should be posed and a biogenetic hypothesis favored only if other hypotheses can be rejected. Failure to do so results in transitory connections being ascribed to historical factors without examining the possibility that they have more proximate causes.

Ebbesson's target article has correctly portrayed the revolution in neuroanatomical techniques, and there is no question that this technology has produced a wealth of new data. There has also been a major revolution in biological thought regarding phylogenetic analysis and evolutionary theory. Unfortunately, the latter is not reflected in Ebbesson's article.

Exploratory neural connectivity

E. Ramon-Moliner

Department of Anatomy, Sherbrooke University School of Medicine, Sherbrooke, Quebec, Canada J1H 5N4

My own long-held views are consistent with Ebbesson's theory about the way in which the various specific neural connections could have become established in the course of evolution. Speculative as it may at first appear, I find the notion of a primordial chaotic diffuse nervous system, evolving towards parcellation and organization, quite seductive. Yet it does not seem seductive to all neurobiologists. One of the problems facing us is the impossibility of finding examples of brains of

living species capable of being arranged in the form of a relatively gradual transition from primitive to modern. Most biologists are probably satisfied with the cladistic tree which places the amphioxus at the beginning and man at the end of vertebrate evolution. But some never seem to be satisfied and keep pointing to "missing links" and other forms of "lack of evidence." This attitude may lead to a belief in the futility of all attempts to reconstruct the course of evolution, a belief which is not compatible with our present aims. As a matter of fact, the topic of Ebbesson's paper could become dissociated from observational data and be formulated in terms of "conceivable or inconceivable processes." Unless we return to far-fetched creationist models, we must admit that modern neural patterns must have evolved from old ones. If so, we are entitled to ask: is it logical to accept that, from the very beginning, neural connections were arranged in the form of well-defined neural pathways and that the most primitive brains were already well parcellated? Of course, the answer is no. Only diffuse connectivity can be *conceived* as an original state. To assume that neural parcellations existed from the very beginning amounts to indulging in unwarranted creationism. In this respect, I am inclined to support Ebbesson's general idea as a logical one: neural evolution must have started with a vast number of connections of which many must have been gradually eliminated, thus leading to system specialization and greater isolation of functions.

There are, however, a few points that must be clarified. To begin with, a neural territory does not necessarily have to evolve toward parcellation. In fact, if the conditions that lead to segregation disappear, the opposite trend can be observed: the structure reverts to heterogeneous connectivity and lack of clear-cut borderlines. As an example, we have pointed out the case of the mammalian tectum, which is more diffusely organized than that of reptiles and amphibia (Ramon-Moliner & Nauta 1966). This could possibly be due to the fact that the monopolization by the visual function, so important in lower vertebrates, is lost in mammals. As opposed to what happens in lower vertebrates, the mammalian tectum shares with the reticular formation a great heterogeneity of connections. The primordial "reticular" net could in fact be regarded as a phylogenetic pool from which specialized structures can derive and to which they can revert, the latter case being exemplified by the mammalian superior colliculi.

I am inclined to believe that well-segregated functions, well-individualized pathways, and well-parcellated brains are not the necessary targets of evolution. They are only a manifestation of the interaction between two forces: on the one hand, the tendency to explore and, on the other, the trimming action of *natural selection*. The tips of growing axons in an embryonic brain explore the invaded tissue in the same way that new biological species explore new niches, and in the same way that genetically controlled neural experiments explore the environment of a given species. From this perspective, some apparent exceptions to Ebbesson's rule lose validity. For example, the direct pyramidal input to motor neurons seems to be a new acquisition, since only primates have it. Where are the lost connections then? One might be tempted to conclude that Ebbeson's theory fails entirely in the case of the most conspicuously segregated mammalian pathway. Not so, if we believe that even in lower forms there are, at the individual level, temporary exploratory connections, from cortex to motor neurons, the genetic perpetuation of which is not achieved until the primate stage is reached.

We must accept that a constant genetic process must be going on, leading to an unsuspected degree of individual variability in neuronal circuitry. Each variation, like the ameboid movement of a growing axonal tip, implies discarding some possibilities and reinforcing others. This introduces an element of creative randomness. If it were otherwise, natural selection would have no material to act upon, and no genetically conditioned circuitry could ever evolve. The problem is, if we accept Ebbesson's notion that neural pathways are arrived at by a discarding process, why should "parcellation" be helpful to species survival?

An evolutionary trend to lost connections (resulting in segregated pathways and increased parcellation) can be accounted for if we assume that the requirements of the environment act over long periods of time and favour the survival of individuals who lose connections. But why should this loss have evolutionary advantages? One answer lies in that we are not merely dealing with the loss of connections but also with the reinforcement of those connections which natural selection sanctions as particularly useful for survival. Another possible way to account for the evolutionary advantage of segregation (or parcellation, to use Ebbesson's terminology) is to assume that in the primordial diffuse network certain functions may be impaired by "distracting processes." For example, if certain neurons are engaged in visual perception the arrival of nonvisual signals may constitute a handicapping interference. By the same token, if a pathway is aimed at direct motor performance its lack of segregation may lead to undesirable autostimulation.

Ebbesson's rule cannot claim the universality that the laws of physics, for example, can have. As often happens in biology, his rule points to a trend, not to an infallible law. He seems to imply that the phylogenetic invasion of a territory by fiber systems which were absent in ancestral forms seldom takes place. This is not so. His own example of the commissural systems shows it. It is true that in higher vertebrates there is an absence or scarcity of interhemispheric connections between those cortical areas that have become monopolized by specific sensory functions. But one cannot forget that the corpus callosum is nearly absent in masupials. We cannot therefore regard the fibers that come from the opposite hemisphere as something that remains after other connections are lost. Interhemispheric connections are indeed new. At some stage they were initiated, but then they were trimmed. Here we have one more example of the fascinating similarity between the exploratory behaviour of the growing tip of an embryonic axon and the formation of neural connections in the course of phylogeny. At first, a massive exploratory connection was conceivably made between the two hemispheres. Then some of those connections were lost. Like growing axonal tips feeling their way in the embryonic tissue, neural connections seem to be made by a process of invasion, then retraction. The difference lies in the fact that this exploratory behaviour does not take place in one individual brain but in a collective brain, that of the evolving species.

In his erudite analysis, Ebbesson often cites examples of ontogenetic loss of connections which seem to recapitulate the phylogenetic history of the brain. He seems to imply that if in the course of embryonic growth a connection is made and then lost, it is necessarily correspond to a pathway that was present in some adult ancestral form. This may often be the case, but it cannot always be so. We are only beginning to understand the forces which guide developing brain, but we can be certain that the tentative paths of growing axons cannot always correspond to lost ancestral pathways.

At a time when neuroanatomy risks becoming an arid inventory of facts with few general guiding principles (even the law of Bell-Magendie [Bell 1811; Coggeshall 1980; Magendie 1841] seems to be contested!), Ebbesson's rule, with all its limitations, deserves to be borne in mind.

Axon development and plasticity: Clues from species differences and suggestions for mechanisms of evolutionary change

Gerald E. Schneider

Department of Psychology and Brain Science, Massachusetts Institute of Technology, Cambridge, Mass. 02139

It is a pleasure to be reminded that species differences in neuronal connectivity are not mere annoyances in our quest for animal models of human biology! Considering such differences

as markers of evolutionary progression, Ebbesson makes an important contribution in pointing out how they can provide clues to mechanisms of brain development and to the brain's plasticity when confronted with injury or other environmental manipulations. Here I will try to indicate how this approach can be extended a little further to glean some additional clues.

The achievement of complex, specific patterns of axon termination in development appears to result from an as yet poorly understood interplay among several kinds of factors. Prominent among these factors controlling the formation of terminal arbors and synapses are the following: (a) chemical affinities, (b) intercellular interactions involving active competition among axons for terminal sites, and (c) intracellular programs of growth which, for example, limit the number of terminals (or synapses) that can be supported by a given neuron.

If we first consider the chemoaffinity factor, species differences in the degree of "parcellation" of the projections of a given population of axons could reflect phylogenetic changes in recognition molecules involved in the development of specific pathways and connections. On the other hand, species differences in parcellation could result from phylogenetic changes in axon–axon interactions that favor a competitive segregation of two axon populations, instead of an overlap. The evolutionary emergence of this method of attaining selective patterns of connectivity may relate to a progressive increase in developmental time course in some phylogenetic lines. The evidence that in some cases sensory experience or neuronal activity in general plays a major role in axonal segregation processes (e.g., Hubel et al. 1977) indicates an adaptive flexibility of interactive mechanisms that supplement chemoaffinity-governed interactions. Conversely, the latter may dominate in species for which time is at a greater premium in initial development (e.g., in many invertebrates) and, consequently, where environmental influences on development are minimal. Also, in some cases such environmental influences may not be adaptive.

Let us consider next the third type of factor listed above, specific intracellular programs of growth, concentrating on the hypothesis that a neuron is genetically programmed to increase the number of synapses formed by its axon up to a set limit, with different limits for different cells (Devor 1976; Schneider 1973; 1979). This idea has some clear implications for the evolution of nervous system connectivity. If parcellation occurs in an axon's projections, that axon loses its branches in specific target cell groups, perhaps as a result of a change in chemoaffinity-governed preferences. Assuming that the genetic limit on the number of terminals (synapses) does not change, then one would expect that the number of connections elsewhere would tend to increase, with larger arbors if we assume that arbor size and synapse number are closely correlated. Of course, changes in the limits on terminal number might evolve also, but these changes would probably be genetically distinct from changes in chemoaffinity molecules, which would encourage the parcellation.

Using similar reasoning, one can also see how an increase in cell number in one terminal area could contribute to the parcellation process in Ebbesson's sense: A greater amount of terminal space in one region that was attractive to a group of axons on the basis of chemoaffinity could lead to expanded terminal arbors there, forming more synapses, with (because of the internal program of the cells) a corresponding reduction, or loss, of terminal arbors and their synapses elsewhere. Such an expansion in one target and accompanying loss in another by one system of axons would also depend, of course, on competitive interactions with other systems.

These considerations lead to the prediction that there may be marked species differences in the degree and type of altered connections that can develop after brain injury. In general, one might expect less capacity for rearrangement in some of the more differentiated brains, to the extent that an increased differentiation reflected increased reliance during normal development on chemospecificities.

It is an intriguing possibility that the transient or "exuberant" projections that appear during development may be nothing more than atavistic residues of evolution that play no role in the formation of selective connections or in maintaining normal function in the developing brain. Such a possibility seems most likely in the case of transient projections from a given locus to completely separate structures, rather than in the case of a developmental progression from diffuse to focalized arborization of axons within a single topographically organized system (Fujisawa et al. 1982; Schneider et al. in press). Ebbesson does not clearly distinguish between these two different kinds of transient axon growth. The latter type of developmental remodelling within a target field may also be a source of variation subject to selection pressures, resulting in parcellation (i.e., the same process of focalization involved in achieving precise topographic order may come to subserve a segregation of axonal populations).

Suggestions for plasticity studies inspired by findings of comparative anatomy, as well as by findings of transient connections in development, are certainly intriguing. Equally thought-provoking, but less testable, are hypotheses regarding the evolutionary history of particular patterns of connectivity that are suggested by findings of abnormal connections after early brain injury. For example, consider the finding of retinal projections to the thalamic ventrobasal nucleus or to the medial geniculate body in hamsters with combined neonatal tectal lesions and deafferentation of these thalamic cell groups (Frost 1981; Kalil & Schneider 1975; Schneider 1973). Such findings imply axon–target affinities that may reflect an earlier stage of evolution during which there was diffuse overlap within the thalamus of axons subserving different sensory modalities (see Herrick 1926). If the retina could be made to project to arbitrarily foreign territory with equal ease, this notion of graded affinities reflecting phylogenetic history would be weakened. However, optic-tract axons do not appear to innervate implanted pieces of neocortex (Jaeger & Lund 1980) or cerebellum (Yoon 1979), as they do tectal implants.

It is fun to speculate, but the way in which various mechanisms underlying development interact is still poorly understood. It is even more fun to find clues to a mystery, and Ebbesson has given us reasons to believe that clues to the nature of this interplay of mechanisms may be obtained not only in the study of the ontogeny and plasticity of neuronal pathways in model laboratory species but also in the findings of comparative anatomy of the sort that he has assembled.

Cytodiversification and parcellation

J. Szentágothai

1st Department of Anatomy, Semmelweis University Medical School, H-1450 Budapest, Hungary

The working hypothesis put forward in the target article appeals to the reader by bringing back phylogenetic aspects of neural organization after a long period of neglect. "Large scale" circuitry is presented with a wealth of new information on a wide variety of vertebrate species and a large number of different pathways. This was certainly beyond the reach of the earlier neuroanatomist, who had to rely on the classical methodical repertoire of the last century. Many neuroanatomists with some interest in general questions have probably had the feeling that some kind of "segregation–isolation" process must be at the basis of evolutionary and ontogenic differentiation, but no one so far has come up with an explicit hypothesis that might incorporate this mechanism into the general framework of neurogenesis.

The general trend in the cytodifferentiation of dendritic patterns is clearly documented. Dendritic differentiation proceeds from geometrically and topologically ill-defined, radiating arbors toward arborization within specific, clearly defined and

restricted geometric spaces with a well-defined sequence, and a determinate arrangement, density, and orientation of first, second and further order branches. Ramon-Moliner (1962) and Ramon-Moliner and Nauta (1966) have provided a very elegant description of the main types of dendritic patterns and have proposed a simple and useful nomenclature for labeling the diverse types. Ebbesson emphasizes only one consequence of the specialization of the dendritic tree, namely an increased homogeneity of input. May I suggest another aspect which probably has more relevance for the process of parcellation: the segregation of arborization space. The more "isodendritic" (in the sense of Ramon-Moliner and Nauta) the arborization, the larger is the interpenetration (spatial overlap) of each other's space; the more this changes toward the more specific "allodendritic" or toward the even more "idiodendritic" arborization pattern, the less the interpenetration (i.e., sharing) of each other's arborization space. In other words, there is a general tendency in dendritic arborization patterns that with increasing specialization of the nerve cells there is increasing separation or segregation of their arborization spaces (Szentágothai & Arbib 1974).

This trend is quite obvious, both in evolution and in ontogeny, in the inferior olive and in the lateral nucleus (dentatus) of the cerebellum, where this process runs toward a virtually complete individualization (separation) of each cell's dendritic arborization space (Eccles, Ito & Szentágothai 1967, pg. 228, Fig. 125). In the primate inferior olive the gradual separation of the dendritic arborizations can be observed directly during fetal tissue differentiation to occur by gradual withdrawal of the longer dendrites and an increasing tendency of the youngest dendritic branches to turn back toward their own perikarya (unpublished personal observation). The same process can be observed in most sensory relay nuclei, particularly in evolution. The segregation of the dendritic spaces does not usually reach the stage of complete individualization of cellular spaces, but is directed more toward establishing distinct cell layers with clear confines that are not transgressed by individual dendritic branches. In this way curved cellular layers are established, such as the superior olive, for example, or multiple layering in the ventrolateral part of the medial geniculate nucleus and in the dorsal lateral geniculate nucleus. The result is that certain types of afferents may come into contact with certain types of dendritic branches. This mechanism is probably the most important single architectural tool by which parcellation is accomplished. One might go on indefinitely in citing similar or even better examples, all essentially in favor of Ebbesson's elegant hypothesis.

The question becomes less clear if we pose it in a slightly different way: Does specification of the dendritic tree always contribute to parcellation? Moreover, does it always mean an increased homogeneity of input? Our answer will obviously be in the negative. The Purkinje cells (having dendritic trees that arborize in virtually isolated compartments of tissue with zero interpenetration between each other's arborizations) are rare examples representing the highest possible multiplicity and diversity of input over the mossy fiber → granule cell → parallel fiber input. Although for the other line of input, the climbing fibers, the local one-to-one relation is well secured, but for the specific "climbing type" input the individualization of the dendritic arbors does not seem to be an essential condition. Many speculations about the possible significance of the peculiar architectural features of the cerebellar cortex, with its extraordinary stability in evolution, have been offered by Eccles et al. (1967) and many others, with no investigator being able to give a really satisfactory answer. Beautiful examples of the significance of very highly specific dendritic arbors of motoneurons in amphibia have been given by Székely (1979) in which particular (specific) dendritic branches for specific synaptic inputs can be distinguished. The elegance in Székely's studies rests on the fact that his models, in addition to being histologically well documented by the application of the cobalt tracing method, are based on organ recombination experiments in relatively early embryonic stages and a functional analysis of their results.

The points mentioned here are by no means intended to call into question the remarkable argument of Ebbesson; they are meant, rather, as new dimensions to which the hypothesis might be extended. More attention might be paid to the microcircuitry (i.e., specification of dendritic and axonal arborizations) and experimental embryology, which are likely to benefit greatly from the modern fiber tracing methods.

Space constraints prevent me from discussing another most interesting aspect of the hypothesis, lateralization and the crossing of pathways. It may suffice perhaps to call attention to a neglected treatment of this subject from more than twenty-five years ago (Szentágothai & Székely 1956) that may appear rather naive from our present vantage point. But, having been based to some degree on embryological experiments, it may show why experimental embryology could have a word to say on the problems under discussion.

The parcellation theory: What does the evidence tell us?

Walter Wilczynski

Department of Psychology, University of Texas, Austin, Tex. 78712

Ebbesson's evolutionary theory of "parcellation" or "segregation–isolation" postulates a very specific change in neural structure: the transformation during which a single population of neurons innervated by two sources splits into daughter nuclei, each of which retains input from only one of the sources. In its most extreme form, the parcellation theory suggests that *each neuron* in the original population is innervated by *both* sources; connections are then lost in subgroups so that eventually the neurons in each daughter population have connections from only one of the original sources. I reiterate this to stress that the model Ebbesson frames is a very special case. It is not the simple loss of connections or nuclei; it is not the retraction of inappropriate connections or the death of overproduced neurons; it is not the hypertrophy or cytodifferentiation of an area (although, as Ebbesson notes, these processes may coincide with parcellation). With these restrictions in mind, one can ask, as Ebbesson asks, does parcellation ever occur? Is it important in evolution? Is it a major, or *the* major, feature of neural evolution – as "universal as the available data suggest," as Ebbesson conjectures in this paper? Ebbesson answers all these questions in the affirmative based on the evidence cited in his paper. But is the evidence presented specific enough to test this very specific model? In fact, is much of it even germane?

The best piece of evidence for a parcellationlike process that Ebbesson presents is a survey of retinal and tectal inputs to thalamic nuclei. The evidence comes mainly from Ebbesson et al.'s 1972 paper on thalamic organization, which described the visual areas in *Ginglymostoma*, a galeomorph (or advanced) shark. In this species a total overlap of retino- and tectothalamic projections is claimed. In nearly all other vertebrates the overlap is at most partial and is usually restricted to specific nuclei, as in teleost fish (Ebbesson et al. 1972), reptiles (Butler & Northcutt 1978), and anuran amphibians (Fite & Scalia 1976; Rubinson 1968). (In their 1972 paper Ebbesson et al. note an extensive overlap in salamanders as well.) In order for the parcellation model to hold in this case, one must establish, first, that the organization in *Ginglymostoma* represents the condition in ancestral vertebrates, and second, that all nuclei that receive either retinal or tectal inputs are homologous among all vertebrates. If both points are not made, then other processes are possible, for example, the invasion of retinal axons into tectal recipient zones in advanced sharks or the establishment of new

retinal targets in other vertebrates. I do not believe a case for either of the two points has been made.

Of course, the bane of comparative neuroanatomy is the inability to actually observe the neural organization of the early vertebrates and unequivocally trace its development to present-day species. But probability statements about ancestral conditions are possible based on cladistic analysis of the character in question (Northcutt 1984, in press), and homologies can be suggested based on specific connectional, topological, and histochemical data available for each nucleus involved. Ebbesson does not provide the specific information, and indeed for many vertebrates little of it may be available. A cladistic analysis here is uncertain because no evidence from lampreys or primitive sharks and bony fish are presented. But it seems at least as probable, if not more probable, that advanced sharks consolidated their visual nuclei rather than that all other vertebrates parcelled them.

Several other systems are presented as evidence for parcellation, but again specifics are lacking. Arranging thalamotelencephalic connections as in Figure 10 gives only a gross view of the complexity of the situation. Which thalamic nuclei and which telencephalic targets are being compared? In frogs, for example, the thalamic nucleus receiving tectal input projects ipsilaterally to the striatum (Wilczynski & Northcutt 1983), while a different retinal recipient nucleus projects bilaterally to the medial pallium (Ronan & Northcutt 1979). Are one or both of these systems being compared with either or both of the mammalian lateral geniculate or lateral posterior/pulvinar projections to the isocortex?

It is unclear whether even at the most superficial level the examples provided really do support the specific model proposed by Ebbesson. Consider the isthmo-optic nucleus. It has bilateral projections in some vertebrates, but unilateral projections in birds. Assuming that the sources of retinopetal systems are homologous in all vertebrates – only an assumption, given the extensive variability in number and position in each vertebrate – one might conclude that a bilateral retinopetal system was the ancestral condition. Does the avian condition arise from parcellation as Ebbesson presents the process? How can it? What is the ancestral parent population and what are the daughters? One cannot suggest that the two eyes were originally a single population which subsequently split (Northcutt & Gans 1983). Nor can one suggest that the retinopetal nuclei of the two sides were originally a single aggregate which parcelled into an independent, dual system in birds. In fact, Ebbesson points out that primitive vertebrates have more retinopetal nuclei than advanced vertebrates. If all are homologous this argues for a consolidation, not a parcellation, of the system.

What Ebbesson has shown us here, and in the cases of telencephalotectal, thalamotelencephalic, and isthmotectal systems, is the selective loss of a connection, in all these cases a loss of one side of a (presumably) ancestral bilateral system. And in showing us this, Ebbesson has highlighted an important aspect of neural evolution. He has shown us that vertebrate brain evolution has not progressed in a linear fashion by adding a new pathway or system at each step. Connections can be lost as well as added. It is clear from the comparative literature that not only some connections but whole sensory systems (e.g., the lateral line system) have been lost during phylogeny. But losses are not parcellation as Ebbesson defines it, with its implications of "diffusely" organized ancestral populations yielding finely tuned daughter populations.

Ebbesson was an important and instrumental figure in breaking down the linearist dogma of brain evolution, which declared that vertebrates progressed inexorably from simple animals with few connections to more complex animals with more connections. This dogma persisted until Ebbesson and several others applied experimental neuroanatomical techniques to describe the neural organization in nonmammals. They found, and much of the evidence which Ebbesson presents in this paper supports the finding, that brains do not evolve by the continual addition of new and better connections. A basic CNS organization arose with the earliest vertebrates. Upon this base connections were added or lost, nuclei consolidated or differentiated, whole systems grew while others shrank or even disappeared as the brain was sculpted in each vertebrate radiation into an organ adapted for a particular niche. Parcellation may have played a part in this, and even a small part would make it an important process to understand. But the evidence presented thus far, in this paper and in much of the recent comparative literature, does not mark it as *the* major process in neural evolution. Parcellation's appeal does not lie so much in its ability to explain patterns of organization, but in its comfortable congruence with our preconceived notions that early vertebrates must have been poorly constructed creatures with a diffuse and unreliable functional organization. In this respect, the parcellation model is a reversion to the linear perfectionist models which Ebbesson himself helped to tear down.

The mammalian spinothalamic system and the parcellation hypothesis

W. D. Willis, Jr. and Golda A. Kevetter

Marine Biomedical Institute and Departments of Anatomy, Otolaryngology, and Physiology and Biophysics, University of Texas Medical Branch, Galveston, Tex. 77550

The parcellation (segregation-isolation) process described by Ebbesson provides a useful framework for the interpretation of studies of the organization, phylogeny, and ontogeny of the mammalian spinothalamic system. It seems reasonable to hypothesize that the three thalamic zones in which spinothalamic tract (STT) cells terminate in the monkey, the ventral posterior lateral nucleus, the medial part of the posterior complex, and parts of the intralaminar complex (Mehler, Feferman & Nauta 1960), may have evolved by a segregation–isolation process. Our anatomic data from work on the rat show that 15–20% of STT cells send collateral projections to both the ventrobasal complex and the intralaminar region of the thalamus (Kevetter & Willis 1983), and electrophysiologic evidence from experiments on the monkey suggests a similar arrangement (Giesler, Yezierski, Gerhart & Willis 1981). The presence of collaterals from some STT cells to different parts of the thalamus is consistent with Ebbesson's hypothesis. Such collateralizing cells presumably represent a transitional condition, and non-collateralizing cells may demonstrate isolation of circuits by loss of collaterals.

However, it is difficult to account for the apparent absence of spinal neurons that project directly to the thalamus in cyclostomes, teleosts, and anuran amphibians and their presence in at least some elasmobranchs, reptiles, birds, and mammals (reviewed in Kevetter and Willis, in press) if connections do not arise *de novo*. It is conceivable that direct projections actually do occur in all classes of vertebrates but that they have so far been overlooked. However, many of the recent experiments that have failed to show such direct connections have employed the most sensitive methods currently available. Alternatively, directly projecting STT cells may represent an exception, along with the corticospinal tract, in systems that otherwise fit the parcellation hypothesis. The connections to the thalamus may represent an extension of an ascending chain of neurons that in the primitive condition formed a spino–spinoreticular system, as discussed in Kevetter and Willis (in press).

With respect to the laterality of the STT system in mammals, two ideas emerge. According to Ebbesson, the primitive spinothalamic system would be a diffusely projecting, bilateral system. Evolutionary pressures would result in loss of inappropriate connections. For instance, it would be a reasonable

hypothesis that the largely contralateral projections of spinothalamic tract neurons in the cervical and lumbosacral enlargements of the rat, cat, and monkey (Carstens & Trevino 1978b; Giesler, Menetrey & Basbaum 1979; Kevetter & Willis 1983; Willis, Kenshalo & Leonard 1979) represent a specialization related to the sensory requirements of the extremities in these manipulative species. The larger proportion of ipsilaterally projecting spinothalamic tract cells in the sacral spinal cord of the monkey than in the lumbosacral enlargement (Willis et al. 1979) is consistent with the relationship of these cells with the sensory requirements of midline structures, such as the tail. A still more primitive organization may exist for a population of spinothalamic tract cells first described by Carstens & Trevino (1978a) in the uppermost cervical segments of the cat spinal cord. These investigators showed that neurons in Rexed's (1952) laminae VII and VIII in the upper cervical cord project to either the contralateral or the ipsilateral thalamus. In fact, in the rat, some of these neurons send collateral projections to both sides of the thalamus (Kevetter & Willis 1983). Furthermore, many of the neurons in this nucleus in rat and monkey also project to the rhombencephalic reticular formation, in part by collateralization of spinothalamic axons (Kevetter, Haber, Yezierski, Chung, Martin & Willis 1982; Kevetter & Willis 1983). Perhaps this nucleus can be regarded as a vestige in mammals of the primitive spinothalamic system, with diffuse connections to the reticular formation and thalamus bilaterally.

In conclusion, Ebbesson has provided us with a useful working hypothesis for interpreting the evolution and functional organization of nervous system pathways. We hope his target article will encourage neuroscientists to use available techniques, such as immunocytochemistry and double labeling paradigms, to examine the spinothalamic and other systems in a variety of species in different classes of vertebrates.

Yes, but what is the basis of homology? An invertebrate parallel

J. Z. Young

The Wellcome Institute for the History of Medicine, London NW1 2BP, England

There has been all too little discussion of the evolution of the brain. I can remember evening sessions in 1935 when Professor Judson Herrick explained the intricacies of the salamander brain to David Bodian and myself over cans of beer. He emphasised that in the absence of similarly detailed work on other classes of vertebrate, evolutionary speculation was impossible. Ebbesson has followed a rather different track, but the need for data for the study of evolution has been filled by his splendid work and that of Karten, Northcutt, Webster, Diamond and others, using the approach and the methods pioneered by Nauta and Cowan. With these data it is now time for syntheses such as that of Ebbesson's target article. At first they will have to be tentative and rather speculative, as were, for instance, studies of the comparative anatomy of the skull earlier in this century (Goodrich 1930). Refinements in the understanding of the evolution and homologies of the skeleton have come from palaeontology, which is hardly available for the brain, and from function and embryology and morphogenesis. Ebbesson here uses function, in the form of connectivity, to an extent which could be dangerous. Of course patterns of connectivity must depend upon patterns of morphogenetic factors, but it is unfortunate that we know so little about these in the nervous system. If "true homology" has any meaning, it will be found in common descent, as witnessed by common genes and morphogenetic systems.

In view of our ignorance, I find it rash, though stimulating, to postulate that sprouting fibres grow into ancestral pathways. Arguments about recapitulation set many traps, especially where little is known about the genetics and embryology that are involved.

Arguments from function have other dangers. Ebbesson says that "some primitive species *may* have several specializations" (italics mine). Surely they nearly *always* have them. Again, with "finer tuning . . . extraneous inputs are reduced." How do we know that they were "extraneous"? The argument that some parts of the body are redundant or superfluous has often proved faulty. What about the pineal?

Finally, an invertebrate parallel. The nervous system of *Nautilus* has exactly the "primitive" characteristics postulated by Ebbesson (Young 1965). There is none of the differentiation into distinct lobes with special functions that is found in modern cephalopods. Again, the inferior frontal system of squids is a simple structure out of which the complicated touch-learning apparatus of an octopus has become differentiated. There are surely many more examples throughout the animal kingdom to witness the rich generality of Ebbesson's concept of "parcellation."

Author's Response

An update of the parcellation theory

Sven O. E. Ebbesson

Department of Anatomy, Louisiana State University School of Medicine, Shreveport, La. 71130

Having decided years ago that it was proper to publish, every ten years or so, a summary of my work and ideas, I published a working hypothesis under the title of "The Parcellation Theory" in 1980. I thought I saw a common denominator, an explanation for widely scattered observations in the fields of comparative neuroanatomy, neurophysiology, developmental neurology, experimental neurology (plasticity studies), and evolutionary biology. The present target article was written two years after the first paper, with the conviction that I was on a useful track but with the full comprehension of the dangers of drawing conclusions from such widely scattered observations. The real reason for publication in the present format was a hope that good reasons for rejecting the theory might be turned up or that additional supportive models or evidence might surface. Considering the tremendous number of publications over the years on all neuronal connections in vertebrates and on their ontogenetic development, I felt certain that I could have overlooked some relevant data.

Having now reviewed some of the reaction to what I wrote, I must say that I am pleased with the result. Not only have we gained many additional insights through the open peer commentary process, but we have also learned about the limitations of my generalizations and identified areas where additional work is needed. The overall confidence in the original hypothesis has been strengthened, and the theory has been modified as more data and insights have become available. This process will no doubt continue over years to come, as additional information becomes available. I am indeed grateful to all the commentators for responding so thoughtfully to the target article, and I hope more will respond in later Continu-

ing Commentary as significant data or insights become available.

Of the 24 commentaries received in this first round, 19 are positive about the theory and provide a collection of additional supportive information. There are challenges to three of the models I have used; I shall deal with each of these separately. Furthermore, five challengers believe that segregation-isolation-parcellation (SIP) either does not occur in evolution and ontogenesis or is of little significance. Since these five commentators apparently also believe that ontogenetic studies tell us little about evolution, I will deal with these together at the end of my Response.

Segregation-isolation-parcellation (SIP) is one of several processes in the ontogenetic and evolutionary development of the nervous system. Considering the data in the target article together with the models provided by the commentators, we can now identify the following components of progressive development of the neural systems:

1. There is a *proliferation of neurons* (there seems to be an inherent capacity to overproduce neurons, comparable perhaps to the overproduction of species that Darwin noted).
2. Increased differentiation is associated with increased *migration* of neurons.
3. Increased differentiation is associated with selective changes in connections, that is, *segregation-isolation-parcellation* (SIP). Some connections (synapses) of daughter cells or aggregates are increased from a given source; others are diminished (or lost) due to given selective pressures.
4. One result is selective cytodifferentiation (*cytodiversification*, or the evolution of new species of neurons).

Ontogenetic development is similar and appears to involve the same components, however, steps 1 and 2 are often accompanied by an exuberance of axonal growth.

The above factors in progressive evolutionary and ontogenetic differentiation and development are, of course, only parts of the picture, since regression, or the opposite, can also occur as a result of selective pressures.

The logical theoretical starting point for chordate CNS development is a short, thin-segmented, poorly differentiated, neural tube in a relatively small animal. With short distances between all neurons, connectional configurations would have been relatively diffuse and responses to stimuli generalized before receptor differentiation and diversification allowed selective responses to particular stimuli.

The individual responses. A very important insight into the relationship of old and current views of morphological evolution and how they relate to the concepts described in the target article has been provided by **Alberch.** I am frankly relieved that I did not overlook some vital datum or concept previously published by evolutionary biologists that runs against the grain of my working hypothesis.

Alberch points out the need to understand what the mechanisms that control change in neural circuits are and whether the change is gradual or discontinuous. My guess is that change can occur either gradually or discontinuously, depending on the system in question. Since changes in neural circuits presumably relate to changes in behavior, it is not difficult to imagine, for example, that circuits related to reproduction might change more slowly than those related to some visual movement detection. We also know that some behavioral traits are highly heritable; for instance, every farmer knows that the introduction of one aggressive, "crazy" bull into his herd is likely to result in future generations of similarly aggressive offspring. Thus behavioral changes can be extensive in just a few generations, and it is not difficult to imagine that such changes can result in further changes, for example, related to invasion of new environmental niches.

I mentioned that neural circuits are the basis for behavior, but it must be said that we know very little about exact relationships. For example, we have no idea about the significance of ocular dominance columns, yet these have evolved independently several times. Neither do we understand by what mechanisms such SIP occurs in ontogeny or how the new character becomes a genetic trait. Here we come to one of the most interesting issues: genetics versus experience, and how selective pressures ultimately affect the genetic changes that result in a genetically programmed SIP.

Bullock's comments are especially welcome because they cover points of particular importance for comparative neurology. For example, he points out the need to distinguish between homology, homoplasy, etc. in nervous system structures. I wholeheartedly agree and wish it were as easy as some believe. We simply do not have the data to make such designations now. There are a number of competent neuroanatomists today who without hesitation draw lines around structures and apply labels from other vertebrate groups, "designating" homologies on the flimsiest evidence. Needless to say, this tendency is dangerous and counterproductive. I believe that it is in the interest of our science to be conservative with labels until more reliable information is available. My own philosophy has been to use someone else's nomenclature if the species in question has been studied before, and if I study a new animal with structures of unknown relations to those in other vertebrates, such as the central telencephalic nucleus or the central thalamic nucleus in the nurse shark, I simply give those structures new, noncommittal, tentative labels in the hope that future work will provide more meaningful names.

We must also realize that at this time comparative neuroanatomists use a diversity of criteria for identifying homologies, etc. Some rely heavily on cytoarchitecture, histochemistry, topology, or connections. My own working hypothesis is that connections provide the best criterion (but the other factors are also important).

Bullock also stresses the need for making a distinction between comparing two closely related species and comparing two very distantly related species. There is no doubt in my mind that this is an important consideration, and I believe the proof for the SIP theory must come from comparing closely related species in a given family as well as repeating similar comparisons in other classes. If the SIP process is comparable in all classes we can assume that we are indeed dealing with a general, basic principle of evolutionary and ontogenetic differentiation. More about the proof has been given elsewhere.

Calvin makes an important point by stressing that the reciprocal of loss is gain, that is, that when some connections are lost in SIP we must assume others increase their

potency, hence there is increased dominance by a given system. We must distinguish, however, between increasing the number of neurons and increasing the number of synapses in the model Calvin refers to. It is possible to increase "potency" by either or both. I agree with Calvin that the mechanism for increased brain size in hominid evolution must be related to heterochrony, as Gould (1977) has suggested. My intuition, however, is that unknown (foreign) connections are not brought into the circuits subserving the behavior in question, as Calvin suggests, but that instead additional neural elements (neurons or synapses) are derived from their ancestors and that the behavior is further served by progressive fine tuning of the circuits by a mechanism of SIP.

Clarke finds my theory hard to test. It is – mainly because an incredible amount of data has to be collected, both from studying many systems in adult specimens of closely related and distantly related species and from suitable ontogenetic studies. What makes it even more difficult is that we will often have to sharpen our tools and use, for example, electron microscopy to ascertain given connections.

It is not as hopeless as it appears, however, even though much of the evidence will be circumstantial. Our understanding of such phenomena as ontogenetic SIP of geniculate neurons and ocular dominance columns and "callosal-free" areas of the neocortex constitutes excellent evidence for the theory. The universality of the theory will require the study of many more models, however. The circumstantial evidence for the evolutionary progression of SIP provided by **Ito** is a powerful piece of supportive evidence. I do believe that all the examples given so far constitute reasonable evidence.

Clarke prompts me to state the conditions for falsification, a task I am not entirely up to because of the relatively meager data available. Nevertheless, I will attempt to do so. I have stressed that we need to distinguish between qualitative loss and gain of connections in ontogeny and evolution. This version of the theory is less strict than the 1980 one in that I now want to consider invasion as a (perhaps rare) possibility. Since I am eager to make a meaningful description of what in fact happens (or appears to happen) in nature, I find now that flexibility in the definition is of the essence. I therefore suggest that the parcellation (SIP) theory can be falsified at three levels:

1. Ontogenetic or evolutionary parcellation (SIP) is not an operating mechanism (or result) of differentiation in any system if it is not found in any system.

2. Ontogenetic or evolutionary parcellation (SIP) is a limited operating mechanism (or result) of differentiation if found to occur in a limited number of systems.

3. Ontogenetic or evolutionary parcellation (SIP) is a general, universal operating mechanism (or result) of differentiation if found in all systems.

The dilemma at this time is that models currently suggesting the rejection of SIP under condition (3) are all based on insufficient evidence. It is possible that the day will come when we have overwhelming evidence for (3) but only limited, controversial, and circumstantial evidence against the theory. If that time comes, we will, one hopes, be able to restate the theory and the falsification criteria.

Clarke's points about the apparently contradictory data on retinopetal connections are well taken. I certainly cannot explain the variability at this time; I can only suggest that we continue studying other species until we have a better picture. Considering that only a handful of species have been sampled, I think it entirely possible that a more meaningful picture will evolve. Clarke is right about the nervous system of lampreys being very specialized. We certainly cannot use modern cyclostomes as a demonstrated reference point in terms of primitive characters, although there no doubt are some. The question is: which?

My initial answer to **Demski's** question, expressed in his commentary title – "Can parcellation account for the evolution of behavioral plasticity associated with large brains?" – is: only partly. As I pointed out, SIP is only one of several operating mechanisms for achieving the functional capacities of large, well-differentiated brains. Another is increase in the number of neural elements (be they neurons or synapses), as Clarke (1981) has so eloquently described. Repetition of cells or characters, apparently, is easily accomplished genetically.

I really do not like the use of the term "primitive species" because it leads to the misconception that we will always find clues about ancestral organizations by studying such species, no matter what the evolutionary lineages are. This is not so, especially since brain structures are related to behavior; and of course we do not know the history of evolution of behaviors in relation to structure of any given species. The logic I have used in discussing primitive brain characters is not as circular as it perhaps seemed from the way I expressed it. What I meant was that the probability of finding a primitive feature in a particular species depends on (1) the evolutionary lineage, (2) what system is studied, and (3) the relative number of relevant primitive characters the species has. Thus it is unlikely that we will learn much about the evolution of man's superior colliculus by studying a highly specialized teleost optic tectum. In fact, if we look for ancestral features we must probably always go first to closely related species with less differentiation of the particular feature we are studying and second to more distantly related species with poor differentiation of the feature studied. The best data, in my view, are those based on the broadest possible spectrum of vertebrates in conjunction with an analysis of the organization of closely related species.

Teleosts have both primitive and advanced CNS features. The optic tectum in most teleost species is very specialized, yet other structures may have primitive features. I am afraid **Demski** misunderstood me with regard to citing "examples [that] represent true evolutionary lineages." It should be pointed out that it is often difficult at this time to ascertain what is a primitive character in the brain and what is not. The parcellation theory defines such characters only indirectly.

Demski and **Bullock** bring up the provocative idea of "interposition of interneurons" during evolutionary development. My intuition is that this does not happen except as indicated by the model I proposed earlier (Ebbesson 1980b; 1981), that is, SIP, but that of course does not mean that I am right. I would love to see someone develop solid models for such mechanisms. The pons, for example, may not be "new" as Demski states. There is a good chance that in some cold-blooded verte-

brates some undifferentiated metencephalic neurons, which have telencephalic input and project to the cerebellum, represent primitive pontine neurons.

Diamond's response was most welcome as he has in great measure influenced my thinking about brain evolution. His paper with Hall (Diamond & Hall 1963) contributed greatly to the formulation of the parcellation theory. He reminds us of Bishop's monumental contributions, especially his important insight that "new" fiber systems are characteristically composed of heavily myelinated, large diameter axons. Bishop's famous paper of 1959 basically outlines our concepts of nervous system evolution over the last 25 years. His insight that the heavily myelinated fiber systems are "new" in evolution has gradually been revised as evidence for their existence in lower forms is obtained. Bishop's figure 3 (p. 98), for example, schematically shows such "new" pathways ascending from the spinal cord, as well as the "primitive" thin-caliber pathways. The fiber systems indicated as "new" are the medial lemniscus and the dorsal spinocerebellar system. Since both of these are now known to exist in at least some poikilothermic vertebrates (Ebbesson 1967; 1969; 1978), it is likely that Bishop's conclusions about "newness" were incorrect. The pathways must have existed long before mammals.

Bishop came to his idea of newness of certain systems from the then available data on many systems. His account follows, in general, Herrick's (1948) interpretation; he thus writes, for example, that the mammalian neocortex evolved from a portion of the primitive pallium, within the olfactory sensory system, when it became *secondarily* connected with the thalamus. The evidence against this invasion of nonolfactory inputs to the telencephalon is now extensive (Cohen et al. 1973; Ebbesson 1980b; Ebbesson & Schroeder 1971) and is one of the findings that precipitated the parcellation theory. The conclusion now expressed in the target article about newness (in terms of existence) of pathways is exactly the opposite to Bishop's, in that I believe that the new data point to an equally early origin (in terms of evolution) of the sensory pathways in question, but that the various degrees of development (including SIP) of a given system relate to specialization and isolation of function. Classification of neural systems in terms of how old a system is, that is, "archi," "paleo," or "neo" is therefore often misleading. What Bishop, for example, refers to as paleo and neospinothalamic pathways may be of the same age, since both pathways have been identified in several cold blooded vertebrates (Ebbesson 1967; 1969; 1976b; Ebbesson & Goodman 1981). In fact, the so-called neospinothalamic systems are better developed than the so-called paleospinothalamic system in some primitive mammals (Jane & Schroeder 1971).

Progressive evolutionary development, including SIP, is correlated with changes in certain quantitative relationships. One of these is increase in fiber diameter and myelin sheath in some systems. Such increases also accompany (to an unknown degree) evolutionary body growth, a phenomenon related perhaps to maintaining proper conduction times. The new insight is that the large axons are not "new" but rather ancient, thin fibers that have thickened to fulfill their specialized role in the given function(s) of the circuit. The logic of this is simple enough.

First, thick axons (and their related cells, etc.) do not appear *de novo*, that is, evolve from nothing. Second, it is logical that small, unmyelinated fibers represent a more primitive grade of development than large heavily myelinated ones. It is also an obvious conclusion that the latter evolved from the former, certainly not the other way around. It is important to note, however, that such progressive development is not always a predictable result, as specialization of a given neuron population may involve a change in role within a given circuit. This could lead to loss of axonal branches or decrease in fiber diameter, or both. For example, neurons may lose a long, thick axonal branch and keep a short, thin one, perhaps converting the neuron to an internuncial type. I know of no specific example, however, that supports this purely hypothetical scenario (see Ebbesson 1980b).

Bishop also made the interesting observation that increase in fiber diameter may have evolved peripherally first and that new large-caliber systems were added more and more rostrally. Such a rostrally directed progression has also been described in relation to parcellation (Ebbesson 1980b and in the target article) and is thought to reflect increased specialization and diversification of receptors, followed by a centrally progressive SIP related to the increased fidelity of a given function.

The reservation **Diamond** has about my emphasis on the importance of the role given to loss of fibers in the theory is understandable, as I apparently did not articulate well the concomitant increase in input from other (existing) sources. In the case of the proposed model of parcellation of DLOC into the pulvinar (nucleus lateralis posterior) and lateral geniculate nuclei, I envisage the cells in the primitive organization as having inputs from both retina and tectum before SIP, but direct evidence from electron-microscopic studies is still lacking.

Ewert has provided us with a beautiful model of how parcellation may take place, although we fully understand that modern urodeles are not ancestral to anurans. We understand that the urodele may in this case present us with a model of organization comparable to that found in primitive anurans. I am also pleased to see that Ewert uses the theory to predict an evolutionary sequence. There is no reason not to, as long as we understand that it is only tentative until more data are generated.

Ewert is one of the very few who bridge the gaps between behavior, electrophysiological response characteristics, and anatomy in his own work. It is therefore not surprising that his results appear so much more meaningful than pure morphological studies. If we do not use this approach more extensively in the future, I am convinced that we will be groping in the dark much longer than necessary.

Falk has viewed the theory from a vantage point so different from mine, yet our conclusions mesh; the puzzle comes together. I am glad that the theoretical framework (of SIP, growth, and migration) allows certain predictions for paleoneurologists.

Fritzsch believes that the ontogenetic and phylogenetic data indicate that invasion is as major a shaping force as SIP in the development of the nervous system. He reasons that since "nerve cells originate from neuroectodermal cells with only short processes" and that since "the neuroblasts spill out their processes to reach their targets," invasion must be an important aspect in

the early phases of neural development. This describes the ontogenetic sequence correctly, but surely does not describe the evolutionary sequence (see Ebbesson 1980b). Although I do not know of any direct evidence for or against this proposal as far as evolution is concerned, I am not convinced that, for example, neurons did not innervate muscles in our most primitive ancestors or that the retina was not in intimate connectional relationship with the brain in our ancestors at the time the earliest eyes evolved. Needless to say, this happened long ago, long before modern vertebrates evolved; and direct evidence about the earliest neural systems will be hard to obtain.

The data **Fritzsch** introduces as evidence for evolutionary invasion (the retinopetal fibers originating in the olfactory bulb and the retinofugal projections to inferior colliculus and to piriform cortex in mammals) are still too sketchy to provide solid evidence against the theory. We need much more data before this can be evaluated. With regard to the direct retino-inferior collicular projections, Meyer, Scheich, and I have indeed seen such projections in several teleost species.

Fritzsch also proposes that acoustic nuclei are invaded *de novo* by acoustic afferents in evolution, thus introducing the acoustic modality in vertebrates. The data may be confusing at this point, but I cannot accept this argument until many more comparative data are obtained (see also **Ito**'s commentary). As I have stated before, the most likely sequence of evolution of a new modality is the initial specialization of receptors that become responsive to a new category of stimuli in the environment but utilize existing central connections. Further development of selectivity in the system and increased utilization by the animal in its behavior must involve an increase in number and specialization of receptors and related neural elements as well as SIP. The latter process appears to proceed from the periphery centrally, synapse by synapse, in evolution (Ebbesson 1980b).

Innocenti has correctly identified the difficulty with showing the theory to be true or false. As I have said above, the best we can do is to systematically compare closely related species, both as adults and by studying the ontogenesis of a particular feature. For example, the extension of Innocenti's important work to a sample of primates would be exceptionally useful. The validity of the theory must rest primarily on circumstantial evidence, and I am therefore most grateful to Innocenti for pointing out several additional potential models for the developmental loss of connections. I think it particularly noteworthy that there is evidence that some axons (perhaps collaterals) are lost without neuronal death.

Innocenti identifies the following additional potential models of SIP:

1. the developmental loss of fibers in the supraoptic decussation of the chick (Rogers & Ehrlich 1983);

2. the loss of transitory callosal projections from auditory to visual cortex in the kitten (Clarke & Innocenti 1983);

3. the loss of transitory ipsilateral projections from auditory to the visual cortex (suggesting that association and callosal connections may develop in a similar way (Clarke & Innocenti 1983).

I do disagree with **Innocenti's** conclusion that a diffusely interconnected neocortex (in an ancestral mammal) necessarily meant that the ancestor had "severe difficulties in making any use of it." I think that depends on what the problem was, but in general, it stands to reason (and experimental verification) that a larger, better-differentiated (i.e., via SIP) neocortex has distinct value.

Ito introduces additional, wonderful possible models of evolutionary SIP:

1. In the case of the corpus glomerulosum pars rotunda, he describes examining some 125 teleost species and finds a range of variability in the specialization of the dendritic trees of two kinds of neurons (what I refer to as cytodiversification). He also describes a model for another obviously important trend namely, that the degree of differentiation and size of one structure is often correlated with the size and differentiation of other intimately connected cell aggregates (Ebbesson 1980b; 1981). He also provides an important example of migration (displacement) of some neurons in association with the degree of development and differentiation of the system as a whole.

2. The vertical parcellation of the vagal lobe in some teleosts seems to be closely related with segregation of inputs, cytodiversification, and specializations of outputs.

3. There is overlap of acoustic and lateral line mechanoreceptive inputs in a thalamic center of the catfish (Finger 1980; Finger & Bullock 1982).

Ito also points to the apparent curious absence of (1) a direct retinogeniculotelencephalic pathway in teleosts and (2) spinothalamic pathways in teleosts, to which I have no good answer (Ebbesson 1980b). It should be pointed out that such pathways exist in sharks; the only explanation I can think of is that the optic tectum is exceptionally well developed in teleosts, in both size and degree of differentiation, and that the absence of the pathways in question is indirectly related to this. There appears to be a good correlation between the degree of development and the probability of absence of a given connection (Ebbesson 1980b).

Kaas has provided a thoughtful commentary on possible mechanisms for the evolutionary increase in neocortical subdivisions, and, considering the available data, I have little to add. Several interpretations are obviously equally valid at present. **Innocenti's** observations and comments are clearly important in relation to interpreting Kaas's suggestions.

I think that these experiments, similar to those carried out by Constantine-Paton and Capranica (1975), tell us relatively little about "normal" development of pathways because completely "abnormal" growth is precipitated by translocating eyes in embryos. They are obviously important, however, in understanding many other mechanisms.

It is important that **Kaas** notes that the early impressions of "graded" degrees of separation of modalities in the cortex of various mammals may indeed be incorrect. Obviously many more animals need to be studied, as adults, and especially during development, before we have a more conclusive picture. A mechanism (for producing multiple cortical fields) not suggested by Kaas is the possibility of pushing the deviation of the segregation backward in ontogenetic development.

Kaas refers to mine as "the gradual differentiation hypothesis" as he envisions his "replication of existing parts and connections" from one generation to the next.

As Kaas emphasizes, there is no evidence that his model of replication occurs, but I agree with him that it is possible. The big problem not explained by either his theory or mine is how mirror fields are formed and how the information makes sense in the ultimate integration. I think there is an urgent need for more developmental material.

I agree without reservation with **Koenderink's** comments; they add another important dimension to the logic of the theory, particularly as it is related to biological systems in general. Surely, structural parcellation, or specialization, must be related to changes in environment and the selective pressures resulting from such a change. It is sad that today, with superb scientific tools, we have hardly an instance of reported correlation between brain structure and functional significance (see **Ewert** for a possible exception). Surely there are few areas in science that deserve more attention.

MacLean's comments are especially appreciated because he is one of the few commentators with both a broad experience in neurophysiology and the historical background to interpret the theory. I am glad that he and others like **Bullock** and **Ewert** see the logic of the idea, especially as it is related to the evolution of fine tuning of neural processes and the reduction of "noise." Such concepts are logically necessary and must coincide with the evolution of other variables.

I find **Ramon-Moliner's** logic seductive, as usual, and I appreciate that we are on the same wavelength. His highly imaginative work on the variability of dendritic structure has always remained in the back of my mind as my own work has progressed. Ramon-Moliner's comments on the target article speak for themselves, but I would like to emphasize a very important point: The reciprocal of loss is reinforcement of connections. As he states, "we are not merely dealing with the loss of connections but also with the reinforcement of those connections which natural selection sanctions as particularly useful for survival." I do not share his interpretation that "interhemispheric connections are . . . new," however, for I believe, tentatively, that the corpus callosum of higher mammals is homologous to the interhemispheric connections between neocortical equivalents of all vertebrates, no matter which route they take.

Schneider's commentary brings into focus several issues important to those concerned with ontogenesis and plasticity of neural pathways. It should be clear to those who work in this area, as well as to comparative neurologists, that our data are highly interdependent. An understanding of ontogenetic mechanisms is important because evolutionary changes occur by changes in ontogenetic development (deviations). I am therefore very grateful to Schneider for clarifying some of these relationships as well as showing how our data appear to mesh.

Schneider discusses the molecular basis for synapse formation, which is certainly one of the key issues today. His pioneering work in this area has profoundly affected our understanding of plasticity of neural connections. His data and theoretical conclusions point to selectivity and specificity in the mechanisms underlying the guiding of axonal sprouts and synapse formation. One aspect with which he has dealt relates to changes in quantitative relationships during sprouting. I, myself, have often wondered what controls the number and site of synaptic terminals. Does the size of the receptive neurons determine the number of synaptic contacts, or vice versa? For example, do homologous Betz cells in humans and in a small primate have the same number of synaptic inputs, or do the larger human neurons require more inputs and hence more presynaptic neurons? One can guess that it takes more synapses to control the firing of a large neuron, all other factors being equal; yet how does this relationship evolve? Is this one of the reasons for the disproportionate increase in the numbers of small neurons in large, well-developed brains?

There must be selective mechanisms for acceptance or rejection of synaptic contacts, related to the ultimate activities of the neuron. As pointed out in the target article, the proper synaptic relationships are necessary for optimal functioning. This means that excitatory and inhibitory inputs from various sources must balance and interact in such a quantitative and temporal manner as to result in an output that is useful to the animal. Random connections would therefore not satisfy highly selective circuitry functions, hence one could perhaps predict an increase in the mechanisms for selective affinity in more parcellated circuits. It seems to me that the output (eventually the behavior) would influence the input since that would have survival value. But, on the other hand, there appears to exist a strong inherent capacity for receptor specialization and diversification that responds to increased sensitivity to the great variety of external stimuli on the organism. This brings to mind the interesting putative sequence of the evolution of man. Gould (1977) points out the very interesting relationship of the retarded ontogenetic development in man to the evolution of the species. There is a further parallel that comes to mind: the delay in evolutionary time in which our ancestors have been exposed to various stimuli, especially visual. The data suggest that our first mammalian ancestors were small nocturnal insectivores from which our presumably nocturnal early primate ancestors evolved. The resulting exceptionally long "evolutionary incubation" before emergence into the sun, and the numerous deviations that followed in this stimulating environment, may be one of the reasons for our good brains. In this case, specialization (and SIP) came late on an undifferentiated multipotential matrix that by luck used the cortex for development and integration of the new sensory inputs.

Reading **Schneider's** commentary, one realizes that however increased parcellation expresses itself, in terms of expanded terminal arbors, and so forth, the increased parcellation should have survival value (although not necessarily always, as genetic control may not always be perfect) and the result of SIP should be greater fidelity in the given function(s).

Schneider brings to our attention an example of abnormal sprouting that appears to contradict my prediction that such sprouting may be limited to reestablishment of connections lost in evolution or ontogeny. He describes "abnormal" retinal projections to the thalamic ventrobasal nucleus and to the medial geniculate nucleus after neonatal tectal ablation. I am glad to respond that exactly such connections may indeed exist in lower vertebrates as we have seen a diffuse overlap of retinal, cerebellar, and spinal inputs in the shark thalamus. Whether the overlap occurs on any given thalamic neu-

ron is not known as neither electrophysiological nor electronmicroscopic studies have been carried out.

The wisdom of **Szentágothai** reflects his long experience as a pioneer neurobiologist. Dealing with the issue of cytodiversification, he adds a very important model: the correlation between increased specialization and increased separation of arborization spaces (Szentágothai & Arbib 1974). Examples are found in the inferior olivary nucleus as well as in the lateral dentate nucleus of the cerebellum. He also makes the important point that increased specialization of the dendritic tree does not always mean increased homogeneity of input.

Willis & Kevetter review some of the best-studied systems, the spinothalamic systems, in various vertebrates and the possible significances of collateral fibers. They also note the problem for the theory presented by the absence of direct spinothalamic fibers in cyclostomes, teleosts, and anurans, to which I have only an inadequate explanation (see my response to **Ito** above). I do not think that we should take the negative data from one species of cyclostomes too seriously; first, because of the many specializations in the brain (which, according to the theory, imply certain losses of connections) and second, because of the poor quality of the histological material on which the preliminary conclusions were made. I pointed out earlier that it is quite possible to miss entire pathways with silver degeneration techniques if the axons and terminals are small enough, which is quite possible in this case (Ebbesson 1970a). The data from teleosts can be judged in the same way, and the sample is entirely too small to be meaningful. Fishes with more primitive characters have to be studied, not only with more sensitive methods, but by ontogenetic approaches. There are spinothalamic projections in anurans (Ebbesson 1976b) and at least in some sharks (Ebbesson 1976; Ebbesson & Hodde 1981).

Willis & Kevetter also introduce more important evidence for the presumed primitive bilateral ascending spinal projections. The evidence for bilaterally projecting individual neurons in rats is indeed in harmony with the theory. The fact that some of these neurons project to the reticular formation as well certainly distinguishes these neurons from those related to the innervation of extremities.

Young adds depth to the discussion by giving examples of possible traps that I may have fallen into. I certainly cannot argue with these and can only hope that my exuberance has not allowed me to fall into too many. The questions he raises are logical and I don't have any good answers for them. What exactly is the advantage of certain cortical regions lacking commissural inputs, or certain layer 4 cells in visual cortex developing a loss of input from one eye or the other? There are no good answers because we do not know precisely what the neurons do with the inputs.

The example of *Nautilus* is important because this organism dates back far beyond modern vertebrates. I regret that more of my colleagues working with invertebrates have not stepped forward and provided examples pro or con, as I have heard of many examples in favor of the theory in that part of the animal kingdom.

Five commentators – **Finger, Campbell,** and **Northcutt** and his two students, **Braford** and **Wilczynski** – are critical of the theory, and since their collective conclusions are in harmony, I will deal with them together. Some of the claims they make are:

a. The parcellation theory is not a theory.

b. SIP is not a process in evolution and ontogenesis (some concede it may play a minor role).

c. There is no relation between the observations of SIP in ontogenesis and the interspecific variability of connections.

d. The data on the variability of ascending spinal projections do not fit the theory.

e. My model of overlapping retinal and tectal input to a thalamic nucleus in sharks is incorrect.

In light of the general lack of acceptance of the many examples I have provided and the commentators' ability to read between the lines meanings I had not intended, I find it difficult to respond in a meaningful way to some points and will therefore only discuss items (c) and (e) as these items seem to be at the heart of the commentators' objections. I dealt with item (d) in my answer to **Ito** and **Willis & Kevetter** and item (a) can be debated more suitably elsewhere as it must be understood that definitions of theory are highly variable and depend on the field of science. I will now respond to item (e).

It is ironic that one of the models used in the formulation of the theory may turn out not to be a good example. This concerns the thalamic nucleus (DLOC or LGN) in the nurse shark, with overlapping tectal and retinal inputs that project to a single area in the telencephalon (Fig. 5 in the target article). **Campbell, Finger,** and others point out that Luiten (1981a,b) has described two independent telencephalic visual afferent systems in the same species, and that I neglected to point that out. The omission was intentional, because I did not feel that the target article was the proper place to deal with the technical difficulties and problematic interpretations made by Luiten. However, since such a strong point is made by these commentators, I shall deal with it here.

The studies in question were performed in my laboratory and involved new methods (autoradiography and HRP) to reexamine pathways studied earlier with silver degeneration methods (Ebbesson & Ramsey 1968: Ebbesson & Schroeder 1971; Ebbesson et al. 1972; etc.). The difference between Luiten's results and mine are that he claims that: (1) the retinal fibers coursing through the lateral geniculate nucleus do not synapse in the nucleus but terminate in the ventrolateral optic nucleus (VLO) and (2) therefore two independent visual thalamotelencephalic systems exist in this species: (a) a retino-VLO-telencephalic system and (b) a retino-tecto-geniculate-telencephalic system. The problems with his conclusions are (1) one *cannot* determine in this type of preparation that synapses *are not* made; this would require verification with ultrastructural studies; (2) retinal projections to more or less the entire dorsolateral optic complex (DLOC), (called by some the dorsal lateral geniculate, LGN) have been described in all elasmobranchs so far studied with autoradiographic techniques (Northcutt 1979) and with silver degeneration methods (Ebbesson & Ramsey 1968; Ebbesson et al. 1972; Graeber & Ebbesson 1972; Smeets 1981a); (3) the long survival time (14 days with temperatures of 20°C) of his 2 (two) proline specimens may not have revealed the primary retinal projec-

tions clearly since three days at temperatures of 10°–13°C have been optimal for the terminal field (Northcutt 1979) whereas 14 days' survival are often used in mammals to show *transneuronal* projections; (4) Luiten's interpretation is further questioned because he also reports the absence of a retinohypothalamic projection described in all other studies on retinal projections on sharks; (5) he contradicts himself by stating in the summary (p. 531 and Fig. 8, p. 547) that "No evidence was found for an earlier-reported projection to the lateral geniculate nucleus"; and in the Result section (p. 534) "Except for a few terminals in the ventral aspect of this nucleus, there was never any evidence for a retinal projection to the LGN"; (6) he ignores our descriptions of tectal projections to such areas of retinal and tectal overlapping zones as the VLO (Ebbesson et al. 1972) and omits them from his conclusions and summary diagram (Fig. 3, p. 547); (7) he ignores (both by his location of injections and in his conclusion) our tentative finding that the visual input is restricted to the dorsal part of the central telencephalic nucleus (Cohen et al. 1973) and that trigeminal input, for instance, is to the ventral part of the nucleus (see Ebbesson, 1980c); (8) our electrophysiological studies, although not very extensive (Cohen et al. 1973), suggest the presence of one visual area in the telencephalon.

In this context I must also suggest that Smeets (1981a; 1981b) reports something completely different from what Luiten reported. Smeets finds the exact opposite, namely, extensive retinal projections to LGN in *Scyliorhinus canicula* and in *Raja claviata*, but tectal projections to "the dorsomedial regions of the thalamus"; he notes that "a few fibers run to the LGN," but "distinct sites of terminal degeneration . . . [have] not been found," yet he distinctly illustrates such terminal sites bilaterally and extensively in the LGN of *Scyliorhinus*. Without commenting further on these studies, it is clear that the lesions were much too small to provide sufficient data to rule out the possibility of much more extensive tectal projections than the report indicated.

My conclusion is therefore that much additional work remains to be done, with the best methods available, including electron-microscopic and electrophysiological techniques, in a number of species from all poikilothermic classes of vertebrates, before the fate of my model can be decided, but even if no vertebrate model of a pure single visual thalamotelencephalic system is found, the circumstantial evidence may suggest that such a system did indeed exist before vertebrates evolved, but is no longer found in extant species. Ontogenetic studies may provide the key pieces of evidence for it, if the visual systems evolved as I suggested.

I think it should interest the student of neocortex and neocortical equivalents that the *Bauplan* in which visual cortex is caudal to somatosensory cortex in mammals apparently exists in the nurse shark as well. Electrophysiological studies gave a hint of this (Cohen et al. 1973; Ebbesson, 1980c) as did the anatomical finding that the dorsal part of the dorsal thalamus (primarily visual) projects to middle or caudal telencephalon, whereas the presumed ventral tier homologues (central thalamic nucleus, etc.) with spinal (Ebbesson & Hodde 1981; Ebbesson et al. 1972) and cerebellar (Ebbesson & Campbell 1974) inputs project more rostrally and ventrally into the central telencephalic nucleus in the nurse shark (Ebbesson 1980c; Luiten 1981b).

Item (c) relates to the validity of learning about evolution from ontogenetic studies. The five critics of my theory do not believe this to be valid, whereas I side with Gould (1977) and others who believe that important insights can be obtained from ontogeny. Gould (1977, p. 2) writes that "Haeckel's biogenetic law was so extreme, and its collapse so spectacular, that the entire subject became taboo; otherwise no modern reviewer would begin with these words his account of a work that dared to mention it": "There are still those who would Haeckel biology" (DuBrul 1971, p. 739). My opponents **Northcutt, Campbell,** etc.) belong to the group that considers the topic taboo (Campbell being a student of DuBrul's). The topic is now indeed again open for review as it pertains to the nervous system. I am certainly not trying to revive the biogenetic law of Haeckel as he defined it, but I have simply described SIP in ontogenetic development and in association with the degree of development in adults of some species. Space does not permit a detailed discussion of the presumed relationships and how evolution is accomplished by alterations in ontogenetic development, but perhaps one example can be emphasized.

Although many examples of evolutionary and ontogenetic SIP are known, perhaps none is better documented than the development of the retino-geniculocortical system. During ontogenetic development, retinal afferents to geniculate neurons originate in both retinae before the SIP process results in monocular inputs. Primates share this segregation in common with all mammals so far examined, except perhaps the hedgehog (an insectivore), where some neurons in the lamina receiving predominantly ipsilateral input appear to have some contralateral input in the adult as well (Campbell 1972). Since complete SIP is not a feature in adult generalized nonmammalian species such as amphibians and reptiles, we can conclude that it is likely that the "deviation" of pure monocular-dependent geniculate cells appeared when mammals first appeared, and is likely to have happened when the highly layered neocortex evolved. It also seems likely that this SIP process accelerated in the mammalian lineages that became more active in daylight.

The SIP of monocular cortical columns appears to be a later evolutionary development, as, with few exceptions, only some primates, including the chimpanzee (Tigges & Tigges 1979) have such columns (see target article). All mammals, however, share ontogenetic stages in which apparently all geniculate neurons and all layer 4 visual cortical neurons have binocular inputs. The ontogenetic parcellation of ocular dominance columns therefore probably reflects (to an unknown degree) their evolution.

Returning now to individual commentaries we can consider first **Finger,** who has made several important contributions to our understanding of brain organization in some highly specialized teleosts, primarily catfish. That he has found few primitive characters is therefore not surprising, yet he appears to believe that his subjects should provide them. This need not be so, since most neural systems in fact appear "highly developed." His finding of modality-specific thalamic nuclei in some tele-

osts is to be expected, considering the high degree of specialization of the sensory systems in these species. One should not expect to find an identical situation in fishes with more primitive characters, however, especially during ontogenesis. One cannot therefore claim that Finger's catfish data do not support my theory. In evolutionary terms, such specialized animals, if also studied ontogenetically, may provide data which directly support the theory.

The discussion of olfactory bulb projections is not very meaningful without more information about many more species. For example, some sharks, more primitive than nurse sharks, have bilateral olfactory bulb projections (Smeets 1982). The Luiten experiments and the case of ascending spinal systems have been described above and will not be repeated here.

Finger suggests that the parcellation theory predicts "that all pathways found in 'higher' vertebrates should be identifiable in nonmammalian vertebrates." This does not follow, since some pathways may have been lost in all extant vertebrates. The theory predicts that *some* lost pathways may be found either in immature stages or adults of other vertebrate species. Finger's rejection of the theory is based on a number of misunderstandings and therefore appears somewhat premature.

Campbell's criticisms are less constructive and involve some misunderstanding of my position. I can only reply with a question or statement in return:

1. What studies of mine and "of many others!" show that *relatively* diffuse and undifferentiated systems did not exist in the beginning of vertebrate evolution? Of course they did (see Ebbesson et al. 1972, for example).

2. Where have I denied a role for gene and chromosome mutation? I have not made such a "remarkable assertion." By *de novo* appearance, I simply meant "evolving from nothing."

3. My work on overlapping tectal and retinal afferents in the nurse shark was not "found to be in error," as I have pointed out above. Luiten simply jumped to some premature conclusions.

4. **Campbell** completely overlooks all the models supporting the theory, such as the SIP of monocular geniculate layers and ocular dominance columns.

5. I certainly did not claim that I *discovered* neocortical equivalents in nonmammals. I described the historical sequence clearly in the 1980 version of the theory, and in the legend for Fig. 3 of the target article I clearly use the term "primitive vertebrate." Karten's contributions to our understanding of the bird brain are legendary, but have little bearing on our understanding of the origin of neocortex in vertebrates and on the issue of the invasion of nonolfactory systems into the telencephalon (see my reply to **Diamond**). It is also worth noting at this point that Karten and I have diametrically opposite points of view on the evolution of neocortex in that he envisions visual neocortex as having evolved from two, quite separate regions of the forebrain (see Ebbesson 1980c, p. 205 for details).

6. I certainly did not mean to take credit away from Scalia et al. (1968), who described limited olfactory bulb projections in the frog. Heimer and I reported similar limited projections in the nurse shark in the spring of 1968 (Ebbesson & Heimer 1968).

Much of what **Bradford** says reflects his bias against the data, something I cannot alter. He claims for example that:

1. The presence of overlap in primitive systems is not well supported.

2. I have referred to a retino-thalamo-telencephalic pathway in teleosts as the retino-*geniculo*-telencephalic pathway. I have done no such thing, since such a pathway has never been identified. I have many times objected to such terms as *geniculate* in nonmammals (Ebbesson 1972).

3. Given pathways "might . . . have been independently evolved, perhaps several times." What is the evidence for that?

4. Telencephalotectal projections may have evolved from different cell groups. What is the evidence for that? (see my conclusion below).

I have no disagreement, however, with **Braford's** description of what is not ancestral to what. The theory was written with full cognizance of such relationships. I have stated explicitly that opossums are *not* ancestral to monkeys (Ebbesson 1980b, p. 194). I agree that I have failed to discuss some alternative interpretations of the data in the target article. My defense is that these have been adequately promulgated elsewhere (Northcutt 1981).

Much of **Wilczynski's** cogent commentary does not require additional response as it is self-explanatory or has been dealt with elsewhere. I will, however, bring up his problematic case of the "retinal recipient nucleus" in anurans that projects to the medial pallium bilaterally. How can that be interpreted in light of present knowledge? Without listing all alternative explanations, one simple explanation is that this nucleus is homologous to the anterior nucleus of mammalian thalamus, since a retinal projection to the anterior nucleus has been described in the tree shrew (Conrad & Stumpf 1975). This retino-anterior thalamic projection may then represent a primitive connection, lost in many species, but retained in some.

Northcutt must know that I have no intention of resurrecting Haeckel, but I have obviously not clarified my views adequately. Haeckel overstated the case for ontogeny recapitulating phylogeny. The demise of his views was correspondingly extreme. Biology has a history of fashionable ideas which are later summarily and severely rejected. This rejection phenomenon has, I believe, been overdone with respect to ontogeny-phylogeny, and my critics are in danger of perpetrating it with the theory under discussion. Several misunderstandings are also evident from Northcutt's commentary, for example: I explicitly and repeatedly stated that I believe the parcellation process to be but *one* of several evolutionary mechanisms, not the only one, as Northcutt states. I also did not say "that it is the major one underlying brain evolution."

With respect to differentiating between homology and homoplasy, I think we need to deal with this important aspect once good examples of homoplasy in the nervous system have been described. Currently I do not know of any.

Conclusion. Various remarks about factors that govern our conclusions about brain evolution are warranted. One must realize that the various assumptions made are ten-

uous at best. These range from interpreting the histological preparations, to identifying homologous brain structures, to theorizing about how evolution occurs. It is clear that the comparative neuroanatomists interpret their results very differently.

The identification of terminal zones of a given pathway really ultimately requires EM verification, although Fink–Heimer preparations, for example, often give good approximations. Tritium labeled amino acids are very useful in many circumstances as they are often more readily detected than other methods. Yet, caution is indeed in order with autoradiography methods. Since we do not know when and where we are dealing with transynaptic transport, especially in lower vertebrates, we cannot simply assume that such transport has not taken place, even with short survival times. Furthermore, proline is *not* incorporated by some neurons (Berkley 1975; Künzle & Cuenod 1973; Molinari & Berkley 1981). It also has a tendency to use extraneuronal channels for transport in mammals (Molinari & Berkley 1981), which raises questions about the reliability of proline in non-mammalian forms.

An additional problem of interpretation of proline preparations occurs in brains of many poikilothermic animals where synapses often occur within the fiber pathway, on far reaching dendrites, belonging to neurons located some distance away. In Fink–Heimer preparations one can identify terminal boutons if they are the means of termination, but synapses *en passant* may go undetected without EM. In proline studies, on the other hand, in this situation, various indirect judgments are made to designate termination. For example, Northcutt (1979) in this instance designates a terminal zone of the optic nerves when the area is labeled after short survival times and when "grain densities [were] higher than those over the optic tract – particularly when they occurred in areas of neuropil or over cell bodies medial to the optic tract." Such criteria are somewhat arbitrary and may be misleading. It is therefore clear that future comparative hodological studies will require EM verification (perhaps in combination with the Golgi technique). Such studies will likely alter many of our current conclusions (Ito, Butler & Ebbesson 1980).

Identification of homologous structures is also often very difficult because neuroanatomists have different views on what the most reliable criteria are. My own bias has always been that connections provide one of the best clues, but that criterion is not shared by some. My bias comes from the available data supporting the SIP process as opposed to homoplasy (for example). One must distinguish here between function and structure, as it seems quite likely that any one of several brain structures may have the evolutionary potential for developing a particular analytical function without changing connections drastically, except by the internal parcellation of the given structure. There is, for example, no reason why a given feature detection is done in the retina of the teleost, in the frog's optic tectum and in the primate cortex. On the other hand, if homoplasy occurs in the nervous system as **Northcutt** and others envisage, it would be possible, for example, in some radiations, for the optic tectum not only to develop the same given function as neocortex in other radiations, but to evolve the same connections (i.e., both afferent and efferent). This could only be done by invasion unless the tectum and the neocortex had identical connections to start with.

Although **Finger, Campbell,** and **Northcutt,** and his students advocate homoplasy as an explanation for observed interspecific variability in brain organization, the data so far collected are not as strong as they suggest. In every instance, the parcellation theory offers a simpler explanation. For example, a case for homoplasy is now made for striatum and neocortex. It is suggested that a structure called the striatum in anurans and teleosts has evolved to assume the role and connections that neocortex or neocortical equivalents serve in other radiations. Several reasons are given for this, including the fact that striatum receives certain thalamic afferents (as in mammals) and that the striatum projects to the brainstem like neocortex, that is, they suggest that the striatum, in this case, has developed new afferent and efferent connections by invasion.

Such a hypothesis of homoplasy would be reasonable if one could ignore the data that support the parcellation theory. Teleosts and anuran amphibians are highly specialized groups of vertebrates that share many specializations in brain organization, including exceptionally well-developed mesencephalic tecti. Parcellation of other systems related to this development may also explain this apparent distinctive telencephalic organization. In anurans the pallium does not project to the optic tectum or the striatum (Wilczynski & Northcutt 1983), yet it does in urodele amphibians (Finkenstädt et al. 1983; Kokorus & Northcutt 1977). These authors found that both pallium and striatum project to the tectum. Since urodele amphibians appear less specialized than most anurans and have, for example, a poorly developed tectum (small, and with minimal migration of neurons), the presence of these pathways in urodeles is predictable from the parcellation theory.

With the parcellation theory, one can postulate that in the primitive common ancestors to sharks, teleosts, anurans, and urodeles, the precursors to neocortical equivalents and striatum had similar afferent and efferent connections and that the arrangements we see today reflect evolution by SIP, that is, the loss of pallial projections to striatum and tectum in anurans and (perhaps in) teleosts, and the loss of striatal projections to optic tectum and brainstem with the development of neocortex and neocortical equivalents in mammals and sharks. This suggests the interesting possibility that neocortex and the striatum may have evolved from the same structure by SIP. There are many complexities to the example given above that cannot be discussed here, such as the possibility that some of the "striato-tectal" neurons in teleosts may indeed represent neocortically equivalent cells. Such data will be discussed in detail elsewhere (Ebbesson, in preparation), but my current conclusion is that the scientific basis is weak for homoplasy occurring in the CNS.

Another controversy relates to what in lower forms is homologous to the dorsal lateral geniculate nucleus of mammals. Here again **Northcutt** and I differ. Butler and Northcutt (1978), for example, have recently provided three possible explanations for the large number of visual thalamic nuclei in reptiles. They suggest the possibility that these nuclei may represent something comparable to the laminae of the dorsal geniculate nucleus of mammals,

or that these retinal targets in reptiles do not correspond to any nuclear region in mammals. A third possibility, they suggest, is the existence of more numerous retinofugal targets in mammals than hitherto discovered. The parcellation theory offers a fourth possibility, namely, that the ancestry of the various dorsal thalamic cell groups with retinal input is the same, a single aggregate with a multitude of connections. From this aggregate evolved a variable number of parcels, each parcel different from the others because each had lost different connections, depending on selectional pressure. While some neurons lost a tectal input, others lost the input from one of the eyes, and yet others lost certain telencephalic inputs. Their outputs may also have changed, some losing a projection to a given telencephalic target, while others would lose all extrinsic projections and become totally concerned with intrathalamic circuitry.

Given these differences in interpretation by comparative neuroanatomists, I feel confident that the data will ultimately show the way, and just as Bishop's ideas were modified by new data supporting the parcellation theory, other, more meaningful theories will eventually replace the parcellation theory.

Summary. It needs to be emphasized that my conclusions are that SIP appears to be but *one* of many evolutionary and ontogenetic processes, and that invasion and homoplasy may be involved as well, but the evidence is still weak. Two parallel and strikingly similar processes have been described in ontogenesis and in evolution. To what extent ontogenetic processes reflect evolution of neural circuits is still uncertain, but the data strongly favor a correlation with increase in cell number, migration, and SIP.

The real question is not whether I phrased the theory properly, or whether I have defined the evidence accurately, but to what extent does SIP occur in evolutionary and ontogenetic development? As I see it, only additional experiments with better techniques can resolve how general this phenomenon is. I believe that SIP is a trend in vertebrate evolution which has been part of the adaptive changes that allowed animals to adapt their behavior to environmental niches whether these required specialization or stability. As such, the concept should help us understand brain evolution itself, as well as the functional organization of the vertebrate brain.

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