

Field homology as a way to reconcile genetic and developmental variability with adult homology

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ABSTRACT: The theoretical and developmental fundament of field homology is here examined, particularly as applied by the authors to comparative neurobiology. Preliminary considerations explore conceptual differences between sameness (homology) and similarity. The source of sameness (the biological evolutionary relationship properly sought in homology analysis) is thought to lie in morphostatic evolutionary and morphogenetic processes, which constrain organismal variation at the level of its fundamental structural organization (Bauplan). This occurs via regulation of the branching mode of the morphogenetic sequence or epigenetic landscape. Of fundamental importance in this context is the role of developmental (morphogenetic) fields. The latter concept is analyzed in its general properties and is postulated to underpin the stability of the developing Bauplan down to the ultimate conserved details. Developmental fields subdivide during ontogenesis into ever smaller fields in a complex hierarchy, defining at each stage the developmental entities which are subjected to regulatory, morphostatic effects via the genome and indirect phenotypic selection. These fields thus represent the natural characters for considerations of embryonic homology, and underlie adult homology, rather than arbitrarily selected embryonic parts. Field subdivision proceeds into the constitution of individually specified cell populations. Field regulatory properties, however, do not extend to all differentiation phenomena observed in embryos. This means there is a limit to the applicability of field homology analysis, leaving space for biological variation and convergence outside of proper homology relationships. Genetic and developmental variability are compensated by the regulatory functions of the developmental fields insofar as they relate to correct Bauplan construction. These ideas suggest the convenience of a more systematic use of field homology methods, which start with appropriately identified developmental fields to expand knowledge on adult homology (sameness) and eventually also on accessory structural and functional similarities or differences. © 2002 Elsevier Science Inc.

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INTRODUCTION

The term *homologue* was first employed by Owen in 1843, before the appearance of Darwin's evolution theory, to define "the same organ in different animals under every variety of form and function" [15,51,65]. After the publication of Darwin's theory of evolution, the concept of homology became a central principle in biology, because evolution theoretically explains why homologues exist. Structures in different animals are proposed to be homo-

logous whenever it is thought that the *same* structures (in some sense) were present in their common ancestor. The identification of cases of homoplasy, that is, of apparent similarities that are not traceable to a common ancestor, but are due to parallel or convergent evolution (i.e., similarity without sameness), also contributed to our understanding of evolution [30,65].

In spite of the importance and widespread use of the term *homology*, it is evident that there exist some problems with this concept. A number of authors have discussed this issue recently (i.e., [15,29,31,51,59,61,62,97–100], this issue). As noted above, the beauty of the concept of homology is that it pretends to identify biological *sameness* without requiring similarity in form or function [51,64]. That a pair of biological entities can be the same without being similar seems such a marvelously intriguing idea that it stimulates scientists now even more than 150 years ago, when it was first formulated. Therefore, every effort to explore this concept in depth and resolve extant problems seems worthwhile. We will approach this issue from the perspective of comparative developmental neurobiologists, referring in general to specific problems of neural homology. However, the ideas proposed should be valid for other biological fields.

The major problems with the concept of homology are derived from: (1) the difficulties to decide at a single level of analysis which are the *relevant features* that need to be considered for analyzing homologies, that is, how should the compared *characters* be chosen; and (2) the possible existence of different levels or types of homology (i.e., structural, developmental, molecular, iterative, functional, behavioral), and consequent difficulties to jump from one level or type to another. In other words, if two items are considered homologous at any single level, this may or may not hold at other levels of analysis. In the case of the brain there exist the same problems. This has been particularly evident in the telencephalon, which shows important variations among vertebrates, as a consequence of divergent evolution from the common ancestors [10,11–13,40,41,53,63,71,81,96]. The term *partial homology* was introduced to deal with cases of apparent homology at only one or a few levels of analysis, but not everybody feels comfortable with this concept [31].

The difficulty of establishing one-to-one equivalences and homologies of adult telencephalic and other forebrain parts among vertebrate groups led several authors to use the concept *field homology* [13,15,93]. This concept postulates that adult brain regions thought to derive in different species from homologous embryonic precursors can be considered homologous "as a field", that is, as whole sets of derivatives. It is implied that more detailed

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comparisons of the respective adult structural subdivisions within the field (i.e., nuclei, subnuclei, or layers) may not be possible, due to divergent evolution and adaptation processes. However, the field homology concept does not seem to exclude the distinction of homologous *cell types* within the field, irrespective of their number and position.

The concept of field homology can be applied in different directions, as in the case of the telencephalic pallium: the avian dorsal ventricular ridge has been variously postulated as field homologue of the lateral part of the mammalian isocortex [13], of a claustramygdaloid region [10,38,70,71,96], or of both ([14], this issue). This means that we are still unsure how to define homologous developmental entities. We do not think this reveals a particular weakness of the field homology concept that is not shared by other homology concepts (consider earlier erroneous conjectures on the structural and developmental homology of the sauropsidian dorsal ventricular ridge with the mammalian striatum; see [96] for review). Obviously, field homology relies on the solidity of the underlying embryology.

Recent criticism of field homology appears centered on two aspects: First, some argue that the definition of field homology often is too vague—i.e., the underlying embryology is adduced or assumed *post-facto*, rather than used as a starting point in the analysis. It is feared that, by this procedure, anything can be homologized to anything [62,97–99]. The implied charge is that some field homology proposals may be banal and devoid of interest, but we believe this is a risk shared by all scientific hypotheses; it is the conjectural, pregnant, and unexpectedly predictive content of an hypothesis that makes it interesting in science, not its form or precedence [67]. Secondly, there is a seemingly widespread belief that developmental homologies (or homologous developmental *stages*; [62]) do not necessarily imply adult homologies, because some homologous adult structures can be produced by non-similar developmental mechanisms (or represent a developmental stage non-existent in other species; [62]). This takes us again to the idea shared by some authors of the existence of separate, unlinked levels of homology [15,62,99,101]. The aim of this article is to address and attempt to resolve these two problems through a more detailed analysis of what the concept of field homology implies for us. This connects with the idea of using developmental fields as the basis for character selection in homology analysis. Some preliminary ideas need to be examined first.

SAMENESS VERSUS SIMILARITY¹

In following the various arguments in the literature, we often felt that ‘homology as sameness’ [15] tends to be confused with ‘homology as similarity’. As noted above, similarity in form and function is not directly relevant to establish a homology [51,56,64]. In fact, a homology proposed exclusively on similarities detected at one level of analysis (behavior, function, form, developmental process, molecular substratum) is clearly not sufficiently supported and may be wholly erroneous, due to the possibility of homoplasy. On the other hand, some very non-similar structures are accepted to be truly homologous (i.e., the vagal lobes of some teleosts as homologues of the solitary complex of mammals).

If we cannot rely on similarity of form or function to define a homology, which are the reliable criteria we should follow? There are at least two, which go hand in hand. In principle, a reliable analysis of sameness must be done within a topological framework, which first establishes the fundamental comparability of the

forms studied, and then allows detailed analysis of the characteristic relationships of the diverse structural parts in morphospace [44]. Comparison of non-comparable elements is meaningless. Topologic morphological comparisons are fundamental for the taxonomic classification of living animals and their extinct ancestors, and, therefore, also for homology proposals.

In addition, it has been long thought that similarity in developmental processes should complement the topological argument, adding a causal line of reasoning, potentially enriched today with biomolecular data. However, this line of thought seemed to stumble upon difficulties, because various instances of homologous adult organs developing by means of what was held to be different developmental processes were detected [97–101]. Moreover, the variety found in the coding and regulatory sequences of genes that underlie developmental mechanisms is bewildering. This is one of the areas where one wishes that ‘sameness’ were better distinguished from ‘similarity’. We intend to explore below how strong is the assumption that developmental processes or *stages* need to be ‘similar’ to underpin adult homology. Perhaps we should search instead for the *same* developmental process, under every variety of embryonic form and function (to paraphrase Owen [64]).

In any case, emphasis on topological and developmental evidence for sameness implies we must rely on historical and causal analysis of the observed structure within both the phylogenetic and ontogenetic landscapes (this was clear to von Baer [104] and Darwin [18]). Evolutionary and developmental *morphostatic mechanisms* are jointly the causes of sameness and, thus, of homology [56,109,110], independently of variations and adaptations in form or function [28,98]. A further point to consider is whether the same should not apply somehow to adaptations in *morphogenesis*. As explained below, true sameness must be produced by developmental mechanisms conserved during evolution (developmental morphostatic mechanisms; [110]), but these mechanisms are, by their nature, intrinsically variable, so that absence of detailed similarity in morphogenesis should not necessarily involve lack of homology. Embryos are not small adult forms, with proportionately smaller anatomical characters that can be homologized one to one in every case [98]. As physical systems, embryos have dynamic properties that are largely absent in adult animal forms. We therefore intend to argue here against the position that adduces lack of apparent similarity in embryonic processes as an argument against a developmental foundation of adult homology. Where would adult homology come from, if not from subjacent stasis in morphogenesis? Our standpoint here was that any apparent difficulty suggesting lack of connection of developmental homology with adult homology (and there may be difficulties that we have not considered yet) actually points to the use of incorrect assumptions, or incorrect selection of embryonic entities to compare. The issue of character selection in embryos needs to be explored in more detail. Such analysis should stimulate search of a more satisfactory interpretation, consistent with available data, which does not postulate independence of adult and embryonic homologies.

Similarities and non-similarities are both produced by developmental mechanisms, which depend on genes and the highly interactive functional cascades or networks of their products. Interestingly, a large number of early regulatory developmental genes appear to be highly conserved in sequence, basic expression pattern in the brain and other tissues, as well as in their functions, even in distantly related animals as *Drosophila* and mouse, independently of the numerous variations accumulated during indepen-

¹We follow here the meaning of “same” implicit in Owen’s [64] definition of homology, that is, an essential property that does not need similarity, even though it often may be accompanied by it (i.e., a person remains “the same” even though his/her appearance may change considerably with time).

dent evolution [90]. Thus, there exist developmental genes related to ultrastable morphogenetic mechanisms, which in principle seem able to support the hypothetical fundamental aspects of morphogenesis underlying true sameness or homology in the adult forms (*developmental morphostatic mechanisms*). On the other hand, a point change in the cascade of regulatory genes and morphogenetic mechanisms that produce a particular structure can lead to divergent morphogenesis and evolution of non-similarity from the ancestral primordium. Nevertheless, this need not affect the fact that the variant derived structures evolved from a common primordium (true homology persists, at least as field homology).

Looking retrospectively at the long search of brain homologues in comparative neurobiology, it seems that some errors in the past were related either to inadvertent disregard for a proper topological framework (causing meaningless comparisons), or to excessively arbitrary selection of characters. Other remarkable failures can be attributed to confusion of sameness (homology) with similarity. Paradoxically, much contemporaneous work in comparative neurobiology does not overtly stipulate the topological assumptions or criteria used for character selection, and most authors still aim their efforts primarily at analyzing similarities outside the context of a topological framework.

THE NEED OF A TOPOLOGICAL FRAMEWORK

As defended by several authors (i.e., [7,39,44,58,59]), the use of a topological framework is extremely important for the analysis of true sameness. This allows placement of every structure or part within a standard tridimensional space, and to give that structure a topological positional identity within it, by which it can be compared with other forms sharing the same framework. Forms not sharing a topological framework simply cannot be compared part by part (i.e., try to compare a glove with an apple, as opposed to comparing the neural tube in all vertebrates). According to Kuhlbeck [44], when different organisms or organs display the same number and organization of units within the reference tridimensional space (i.e., have the same morphological Bauplan, or building plan), they are considered *homeomorphic* or *isomorphic* (topologically identical), independently of differences in size and shape of the parts. Comparison among isomorphic configurations is based upon mapping the constitutive units relative to one or several spatial reference axes and finding the one-to-one correlations among the different units. In principle, the basic neighborhood relations are expected to be preserved, that is, topological invariance is assumed [44]. Developmental studies characterizing successive changes in structure and relative position of embryonic parts have proven to be extremely useful for analyzing which are the basic units in the Bauplan of the body or the brain.

We shall apply this approach below to our definition of field homology, because we feel this idea may serve to link together the different levels of homology. In essence, all sound homology hypotheses seem to stand upon explicit or implicit field homologies, i.e., have either known or intuited developmental underpinnings within an objective Bauplan. Analysis of the concepts of “field” versus “character” suggests that they have points in common, though they are not identical, particularly when developmental fields are considered. We suggest below that *proper embryonic characters may need to be first identified as fields*. Moreover, properly formulated “fields” tend to be less rigid concepts than “characters”, and may allow more useful causal and evolutionary insights. In the following sections we will first address the concept of *field in general*, leading to those of *morphological field*, and

developmental field within a Bauplan. We shall then analyze the relevance of the latter for character identification and homology across different levels of causal analysis.

THE BASIC ORGANIZATION PLAN OF THE BRAIN AS A TOPOLOGICAL FRAMEWORK

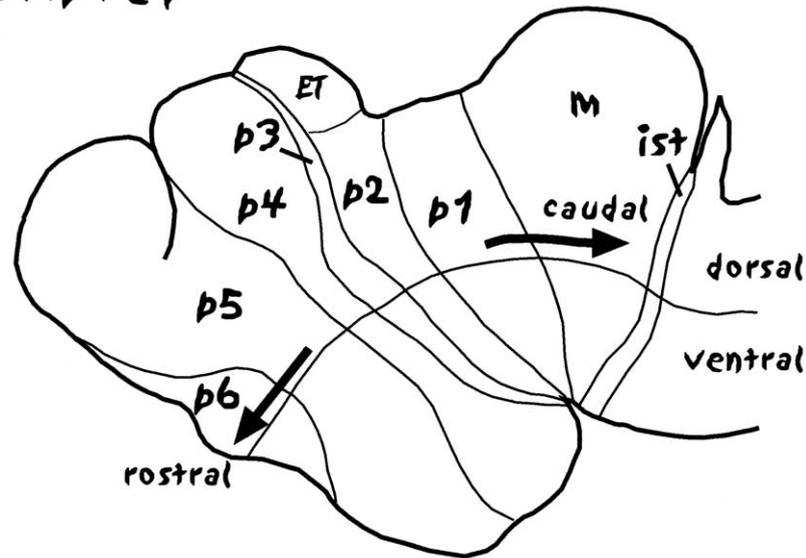
The idea of Bauplan (German term meaning literally “building plan”) represents a primary analysis of topologic sameness of animals or plants, which served historically as the fundament for modern taxonomic classifications [17,24,104]. This concept initially came associated to functional or developmental considerations, and, at the time, generated much discussion about the relative importance of form versus function as the main sources of the observed pattern variations (see historical reviews in [26,28,65]). In the end it became clear that, as fundament of the Bauplan, form and topology were predominant (revealing ancestrally acquired internal order during morphogenesis; ([18], reviews in [28,103]), while function and external environmental forces were practically irrelevant (a vertebrate embryo autonomously acquires vertebrate morphology, irrespective of the events in the life of its parents, and within a considerable range of environmental conditions, including some not allowing its survival).

This view is strongly defended by the purely topological definition of homology postulated by Kuhlbeck ([42,44, see also [59]). Kuhlbeck even saw ancestor relationships as irrelevant for the purpose of homology analysis, given that homology of the basic building plans of different organisms is itself the basis of taxonomy, and, therefore, it implies circular reasoning to use taxonomy for determining such fundamental homologies. We can instantly decide whether a new animal discovered is homologous as a vertebrate, judging on its Bauplan, without needing to know its ancestors. We will actually use this homology information to find its place in taxonomy and thereafter deduce its possible ancestors. The above strong statement nevertheless should be qualified by realization that, apart of the Bauplan, other aspects of morphology certainly involve adaptive modification of form and function [28]. It is in these more variable features of the phenotype where a knowledge of the taxonomic hierarchical positions and related cladistic analysis become necessary instruments for homology studies.

The Bauplan, also known as the basic organization plan or morphological model, actually underlies all our morphologic and developmental reasoning as a shared belief, that is, as a paradigm. Whenever we discuss homology of any character among vertebrates, we assume the vertebrate basic organization plan. Similarly, when we deal with the brain of vertebrates, we necessarily assume a vertebrate neural tube developmental paradigm, as well as an adult brain model or basic plan [69]. It should be noted that both of them have been changing drastically in recent years. Proposed scientific models need to be revised when new data appear in scene and our state of understanding increases [51]. The 20th-century neurobiology was dominated jointly by the human brain model conceived by His [36,37] and colleagues (five brain vesicles, etc.) and a *columnar model* of brain morphogenesis [34,35,43], whose formulations for the forebrain, in particular, have run against insurmountable difficulties in the era of molecular biology ([32], this issue; [69,70,72,92]). Recent reformulations of the equally old *segmental or neuromeric model* of brain morphogenesis (Fig. 1) have been proposed as likely alternative² models, able to deal with extant molecular developmental complexities ([7,68,84]; reviews in [22,58,69,70]). The adult basic plan of the

²This term does not imply there is complete disagreement between these models; the segmental approach accepts the existence of longitudinal neural tube domains (i.e., columns), but defines them differently in the forebrain.

Lamprey



Rodent

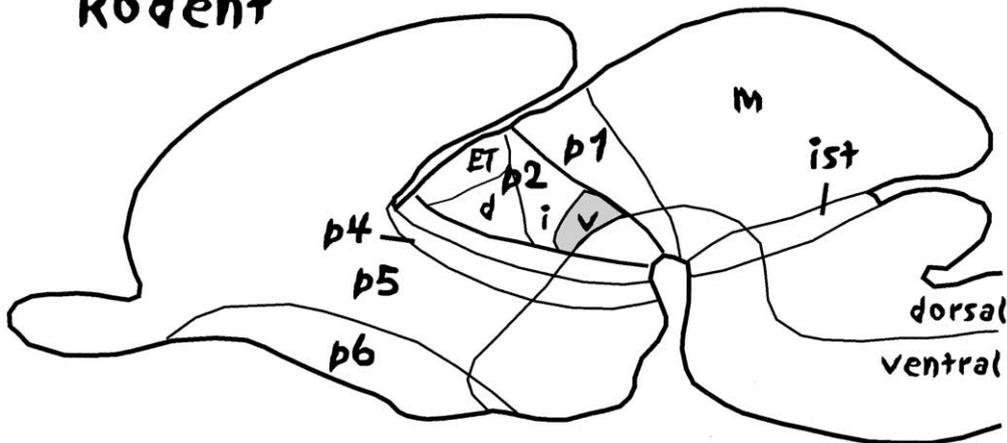


FIG. 1. Schematic sagittal views of the lamprey and rodent forebrain, showing a comparable basic organization plan (Bauplan), with an apparently equal number of transversal (segmental: ist, m, p1, p2, etc.) and longitudinal divisions (dorsal, ventral). Each division has a specific rostrocaudal and dorsoventral topological position, and we assume a one-to-one correspondence and field homology of the corresponding brain divisions showing identical positions in these distant vertebrates. Each particular division can be further subdivided into smaller rostrocaudal and/or dorsoventral areas, and the number of these subdivisions may differ among vertebrate groups. An example of this is shown for the dorsal part of p2. This region is subdivided into the epithalamus (ET, containing the habenula) and the dorsal thalamus in both the lamprey and the rodent. In rodents (as well as in birds and reptiles), the dorsal thalamus shows at least three additional subdivisions (dorsal [d], intermediate [i], and ventral [v], which have not been observed yet in the lamprey. Each basic division and subdivision of the brain is specified during development through complex interactions between internal and external signalling factors, which lead to the establishment of distinct areas in the neuroepithelium. The neuroepithelium of each distinct area gives rise to specific cell populations, which then migrate into the mantle mainly moving along radial glial fibers, transforming the bidimensional neuroepithelial code into a tridimensional space, the radial histogenetic unit. An example of the cell derivatives of a particular portion of neuroepithelium is shown in Fig. 2 for the ventral division of the dorsal thalamus in a reptile and a rodent. Abbreviations: d, dorsal division of the dorsal thalamus; ET, epithalamus; i, intermediate division of the dorsal thalamus; ist, isthmus; m, mesencephalon; p1–p6, prosomeres 1–6; v, ventral division of the dorsal thalamus.

brain is clearly affected by this change in the developmental paradigm [88]. The most notable changes in the adult brain model, after considering segmental phenomena and related molecular specification of brain regions, occur either in the hindbrain, where the classic metencephalon and myelencephalon concepts become hopelessly obsolete (i.e., pons and cerebellum are not a developmental unit and the isthmus becomes independent from both the

pons and the midbrain), or in the forebrain, where the hypothalamus and preoptic/peduncular regions no longer form a developmental unit with the diencephalon proper, and the prerubral tegmentum is diencephalic, instead of mesencephalic [69,73,74]. However, such important conceptual changes and the resulting logical consequences are not yet accepted by all actors in the field. Therefore, a difficulty for the present discussion is that, at the

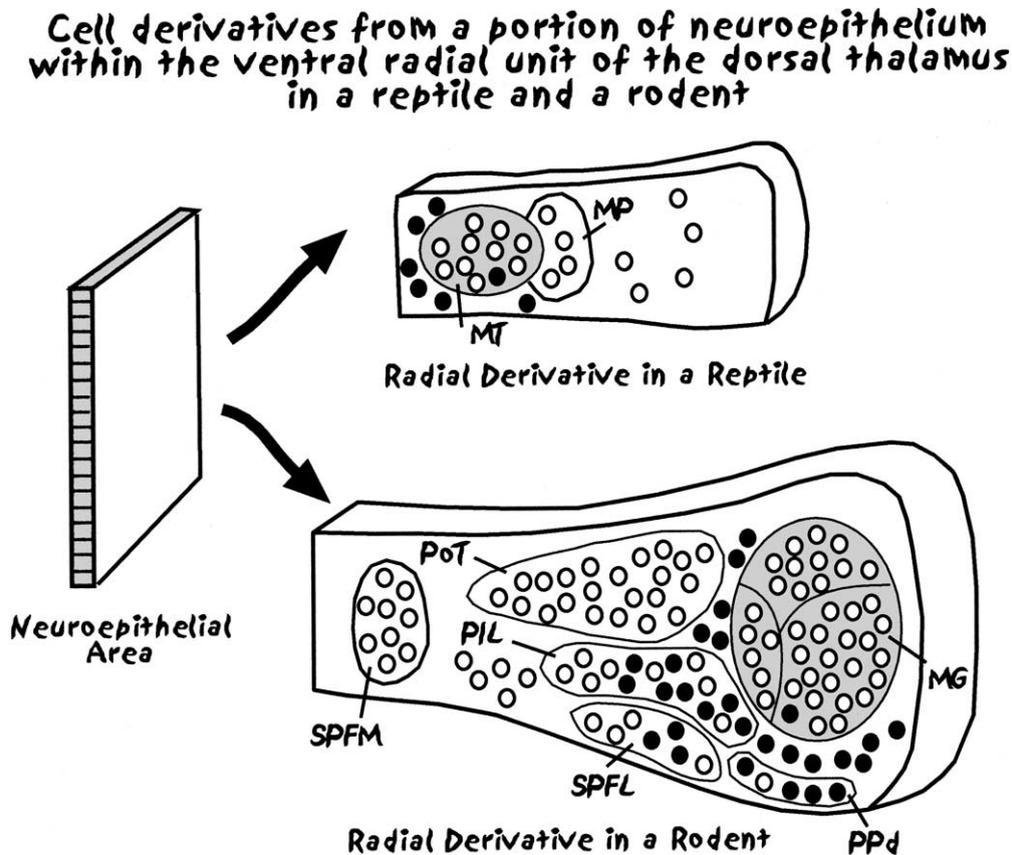


FIG. 2. Schematics showing the nuclei and other cell populations derived from the same neuroepithelial area of prosomere 2, in the ventral radial division of the dorsal thalamus (shaded in gray in Fig. 1), in a reptile and a rodent. In both reptiles and rodents, this specific area gives rise to cell populations that migrate into the mantle where they either are grouped into specific nuclei or remain dispersed (cells are represented by circles). The number of cells produced in the radial unit and the migration that these cells undergo are of larger magnitude in rodents than in reptiles. However, some of the cell populations produced within the equivalent radial unit in rodents and reptiles appear to be the same (same neurotransmitter or neuropeptide content, and same connections). This is the case of the neurons of the medial thalamic nucleus in reptiles (MT, named nucleus reuniens in turtles; shaded in the schematic) and at least part of the neurons forming the medial geniculate nucleus in rodents (MG, shaded in the schematic). The neurons in these nuclei are glutamatergic, receive auditory input from the inferior colliculus (called Torus semicircularis in reptiles), and project to the ventrolateral pallium in the telencephalon (DVR in reptiles and basolateral amygdala in rodents) [8,11,45,81]. The same neurons of MG in rodents projecting to the ventrolateral pallium also project to the temporal isocortex, but a comparable projection has not been described in reptiles. Nevertheless, the origin and location of reptilian MT and mammalian MG in a homologous radial unit (field homology), and the similar neurotransmitter content and connections of their neurons strongly support that these nuclei are truly homologous. The mammalian MG, however, shows at least three divisions and a higher number of neurons than the reptilian MT. It is at present unknown whether the reptilian MT is homologous to one or more of the MG divisions, and a closer analysis needs to be done to know whether the neuronal subpopulations found in each division of the MG are present in the reptilian MT. Another example of possible homology between cell populations formed in the same dorsal thalamic radial unit of reptiles and rodents is found for neurons expressing the neuropeptide CGRP (calcitonin gene related peptide [8]; filled circles in the schematics). In both vertebrates, CGRP-positive cells are located in the ventral radial division of the dorsal thalamus mainly surrounding the MT/MG nuclei [8]. In rodents, the CGRP-positive neurons are more numerous and more displaced to the surface compared to the equivalent cells in reptiles, as is also true of the MG cells compared to those in MT. Other cell populations within the equivalent radial unit of reptiles and rodents may or may not be homologous, and each case needs to be evaluated separately. Abbreviations: MG, medial geniculate nucleus; MP, medial posterior thalamic nucleus; MT, medial thalamic nucleus; PIL, posterior intralaminar thalamic nucleus; PoT, posterior thalamic nucleus, triangular part; PPd, peripeduncular nucleus, dorsal part; SPFL, subparafascicular thalamic nucleus, lateral part; SPFM, subparafascicular thalamic nucleus, medial part.

moment, different authors widely disagree on the fundamental organization plan of the brain. Yet, we continue discussing homologies and, particularly, similarities, without first resolving the extant basic plan discrepancies. It cannot be hidden that this momentary situation adds confusion to the comparative arena, and

it can only be hoped that highlighting this scenario may help the workers in the field to test the alternatives personally, in order to select the best option or produce new ones.

In principle, a basic plan is composed of fundamental units or divisions, which are usually represented by more or less well-

defined aspects of form or structure. For instance, consider limbs as body appendages. Their number and position along the body axis, as well as their internal structure (or subdivisions) are crucial aspects for the basic plan of vertebrates and the consequent proposal of homologies. It is less clearly appreciated that a limb, understood as a functional body unit, is vaguely defined regarding its limits. Where does it begin? Should we consider the shoulder and pelvic girdles part of the respective limbs, or of the trunk? Note that our first impression may depend on the degree of fixation to the trunk skeleton (slight in the shoulder, strong in the pelvis). Moreover, there are limb muscles that have insertions in the vertebral column, or the ribs, and all limb nerves originate in the spinal cord. There is no way to cleanly isolate a limb! We have to cut arbitrarily through bones or articulations, muscles, nerves and blood vessels to separate such a body part. The same would happen with the head. We must realize accordingly that, when we conceive limbs or any other body parts as fundamental elements of the basic plan, we are assuming not only a given topology relative to the body axis and a given internal structure (subdivisions), but also a set of more or less complex boundary relationships, which characteristically “connect” or “bind” the element to the whole [24]. These “connections” in some cases deeply penetrate the body part (as in the case of nerves), and we thus conclude that body parts are necessarily intermeshed one with another, building a structural field that embodies the unity of the body plan. This brings us to the wider concept of field applied to morphology.

As used in physics (i.e., electromagnetic, caloric, hydrodynamic, or gravitational fields), the idea of a field implies an individualizable, but vaguely delimited, phenomenal continuum with characteristic system properties. The field center(s), position, and shape at least can be roughly located and schematically represented in tridimensional space (i.e., it has a topology). Intrinsic properties and relationships of parts (internal rules) regulate the specific details of what happens (or might happen) within the field. In contrast, the operative extent of the field may depend on the circumstances (i.e., may need an arbitrary definition), depending on the sort of interactions maintained with other surrounding or partially overlapping fields. The relevant boundaries or areas of influence are often empirically determined, i.e., studied phenomena controlled by one field shift to be dominated by the adjacent field across a boundary (i.e., a spacecraft may pass from the Earth’s gravitational field into that of the Moon, with differential consequences). Specific boundary phenomena may serve as parameters with regard to the interplay of variables inside the field. No matter how we separate them conceptually, neighboring physical fields can interpenetrate each other energetically and causally (i.e., gravitational fields of Earth and Moon interacting on the shape of sea waves), and even materially (gas particles, or chemicals in solution). Our tendency to give names to each discernible element in the world prior to causal scientific analysis usually obscures the variety, interactions and dimensions of the underlying fields. Fields, understood therefore as coherent causal systems, are apparently found everywhere, from galaxies to molecules, subatomic particles, cells and animals. We often can point out several sorts of fields at different levels of physical magnitude, in a variety of dynamic equilibria or states of stability. The size, complexity, and normal lifetime of such diverse field phenomena naturally change radically between different sorts of field, depending on the rules of the larger fields in which they arise.

Biological entities can be conceived as particularly complex sorts of fields, characterized by the enormously increased amount

of internal order (information) introduced by their genetic DNA backbone and the consequent large interactive versatility and emergent self-reproductive capacity [19,95,102,105–107,111]. The organismal parts building the Bauplan of an animal can be conceived as partial biological fields (*Grundgebiete* of Bergquist and Källén [7], meaning “fundamental region”).

DEVELOPMENTAL FIELDS

Each successive state in the development of an embryo is field-like in the sense sketched above, and morphogenesis largely comprises branching of field phenomena within an increasingly diversified causal process, as emphasized in the epigenetic landscape concept of Waddington [106,107] or in Thomson’s [103] and Striedter’s [98] more recent analyses. Earliest zygotic development possibly occurs within a single primary developmental field, wherein general features of the basic plan are established, like the head-tail and dorsoventral polarities and the overall bilateral symmetry. Subsequent secondary subfields appearing at blastula and gastrula stages are typically formed by highly unstable cell assemblies with characteristic internal properties. These cell groups tend to grow and differentiate beyond their capacities for coherence, and thus necessarily divide further into derived subfields, which again grow and subdivide. The basic organization plan of the animal, the zootypic stage, and the corresponding subdivisions originate from these early embryonic morphogenetic fields, whose dynamics become strongly constrained during evolution [19,103,108,111]. The extraembryonic tissues (and mother tissues beyond them) can be conceived as the primary boundary field elements. During subsequent organogenesis, the differentially determined state acquired by various embryonic parts causes the continuing appearance of new field subdivisions (i.e., the ecto-, meso-, and endodermal leaflets, or head, trunk, and tail fields at early neural plate stages), which later become variously subdivided again at late neural plate and closed neural tube stages. Factors contributing to the establishment of new interfield boundaries may be represented by constraints or limits in the vertical or planar diffusion of signalling molecules or other means of intercellular communication, the local appearance of novel restricted sources of signalling morphogens, and/or the differential regulation of proliferative growth.³ In the end, a presumably constant (conserved) set of developmental fields and boundaries are positioned over time along the anteroposterior (AP) and dorsoventral (DV) axes of the embryo, a process that is fuelled by the increasing relative independence of some internal phenomena from local systemic and/or surrounding phenomena (i.e., by loss of initial coherence by aleatory singularities, subsequently amplified by auto-activation and lateral inhibition phenomena; [54,55]). In this way, new boundary relationships are created, which may further organize subsequent field subdivision phenomena [33,55]. Developmental fields, understood as *coherent interactive biological systems* (Weiss [111] was the first to apply this concept to biological systems, as cited in Spemann [95] and Davenport [19]), are therefore causally embedded transient phenomena, which appear, operate, and then disappear, as new field-like derived entities are formed. A developmental field nevertheless may persist some time with causal potency even after its normal derivatives have been formed. Exceptions apart (particularly in anamniotes), the developmental fields usually no longer exist as such in the adult, where we only detect the long-living *consequences* of the field’s operation, in the form of derived structures, boundaries and patterns in general.

³“Vertical” refers to interaction between two germinative layers of the embryo, such as mesoderm and neural ectoderm located above; planar refers to interaction within the plane of one single germinative layer, such as neural and non-neural ectoderm.

Internal phenomena within a developmental field typically show *cohesiveness* (i.e., common proliferative, cell-adhesion, and cell-communication properties) and *self-regulative capacities* [19, 95,111]. Developmental fields have a tendency to build a given part of the mature basic plan. Experimental embryology has shown that, once a field is well established, it can be removed, leading to complete absence of its derivatives. Alternatively, a field can produce the normal derivatives when it is isolated *in vitro*. Moreover, partial remnants of a field may be able to regenerate the whole field (all or nothing seems to be the rule; half organs or half brain parts usually do not form). The intrinsic properties and specific fates of these fields depend on the successive constellations of genes activated in their cells and boundary elements (not necessarily the same genes in all the cells). The stability of the field (its capacity to achieve its normal fate independently of perturbations, or of the actual number of cells) is secured by a highly interactive network of transcription factors guiding local specification, proliferation and differentiation. Missing cell types are replaced by newly induced or generated ones and missing molecules are similarly induced to appear, or are substituted by functionally redundant molecules already present in the field. Appropriate changes in the characteristic genetic codes (by mutation, transfection or electroporation of DNA) may lead to homeotic transformation in the morphogenetic system, that is, the appearance of an alternative fate coded by the new genetic combination, usually with some size and shape adaptation, due to the different boundary conditions (embryonic *plasticity*). However, given fields can be either sensitive or insensitive to signalling molecules active in other fields (concept of embryonic *competence*). Boundary effects can position the polarity of the field as a whole relative to the Bauplan reference axes, but the field itself decides what structure is formed, as noted, for instance, when an ectopic cerebellum or an ectopic caudal midbrain pattern is induced by the isthmus organizer in rhombomeres or prosomeres, respectively [47–49].

Recognition of the isthmus organizer at the boundary of the midbrain and hindbrain regions exemplifies either a boundary region exerting partial control of the intrinsic properties of the two adjacent developmental fields, or the center of a single field divided into two subfields. This interpretive principle can theoretically be extended to other observed embryonic boundaries and to subsequent stages of neural regionalization. Additional secondary or tertiary neural organizers are being postulated and experimentally tested; they are usually associated to morphologically distinct embryonic boundaries (i.e., the rostral neuropore, the zona limitans intrathalamica, the roof plate, the floor plate, the cortical hem, the palliosubpallial boundary) [23,27,76,87,89,113]. Perhaps in the end all distinct embryonic boundaries will prove to have signalling/organizing properties. In that case, the course of molecular and, later, histogenetic regionalization of the neural tube wall may well reflect the progressive subdivision of the initial neural plate field into smaller and smaller field subdivisions with more restricted cohesive and regenerative properties (i.e., more restricted range of internal signals). This branching causal process potentially may extend down to the level of individual neuronal populations. At the moment this is largely speculative, but represents a concept that seems likely to be corroborated by the rapidly accruing novel molecular and experimental data. All the evidence gathered so far strongly suggests that the initial number of AP and DV brain subdivisions, as well as the sorts of genetic constellations observed in brain primordia, are essentially conserved across vertebrates from lamprey to man, suggesting that they form part of, or give rise to, the neural basic plan common to all vertebrates [32,66,69,89]. In other words, these conserved fundamental morphogenetic aspects bespeak of genetic and developmental regulatory mechanisms conferring to them *metastability*, irrespective of

massive accumulated evolutionary variation and adaptation of the derived adult structures in the diverse environmental conditions. We believe this idea is extremely useful when applied to find sameness in the brain of different vertebrate species, because it embodies both topological and causally conservative fundamentals of the prospective adult characters (morphostatic mechanisms of Wagner [110]). In the case of the telencephalon, for instance, initial areal subdivisions in the telencephalic pallium seem to be common in most vertebrates up to the distinction of medial, dorsal, lateral, and ventral pallial domains (a possible exception may be found in agnathans) [9,66,70,71]. In contrast, finer areal subdivisions and radial neuronal migrations in the pallium, and particularly in the dorsal pallium, are major sources of variation among vertebrates [53,58,63,71].

During more advanced brain development, in which various histogenetic processes transform the practically two-dimensional topology of the early neuroepithelium into a more complex, expanded three-dimensional topology, the radial epithelial and glial structure of the brain wall provides cohesiveness to the derivatives of each specific area of neuroepithelium [57,58,60,77,78]. This is consequent to the parallel processes of neuroepithelial cell elongation and associated migration of postmitotic neurons and free glial precursors into the mantle layer. There is substantial evidence that, while neural histogenetic areas are conservative in number and positions across the phyla, histogenesis of the mantle is essentially variable for each histogenetic area among extant vertebrates. Radial neuronal migration (both migration range, and number and types of migrating neurons) is generally more limited in anamniotes compared to amniotes, and the largest migration rate is found in birds and mammals [58]. However, both elasmobranchs and teleosts have independently evolved specific superficial neuronal populations, difficult to homologize with tetrapod formations [115].

The limited range of radial migration found in amphibians (particularly in urodeles) has been variously held to be primitive, atavistic or paedomorphic (review in Roth and Wake [86]). Nevertheless, various lines of evidence on morphologically and hodologically identified neuronal types indicate that the compacted periventricular neurons of urodeles and frogs apparently include most hodological and functional varieties observed occupying other radial positions in tetrapods (thalamus: [112]; tectum: [21, 85]). This suggests that radial expansion of a stratified mantle layer is not required for full-fledged regionalization down to individual cell types, though that trend possibly introduces novel, adaptive functions in the conserved intrinsic circuitry.

Other complexities of variable mantle histogenesis in the brain are related to the occasional occurrence of tangential neuronal migration, by which significant numbers of neurons produced in one radially cohesive histogenetic field escape its boundaries and colonize neighboring radial domains, or even more distant areas. Apart from motoneuronal migrations, major instances of tangential migration occur in neurons coming out of the rhombic lip [2], the isthmus [68], and the subpallium [3]. Cells arising in the subpallium (ganglionic eminences in mammals) tangentially migrate into the pallium, giving rise to the major populations of pallial inhibitory interneurons, a phenomenon that occurs at least in mammals and birds, and possibly throughout tetrapods [3–5,9,16]. Additional unpublished data suggest a similar migration in lampreys (Puelles, Martínez-de-la-Torre and Pombal, submitted).

Thus, as concluded for the basic brain organization plan, processes of molecular and morphologic areal regionalization are largely conserved down to individual cell populations, and seem reasonably well-delimited time- and position-wise. Therefore, they serve as a strong topologic and causal basis for field homology, insofar as they seem to derive directly by subdivision from a

hierarchy of developmental fields. For this, the radial histogenetic domain across the whole brain wall should always be taken as a unit for any homology comparison (from ventricular surface to pial surface, with all derivatives, including tangentially migrated cells). On the other hand, mantle histogenesis (including neuronal migration, stratification, compartmentation into nuclei or layers, and perhaps also differentiation of some functionally-specified varieties of cell types and synaptic patterns) can be highly variable and needs to be treated with caution in comparative analysis, particularly when tangential migrations are involved. Analysis at the level of individual neuronal populations may be useful to resolve some of the underlying uncertainties (Fig. 2).

Field homologs are accordingly conceived as *sets of derivatives from developmentally cohesive, self-regulatory and molecularly identifiable embryonic fields of neuroepithelium, positioned unequivocally within a conserved basic organization plan*. The homology hypothesis in this case stands both upon an experimentally testable causal background, also illustrated frequently by a conserved constellation of genetic determinants, and a conserved areal topology in the Bauplan. What is recognized is actually the *causal sameness implicit in the shared location within the topologically invariant, branching hierarchy of developmental fields*. We think this conception is largely in agreement (and complementary) to the epigenetic homology concept of Striedter [98]. In addition, our approach suggests how to identify the conserved attractor fields postulated by this author in the epigenetic landscape.

The corresponding field derivatives in different species are globally field homologous because they share a given fraction of causal history in the ontogenetic and phylogenetic landscapes, irrespective of the presence or absence of appreciable similarities; any substantial differences in mantle developmental features theoretically should be amenable to explanation via clade- or species-specific divergent histogenetic properties. However, a total absence of similarity would be an extreme hypothetical case, which does not exist, as far as we know, because all brain homologies proposed within the context of the basic plan do show some associated similarities, particularly at the level of chemoarchitecture and connective properties. It needs to be evaluated by means of cladistic analysis of extant forms whether such similarities imply further subdivisions of the field (always within the context of the basic plan). In many cases, one-to-one correlations can be observed among given nuclei or cell populations within homologous fields; this allows postulating the homology of such structures. It may be difficult to fully disprove some sort of homoplasy, because mantle structures in the brain can resist homology analysis in many ways [96]. This leaves the conclusion that only field homologies (and cell type homologies, when they represent a special case of areal causal specification) can be fully established, thanks to the conservative properties of the Bauplan and of radial histogenetic domains.

Analysis of specific neuronal types therefore is highly relevant as the extreme case of field homology, when it can be demonstrated that a cell type represents an endpoint of brain regionalization (further variation within the type may still appear in cell number, migration range and relative position in the wall, and eventually also in neurite geometry, details of projections, and even in transmitter metabolism and other potentially inducible chemoarchitectonic aspects; [52,53,80–83]). The radial dimension of the single cell type field is saved here by the ventricular mother cell giving rise directly to the specific cell type found later in the mantle (together with any accompanying radial glia cells). However, it is important to keep in mind that some mature neuronal types may also result from essentially more variable inductive and/or trophic phenomena among non fully specified postmitotic neurons in the mantle layer. This possibility explains why this sort

of detailed study may require sophisticated clonal analysis, to assess how far the cell populations considered can be assumed to be really comparable. This last aspect has been considered very rarely in published work. Most studies of specific cell types tend to insist on more distantly relevant similarities in connections, cytochemistry, and function. We think functional similarity (eventually functional homology) at the level of neuron types is relevant for homology only when it stands on previously established field, neurogenetic, clonal, chemoarchitectonic, and hodologic homology. Otherwise, the risk of confusing mere functional analogy (as a result of homoplasy) with proper functional homology increases considerably. Our concept here partially agrees with that of Jacobshagen [39], who strictly separated homology from analogy, though, in contrast to us, he negated the possibility of functional homology (i.e., the visual function of vertebrate eyes and the olfactory function of vertebrate noses, irrespective of emergent variant aspects, like the grasping function of elephant noses). In conclusion, comparisons of specific cell types help clear out detailed cell-population homologies hidden, e.g., by non-similar migration properties, but the supporting argument always needs to be construed upon a previous field homology.

The field homology concept sketched above follows and underlines the rule of thumb to only compare brain elements which occupy the same place in the basic two-dimensional neural tube organization plan (topological identity; [39,44,59]) and are known precisely to derive from sufficiently distinct (even if transient) cohesive and self-regulating developmental fields. An important consequence of this is that the portions of tissue selected for comparison (the “characters”) cannot be chosen freely by the scientist. Only entire developmental fields with their boundaries and their entire sets of derivatives are theoretically sufficiently constrained as *embryonic characters* (or as epigenetic attractors of Striedter [98]) to achieve a measure of stability (morphostasis) across the ebb and flow of causal molecular developmental fluctuations. Note that the size limit of such fields may be pushed down to the single cell type level in favourable spatiotemporal conditions, thus potentially making the analysis as precise as possible. It is true that the details of the field subdivision sequence and the persistence of individual fields are only partly known. In any case, concepts in this area will permanently remain subject to revision in the wake of any future paradigm changes. This does not eliminate the need to base homology on such data and only underlines the need for continued research on these topics.

ADVANTAGES AND DISADVANTAGES OF THE FIELD HOMLOGY CONCEPT

This section addresses one of the problems attributed to the field homology concept, namely that a field homology is or can be too vague (see Introduction; [62,98,99]). We think in contrast that the present field homology concept allows a much more precise way of homologizing than is generally used. We agree with these authors that it is inappropriate to postulate a field homology by recourse to mere developmental speculation, as has been often done in the past (hodologic or chemoarchitectonic data are compared in adults and any lack of one-to-one similarity correlations is explained away as a case of “field homology”, in the absence of any other developmental evidence than a cursory analysis of previous developmental data). The field homology analysis proposed here would optimally start from a critical study of developmental materials (investigating first by virtue of which criteria given developmental fields can be defined as being topologically and causally comparable among the species of interest) and exploring to full extent the crucial information on successive field boundaries formed around or within the area of interest, as pre-

requisites for a consequent minimally complete study of mantle layer development and resulting adult characters.

In practice, a potentially sound homology analysis first needs identifying the best possible characters, which means consciously referring to the current developmental paradigm and basic plan, to choose a reasonably credible developmental field. We obviously need to be able to identify the field objectively. Often, pure morphology does not help much (ventricular sulci in the brain, frequently used in former times, are by now notorious for being the wrong stepping stones, and neuromere or longitudinal column boundaries may not be easily visible in slowly proliferating species, or at late developmental stages). Molecular markers (RNAs, proteins, glycoproteins, etc.), if well chosen, may be useful for identifying the developmental field or its boundaries at appropriate developmental stages (available fate maps are also very useful here).

Distinctive histogenesis within the identified field can be next followed step by step by appropriate analysis in several planes of section, also with the eventual help of available molecular markers. A convenient aspect to check is the topography of radial glia lines (data complementary to fate maps). These assure us that we know which are the spatial directions being read out by the cells in the developmental field, thus reducing classic sources of error. Often the optimal sectioning plane for a particular neural field can be only decided after a first round of careful analysis in several planes of section (section planes can be also topologically comparable or not, accounting for the differing axial curvatures of the compared brains; many errors in the literature stem from lack of attention to this fundamental aspect; see Puelles [70]). This sort of field analysis, performed in alternative species presumably having the same basic plan, first indicates whether a comparable developmental field exists with comparable molecular markers, boundary profiles and even some cell fates (this is usually the case, in our experience, irrespective of eventual differences in relative size of the comparable fields). The identity of the field can be checked with as many molecular markers as are available, and can be correlated with fate maps studies, embryonic experimental results, and other experimental data. Subsequent analysis of the mantle derivatives of the field gives important indications on similarities and differences in proliferation, migration, axonal navigation, stratification, compartmentation, and differentiation in general, as well as informing on specific cell types which can be identified with appropriate markers. Next comes consideration of additional relevant chemoarchitectonic aspects (cell adhesion proteins, calcium-binding proteins, neuropeptides, neurotransmitters, signalling, and/or trophic factor receptors, etc.), as well as hodologic analysis of projection neurons, afferent projections and internal circuitry, all of which jointly establishes the neural basis for understanding the variety and function of the cell populations in the field. Particularly complex cases may need going back to early development, to check out detailed aspects of clonal regulation of differentiation of given cell types, or the possibility of tangential migrations complicating the scenario. Eventually, physiological analysis of cellular membrane properties and firing patterns in the context of autonomously generated or extrinsic physiological stimuli may contribute further to assess the types of similarity and variance observed in the compared fields.

All these data on the mantle layer derivatives of the field need to be further analyzed cladistically, thus reaching reasonably satisfactory conclusions on the phylogenetic relationships of the observed details. In most cases, this will allow a more precise definition of the field homology, indicating precisely in which aspects (areal or radial subfields) the primary field retains homology, with or without similarity, and in which others we simply see species-specific adaptive structural or functional adjustments. This

approach, even if only partially fulfilled, is apt to increase our understanding of the phylogenetic and ontogenetic landscapes. As a corollary, any new insights into the number and characteristics of developmental fields hold immediate promises and consequences for homology analysis throughout the relevant animal kingdom, as evidenced recently in the case of new pallial subdivisions [70,71,94] or of dorsal thalamus subdivisions [20,25,50,70,79,116].

FROM GENES TO EMBRYOS AND ADULTS

The other sort of difficulty frequently discussed, not only in relation to field homology, centers on the issue whether adult homology can be reduced to embryonic homology and this to genetic homology [28,31]. Is there a link between these levels of homology? There are well-known instances in which different developmental processes seem to achieve development of the same form or structure, as well as cases where substantial variation in the molecular underpinnings of given developmental processes courses nevertheless with a conserved outcome [1,75,114]. One peculiar recent example is the case of the genes *Slug* and *Snail*, which seem to have mutually exchanged their usual vertebrate developmental roles at an early point in the evolution of sauropsids [46,91]. Molecular biologists who analyze phylogenetic and ontogenetic variance of developmental genes come to regard with wonder and hardly concealed doubt that such a thing as homology is actually possible [1]. Probably the main reason why they have not yet pronounced themselves collectively against that idea is the equally pervasive evidence of conserved body plans.

Striedter and Northcutt [101], Striedter [97–99] and Northcutt [62] analyzed this problem, reaching the conclusion that homology can be stipulated separately for each of the main levels of analysis (genes, embryos, and adults), but homology at any of these levels (or stages) does not imply homology at the others (see also [15,31]). This conclusion seemed paradoxical to us, insofar as it was apparently implied that the mature sameness emerges irrespective of all that happens at the underlying levels of genetic/epigenetic regulatory phenomena and morphogenesis. Furthermore, we fear that support of this conclusion may insidiously lead workers in the field to assume that developmental and molecular causal analysis is irrelevant or even suspect for comparative purposes in adults, a position that we know the cited authors do not personally endorse, but that unfortunately seems to be held by a number of morphologists and also by some functionally oriented neurobiologists. Striedter [98] already went a long way to propose solutions to this apparent paradox, within his analysis of epigenetic homology.

Our starting position here is that we know that adult homology exists (even if possibly in less cases as we might first think, as reasonably suggested by Striedter [98,99], and also implied in our analysis of field homology limits above). However, if any homology does exist, it necessarily must have a causal background in ontogenesis and in the constrained evolution of genetic regulatory mechanisms [98,110]. The fact that we may not yet have resolved all complexities implied in this difficult issue does not mean that we should assume no solution exists. Actually, we believe that the concepts of developmental fields and field homology presented above may allow us to look at the problem in a more positive light.

One of the problematic features we notice in the habitual treatment of embryonic homology is that the embryo is conceived as a small adult (also pointed out by Striedter [98]). Because it obviously has the same basic plan as the adult form, it seems natural to freely select any embryonic “character”, as we would in the adult, and compare it cladistically across species. However, in doing so an essential difference is disregarded. Adult characters tend to be the derivatives of either terminal developmental fields,

or of sets of them (in the best of cases), though at times they may be a haphazard mixture of partial derivatives of several developmental fields. In contrast, embryonic primordia of these same “characters” most probably will form part of larger, as yet undivided, developmental fields. In that case, most of the results on variable mechanisms and different molecules achieving identical fates can be understood as the effect of normal interactive and regulative cell behavior within a coherent, self-regulating developmental field. The field regulatory properties do explain the stability of the morphogenetic result in spite of perturbations, or of different starting points of the values in the system variables (i.e., the cases of the Woffian⁴ lens, or of the cavitating neural tube of teleosts, as mentioned by Striedter and Northcutt [101]). These field properties clearly constrain the end result of local morphogenesis and are based on a complex network of underlying signalling molecules. The observed variability in the particular morphogenetic route followed to generate a shape or a structure does not represent singularities we cannot explain; we just need more knowledge on all the internal rules that may apply within the relevant field, as well as all the relevant parametric influences coming from the boundary elements. Self-regulation means a causal valley in the ontogenetic landscape, where multiple courses of events may still lead to a common result, symbolized by the bottom or attractor of the valley and the constrained gorge leading into the next group of valleys [98,106,107]. The interesting treatment of this problem by Striedter however leaves unresolved the issue of delimitation or definition of the postulated attractors; this problem may be approached, as we suggest, by the Bauplan-based analysis of developmental fields.

Understanding the regulatory, equilibrium-prone properties of the developmental fields also clarifies much of the remarkable molecular variability and redundancy at the gene level. We must remember that developmental fields are strictly constrained and regulated entities. Underlying functions of many if not most molecules—particularly the transcription factors and the signalling morphogens—fall within the realm of a “regulation of regulators”, instead of having direct effects on adult structure. As was clearly explained by Ashby [6], it is typical of regulators to block external variations with regard to the internally regulated state variables of the system (if your room thermostat is working properly, you do not notice external fluctuations in temperature). In the case of gene networks controlling the embryonic state variables of developmental fields, there are actually many superposed levels of regulators, thus increasing the reliability of the system and its independence from perturbation, even at the genetic level.

To provide just a glimpse into the complexity of the involved molecular elements, there are genes that code for proteins whose function is to form heterodimers with transcription factors, altering positively or negatively their DNA binding properties. The cascades of molecular effects may be initiated by secreted morphogens acting through various membrane protein receptors (previously active or inactive) upon sets of cytoplasmic factors also capable of alternate states (bound/unbound; phosphorylated/dephosphorylated; etc.). These factors eventually activate or inactivate nucleus-homing factors subject to further regulation inside the nucleoplasm, before any effects are produced upon DNA transcription. Later regulatory instances still operate during transcription of DNA code into RNA and subsequent translation into protein, protein assembly and positioning within the cell. This clearly illustrates the extent to which the basic organization plan of organisms can be minutely regulated at the level of each single

cell. In this scenario, we will be perplexed if we naively expect one gene to have one developmental function (too simplistic a phylogenetic landscape), or one embryonic primordium or adult character to become potentially established only along a single path in the morphogenetic landscape. The more we consider the cybernetic field properties of development and reproduction in a fluctuating external environment, the better we will understand how the basic plan once arose historically, millions of years ago, and was maintained since then, irrespective of endless variation and adaptation.

This thought also illuminates the fact that during evolution there probably was an early trend for large-scale variation among basic organization plans of animals, with correlative drastic selection events, which were followed by a secondary trend for stabilization and conservation of selected body plans. In this way it became increasingly unlikely that stabilized body plans varied or disappeared. It may be easily conceived that primordial animal morphogenesis was highly variable and unstable. Opportunistic co-option of any molecular-regulatory mechanism that incremented stability and fitness would be expected, thus leading in the long run to emergence of the cohesive developmental field properties. These early morphostatic features provided self-regulated and stable stepping stones for more complex morphogenetic dynamics, capable of dealing with a larger amount of molecular and functional variability without losing viability (which in most cases lies in reliably producing the descendant developmental subfields and the derived functional organs). All elements of the fundamental organization plan have been the subject of such opportunistic morphostatic underpinning. True evolutionary innovations stand out as cases where novel or changed equilibrium states in the morphogenetic tree are explored, tested, and selected for or against, from the base of preexistent stable developmental fields (see also Striedter [98]). The increasing complexity of the fields and their capacity to buffer perturbations occasionally may tilt favourably the improbability of finding unexpected alternative positive uses for already functioning, but relatively redundant molecular mechanisms. Why dynamically stable developmental fields should gradually or suddenly expand, reduce, or change their fates (and/or properties) is not difficult to understand, given the accumulating statistical incidence of micromutations and recombination events acting on all parts of the genome and permanently generating novel variable values in the causal flow chart.

In conclusion, strict molecular comparability is one thing (in chemistry), but, for homology purposes, the most meaningful comparison of molecules lies in discerning their interactive properties within autoregulatory complexes operating within the only relevant “embryonic characters”, the unfolding developmental fields. The same molecule may have different regulatory properties at different times, even in the same developmental field, because chemical functions are context-dependent. As development proceeds, the available fields become more regionalized and specific, eventually to the level of single cell populations. This means that, depending on the question asked, or the system chosen for comparison, *proper analysis will need to start at the appropriate moment in which the relevant developmental field became first established*. As a distinct part of a morphogenetic tree, this particular field allows by itself the proposal of *hypotheses of field homology, limited in range and precision to our capacity to define the set of all its derivatives in all the species sharing the field*. It will have to be decided whether the analysis is pursued for more detailed conclusions into the field subdivisions, once these are

⁴This is a well-known experimental embryological result from Gustav Wolff (1894; cited in [39a]), where, after removing the eye lens in newt larvae, it regenerates starting from the edge of the iris.

established in their turn. It will be important to distinguish here between areal neuroepithelial subdivisions, which typically represent radially complete developmental fields, and tend to be evolutionarily conservative, from radial histogenetic subdivisions (strata, layers, nuclei in the mantle zone), which simply represent the neuronal phenotypes developed within the field. The resulting brain radial histogenetic units are intrinsically more variable (less constrained) along their radial dimension, where they do not show the cohesive and regulatory field properties characterizing their planar neuroepithelial matrix. Even further removed lie instances of true functional homology, which are certainly possible, but need a proper fundamentation upon field homology and homologous cell types and circuitry to be established properly [100].

In this article, our aim was *not* to prove that field homology, contrary to some current criticism, can be admitted as an additional sort of homology to be used alternatively, due to our ignorance of other comparative details, or to the lack of apparent similarities. Field homology is postulated here rather as the *necessary fundament* and *correct methodology* for integrating meaningfully historical, topological, biological (developmental), epigenetic, and molecular homology approaches, and even as a prerequisite for any consideration of functional homology. The viewpoint presented seems largely complementary to Striedter's [98] approach. The scenario pictured is unfortunately still sketchy and much research will be needed to fulfill present expectations.

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