Forebrain Development: Prosomere Model

L Puelles, University of Murcia, Murcia, Spain

Definition

The prosomeric model is a segmental structural model of the brain of vertebrates that explicitly holds that the brain is formed by an uninterrupted series of transverse subunits of the neural tube, generally called neuromeres. Among such subunits is a large rostral forebrain unit – the secondary prosencephalon – that encompasses hypothalamus, eyes, and telencephalon, followed by three caudal forebrain or diencephalic neuromeres (i.e., prosomeres), which are regarded as being serially homologous with more-caudal neuromeres, namely, a single midbrain mesomere, 11 hindbrain rhombomeres, and the spinal myelomeres. It is important to note that for descriptive purposes, the model postulates in all vertebrates a morphogenetic bending of the longitudinal axis of the tubular neural primordium, most marked at the cephalic flexure, whose incurvation causes wedge-shaped deformation of the topologically transverse cylindrical neuromeric sectors of the neural tube. These units share a set of fundamental longitudinal zones (due to common dorsoventral (DV) patterning processes) and therefore represent segments, that is, metameric developmental units (anteroposterior (AP) patterning). The common causal background of the longitudinal zones establishes the property of metamery (i.e., serial homology) across all neuromeres, irrespective of their differential molecular identities and individual prospective adult fates and of the variable border properties of the cells found at the interneuromeric boundaries. Therefore, the prosomeric model visualizes all vertebrate brains as segmented structures constructed along the same Bauplan (same set of DV and AP developmental units). Orthogonal intersection of DV and AP boundaries in the neural tube wall defines a checkerboard pattern of domains (histogenetic areas) in which specific properties and finer regionalization phenomena appear (shared or not among vertebrates). This makes the model useful for systematic descriptive neuroembryology, comparative neuroanatomy, and causal analysis of conserved or variant brain morphogenesis.

Characteristics

Why We Use Models

Structural neurobiology studies the form and functional inner structure of brains. This needs a conceptual model in which all sorts of detailed data on form and structure down to cellular aspects can be systematically accumulated, organized, compared, and differentiated one from another in their mutual relationships. The basic model of the vertebrate brain is the concept of the closed neural tube, from which adult brains emerge via differential morpho- and histogenesis. Since we cannot know all from the beginning, morphological models essentially are reasonable and useful conjectures about how many parts there are and how they are patched together. Such models are periodically perfected over time, becoming in the case of brains increasingly complex operational scaffolds based on accumulated data and a number of assumptions. There is always the possibility of constructing better (or worse) models.

A good model in essence should be parsimonious; that is, it should identify a minimal set of characteristic parts or landmarks in the modeled system, which can be generally recognized and seem to encompass, or be able to explain, most if not all available structural data. A good model also may delimit various 'unfilled' conceptual domains, where new data should fit in (as the periodic table of chemical elements did when it was first formulated). Such predictive aspects of models are highly useful because they implicitly indicate which new questions might be meaningful or how best to pose and answer them in practice. Simultaneously, models are instrumental in providing possible significance to any new, unexpected observation. Scientists in principle believe in and use a particular model as long as it seems to accommodate established knowledge, inspire significant research, and allow satisfactory incorporation of emerging sets of new data. Historical periods in which technological improvements produce radically novel sorts of data are particularly critical for the survival of a model.

Models widely shared among a scientific community represent a scientific paradigm. In contrast to hypotheses and theories, paradigms are not meant to be tested, since one must believe in one of them and use it as if it represented the truth, in the very process of testing a hypothesis experimentally. A paradigm comes dangerously close to becoming a dogma, a belief that wholly escapes criticism or doubt and is considered ascientific. Several models may coexist historically, sometimes because each one is perceived to have different advantages, but usually due to lack of awareness that one of them is distinctly better than the others, compounded with the human tendency to persist irrationally in long-held beliefs. Nevertheless, models and paradigms eventually may be perceived as

obsolete and be discarded by newer, less committed generations of scientists, particularly when they are manifestly unable to account for some data and efforts to apply them lead to highly unparsimonious, complicated lines of thought. Continued use of an obsolete model, or mixed-up joint use of elements of different models, tends to obstruct the progress of science.

Some neuroscientists wrongly think that they do not use a neural model. This means they simply are unaware of the model they are using. Frequently, some aspects they mistakenly regard as facts actually are conjectures. Dogmatic conscious or unconscious belief in models is a condition that is prone to poor thinking and poor science. Due to the great complexity of the studied organ, brain science is a field where such interpretive malfunctioning is not uncommon.

Neuromeric Models

The earliest morphological models of the brain were based on the adult form of the human and animal brains. This approach provided over time a rich set of neuroanatomical terms and conjectural meanings, many of which are now obsolete, although some old terms and concepts still persist in textbooks. During the late nineteenth century, and as a result of various important advances such as microscopy, evolutionary theory, and cell theory, comparative anatomical and embryological knowledge of brains advanced enough to allow the initial formulation of developmental brain models generally valid for all vertebrates. Developmental models also appeared for the entire body. The first generally accepted developmental structural paradigm for brains was a segmental model of the neural tube, which appeared hand in hand with a segmental model of the body and head of vertebrates. The axial skeleton was conceived as being segmented into metameric vertebrae (with a number of units fused together in the sacrum and in the cranial basis). The branchial apparatus also seemed segmented into serial branchial arches and slits. The brain and the set of spinal and cranial nerves were postulated to consist of a number of segmental units correlated one to one with the vertebrae and/or branchial arches.

The term 'neuromere' that was soon applied to these transverse neural units was coined by the American scientist Orr, who very ably characterized histologically in lizard embryos the relevant hindbrain, midbrain, and forebrain neuromeric units. He also provided a clear-headed morphological analysis of longitudinal zonation and axial bending of the brain, largely consistent with the present-day prosomeric model (**Figure 1**). Orr's study is the historic root of the prosomeric model, though previous and subsequent

writings by von Kupffer, Hill, His, Neal, Palmgren, Rendahl, Tello, and Vaage, among others, contain less explicit antecedents. A large-scale review of shared neuromeric structural data collected for all vertebrate lineages from agnatha to mammals was published by von Kupffer at the turn of the twentieth century.

Wilhelm His produced an alternative very influential neural model, though he certainly must have known the neuromeric views of von Kupffer and other contemporaries well. His defined the floor, basal, alar, and roof plates, the alar-basal boundary (sulcus limitans of His), the concept of isthmus, and the idea of neural tube morphogenetic deformation due to axial bending. This model was very influential because it underpinned the first Nomina Anatomica in 1895, whose committee was presided over by His. The model was not explicitly neuromeric, though His' concepts of axial bending and longitudinal zonation and most of his transverse boundaries, including those of the isthmus, clearly were consistent with neuromeric models (**Figure 2**).

Columnar Models

At the height of the prestige of neuromeric brain models, an important unrelated breakthrough resulted from the analysis of functional components in the cranial and spinal nerves. It was discovered that each nerve component (motor or sensory fibers) either originates from or projects on a distinct columnar domain of the hindbrain or spinal cord. Separate columns could be assigned to visceral and somatic nerve components. Afferent fibers usually bifurcate into ascending and descending branches that distribute widely within the corresponding column. In so doing, they do not respect the neuromeric boundaries. These data were widely perceived as important, and they threw doubt on the neuromeric models, at least for application to advanced embryos and adults, since the basic functional organization of the hindbrain and spinal cord seemed to be columnar and not segmental, irrespective of the separate, more or less periodic nerve roots, and the peripheral dermatomes and myotomes. It was increasingly thought that maybe neuromeres were transient early embryonic phenomena without impact in the mature brain, in which a columnar arrangement of functions emerges. While Europe immersed itself in World Wars I and II, a new school of US neuroanatomists bloomed, led by JB Johnston and CJ Herrick, and its members proceeded to explore these new columnar ideas. Already in 1910, Herrick postulated columnar subdivisions in the diencephalon, which he initially thought might be continuous caudally with brain stem columns and extend rostrally into telencephalic ones. This work
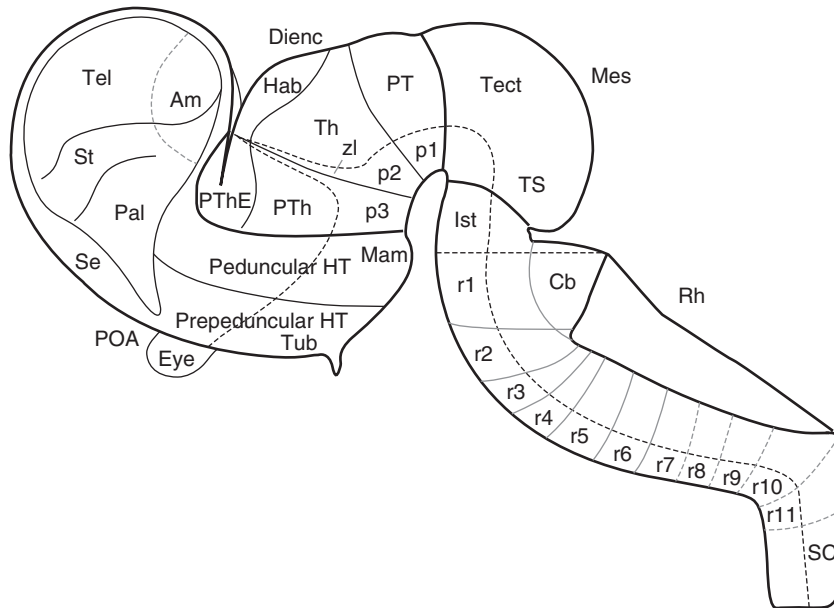
Figure 1 Schema of the prosomeric model of Puelles and Rubenstein (2003). The forebrain lies to the left. Note axial bending at cephalic flexure. The longitudinal alarbasal boundary is present throughout the lateral wall of the neural tube, symbolizing all longitudinal components (floor and roof plates not represented); a singularity known as zona limitans (zl) is a transversal spike-like deviation of the general alar-basal boundary. The secondary prosencephalon (Sec.Pros.) is the rostralmost and most complex unit, consisting of telencephalon (Tel), eye and hypothalamus (HT: divided in two parts). Septum (Se), striatum (St), pallidum (Pal), preoptic area (POA), and amygdala (Am) regions are identified within the telencephalon; the pallium lies under the label Tel. Tuberal (Tub) and mammillary (Mam) subregions of the hypothalamus are marked. The caudal forebrain or diencephalon consists of three prosomeres (p1–p3), whose alar regions include the pretectum (PT), the thalamus and habenula (Th–Hab), and the prethalamus and prethalamic eminence (PTh, PThE); a specific tegmental domain corresponds to each of them (under p1–p3 labels). A simplified view of the large mesencephalic alar plate (Mes) divides it into superior colliculus or tectum (Tect) and inferior colliculus or torus semicircularis (TS); 'colliculi' are mammalian terms. The hindbrain or rhombencephalon (Rh) contains 12 neuromeric units, from the isthmus (Ist) and ehombomere 1 (rl) down to rhombomere 11 (r11), which limits with the spinal cord (SC). Note the cerebellum (Cb) forms mainly across isthmus and r1.

originated the prevalent present-day dogma of the structural division of the diencephalon into epithalamus, dorsal thalamus, ventral thalamus, and hypothalamus, considered to be longitudinal columns of the forebrain. This emphasis was accompanied by negation of the cephalic flexure (or simply, not attaching morphological meaning to it).

Soon afterward it was recognized that the postulated diencephalic columns are not continuous with the brain stem and telencephalic ones. As a consequence, each of these sets had to be conceived of as forming independent partial models of the respective brain parts. This left in between three vaguely defined, unmodeled, and badly understood transition areas: isthmus, pretectum, and telencephalic stalk. Efforts to extrapolate to diencephalon and telencephalon the columnar 'functions' of the brain stem and spinal cord (i.e., visceral-somatic sensory and motor functional correlations) were also unproductive. Paradoxically, though the promise of the columnar model stumbled on the forebrain, this did not lead to any doubts about its potency as a paradigm or usefulness as a forebrain model, because by that time it had

become a neuroanatomical dogma. For a long time, dogmatic transmission of the columnar Herrick model in research and classroom pushed the alternative neuromeric models nearly to oblivion. Most neuroscientists to this day have been made to believe that the supposedly dorsoventral columnar series of epithalamus–dorsal thalamus–ventral thalamus–hypothalamus is a fact, not a risky conjecture of a hundred years ago.

The fundamental failure of the columnar forebrain model was that it redefined the observable forebrain axis, negating its observable curvature and substituting an arbitrary ideal straight axis which is not supported by any specific data. The columnar straight brain axis crosses from the pontine brain stem into the the 'caudal' hypothalamus, then traverses the hypothalamus and preoptic area 'longitudinally,' to enter the telencephalon and end in the olfactory bulb (this last part is obviously inconsistent with the paired paramedian nature of the olfactory bulbs and telencephalic hemispheres). Herrick curtly explained such pragmatic axial redefinition as "controversial . . . but convenient."
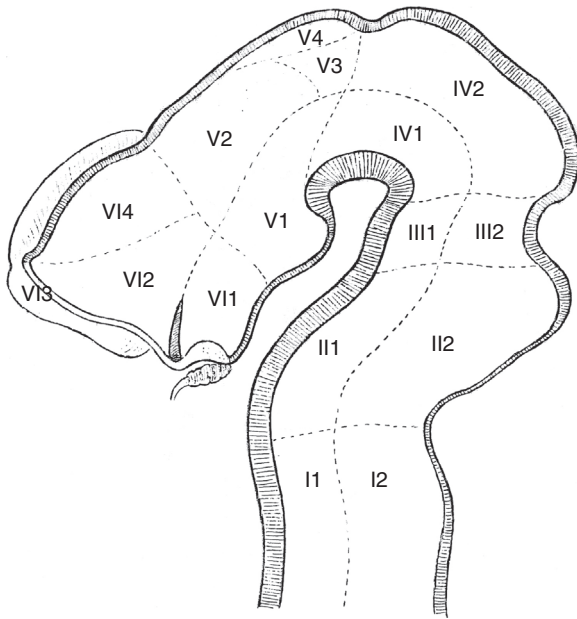
Figure 2 Model of W His (1895). Six transversal units (I–VI) are recognized along the bent neural tube. The alar-basal boundary appears through the entire lateral wall, parallel to the floor and roof plates. Domains I and II correspond to the myelencephalon and metencephalon, respectively. Domain III is the isthmus. Domain IV is the midbrain, and domain V is the 'diencephalon proper.' Domain VI contains part of hypothalamus, the eye, and the telencephalon. Basal plate domains are identified as I (II–VII) and alar plate domains are marked as 2 (I2–VI2). An additional domain VI3 represents the olfactory bulb, and the V3 and V4 domains refer to the metathalamus and habenula, respectively.

In the subsequent era of spectacular experimental neuroanatomical advances (axonal degeneration, axonal transport, electron microscopy, chemical anatomy), which extended up to the recent 1980s, Herrick's columnar model seemed to encompass without problems the accumulating hodological and chemoarchitectonic data on the forebrain. Stereotaxic topographic references for lesions and tracer injections worked well with the idea of a straight axis of the entire brain, which could be naively thought to be reproduced by the length axis of the stereotaxic apparatus. Only isolated embryologists (and then only those who looked at whole mounts and sagittal sections, procedures that curiously fell into disuse) insisted now and then that the brain axis is always curved and therefore topologic transversal and longitudinal dimensions had to be defined in accordance with the specific part of the neural tube considered.

The Rebirth of Neuromeric Models

A fully new set of neuroanatomical developmental data started to accrue during the 1980s and 1990s. These data included observations on the expression domains of neural developmental genes, possible thanks to the new *in situ* hybridization protocol for transcribed messenger RNA (and other correlative molecular biology and genomic advances). This procedure renders visible the cells that are in the process of reading out piecewise the information coded in the genome. Since many of these genes are causally determinant of the structural and histogenetic patterning of the neural tube wall, their expression patterns and the boundaries defined by them are highly relevant for brain models. It was soon discovered that some genes show longitudinal patterns of expression and others show transversal patterns (actually, both aspects usually appear in combination). All efforts to encompass these patterns within the forebrain columnar model have failed or have led to unparsimonious and highly convoluted *ad hoc* interpretations. On the other hand, the hindbrain and spinal cord columnar model does agree significantly with longitudinal gene patterns but highlights at the same time that observed transversal patterns relate specifically to the old neuromeric models. It turns out that neuromeric and columnar patterns coexist in the hindbrain and spinal cord, as predicted long ago by defenders of the segmental approach.

Similar analysis of forebrain gene expression data in the context of a forebrain neuromeric model (using the original bent axis) showed the capacity of this model to encompass and give morphologic significance (developmental function) to the new set of molecular causal data. The apparent rebirth of a neuromeric paradigm in the forebrain and hindbrain (where neuromeres are best visible) pointed the way to the possibility of conceiving a general segmental model of the entire central nervous system, in which longitudinal zones (columns, but different ones in the forebrain than those postulated by Herrick and his followers) and transverse neuromeres combine to interpret and predict the nature of causal phenomena operating in the construction of the brain. This sort of ultimate or synthetic brain model was called the prosomeric model, as developed in several reports and reviews by Puelles and Rubenstein.

See also: Brains of Primitive Chordates; Evolution of Vertebrate Brains; Forebrain Development: Holoprosencephaly (HPE); Forebrain: Early Development.

Further Reading

Herrick CJ (1910) The morphology of the forebrain in amphibia and reptilia. *Journal of Comparative Neurology* 20: 413–547.
Herrick CJ (1933) Morphogenesis of the brain. *Journal of Morphology* 54: 233–258.

Herrick CJ (1948) *The Brain of the Tiger Salamander, Amblystoma tigrinum*. Chicago: The University of Chicago Press.

His W (1892) Zur allgemeinen Morphologie des Gehirns. *Archiv für Anatomie und Entwicklungsgeschichte* 346–383.

His W (1893) Über das frontale Ende des Gehirnrohres. *Archiv für Anatomie und Physiologie/Anatomie Abteilung* 3/4: 157–171.

His W (1893) Vorschläge zur Eintheilung des Gehirns. *Archiv für Anatomie und Physiologie/Anatomie Abteilung* 3/4: 173–179.

His W (1904) *Die Entwicklung des menschlichen Gehirns während der ersten Monate*. Leipzig, Germany: Hirzel.

Kuhlenbeck H (1973) *The Central Nervous System of Vertebrates, Vol. 3, Part II: Overall Morphological Pattern*. Basel, Switzerland: Karger.

Orr H (1887) Contribution to the embryology of the lizard. *Journal of Morphology* 1: 311–363 (plates XII–XVI).

Puelles L (1995) A segmental morphological paradigm for understanding vertebrate forebrains. *Brain, Behavior and Evolution* 46: 319–337.

Puelles L (2001) Brain segmentation and forebrain development in amniotes. *Brain Research Bulletin* 55: 695–710.

Puelles L and Rubenstein JLR (1993) Expression patterns of homeobox and other putative regulatory genes in the embryonic mouse forebrain suggest a neuromeric organization. *Trends in Neuroscience* 16: 472–479.

Puelles L and Rubenstein JLR (2003) Forebrain gene expression domains and the evolving prosomeric model. *Trends in Neuroscience* 26: 469–476.

Von Kupffer K (1906) Die Morphogenie des Centralnervensystems. In: Hertwig O (ed.) *Handbuch der Vergleichende und Experimentelle Entwicklungslehre der Wirbelthiere*, vol. 2, pp. 1–119. Jena, Germany: Fischer.