Opinion

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A developmental ontology for the mammalian brain based on the prosomeric model

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In the past, attempts to create a hierarchical classification of brain structures (an ontology) have been limited by the lack of adequate data on developmental processes. Recent studies on gene expression during brain development have demonstrated the true morphologic interrelations of different parts of the brain. A developmental ontology takes into account the progressive rostrocaudal and dorsoventral differentiation of the neural tube, and the radial migration of derivatives from progenitor areas, using fate mapping and other experimental techniques. In this review, we used the prosomeric model of brain development to build a hierarchical classification of brain structures based chiefly on gene expression. Because genomic control of neural morphogenesis is remarkably conservative, this ontology should prove essentially valid for all vertebrates, aiding terminological unification.

What is ontology?

The concept of ontology (see Glossary) was borrowed from the realm of philosophy by information scientists, who now use it as a way to represent an existing domain of knowledge in the form of a hierarchical taxonomy [1]. The availability of a brain ontology is vital for the field of neuroinformatics. There have been several attempts to create a brain ontology, the most notable of which are NeuroNames [2–4], the Biomedical Information Research Network (BIRN) [5], and the Brain Architecture Management System (BAMS) [6,7]. However, these ontologies are largely based on traditional topographic classification of parts of the adult brain, whereas the discovery of gene targeting in mice [8] has revealed details of gene expression, lineage mapping, and causal inductive mechanisms during development, leading to a new form of hierarchical classification based on ontogeny.

Conventional ontologies have the weight of tradition, but they do not include fundamental ontogenetic data, such as neuromeric developmental units, genoarchitectonic evidence for natural boundaries between brain parts, or their inner subdivisions (as opposed to many arbitrary classical divisions unrelated to causal mechanisms). Therefore, they have little power to encapsulate emergent understanding of brain development and structural evolution. By contrast, a developmental ontology connects adult neuroanatomy with the tradition of comparative embryology; it contemplates developmental structural units shared

Glossary

Diencephalon: the caudal subdivision of the forebrain that joins the midbrain to the secondary prosencephalon; it contains three major alar domains (pretectum, thalamus, and prethalamus), as well as the corresponding tegmental regions.
Evo-devo: an approach to the analysis of brain structure based on the merging of concepts drawn from evolution and embryonic development.
Hodology: the study of connections within the central nervous system ('odos' is Greek for a road).
Neuromeres: transverse unitary subdivisions of the neural tube that share a common dorsoventral structure (floor, basal, alar, and roof plates), but each have differential molecular identities and fates; they comprise the secondary prosencephalon, diencephalon (prosomeres), the midbrain (mesomeres), and the hindbrain (rhombomeres).
Ontogeny: Greek for the genesis of being: the process of development.
Ontology: a formal conceptualization of the structure of a knowledge base, usually in the form of a hierarchical classification.
Pallium: major subdivision of the telencephalon, usually visualized as covering and surrounding the subpallium; in mammals, it gives rise to the cerebral cortex and several claustroamygdaloid pallial nuclei.
Prosencephalon: Greek for forebrain: the part of the brain that appears at the rostral end of the neural tube.
Secondary prosencephalon: the rostral major subdivision of the developing forebrain that separates from the diencephalon caudally (early in development, both are encompassed within the primary prosencephalon); the secondary prosencephalon includes the telencephalon, the eye, and the hypothalamus.
Subpallium: a major subdivision of the telencephalon usually visualized topographically as lying under the pallium, at the brain 'base'it generates the so-called 'basal ganglia', including the striatum, pallidum, diagonal-basal area, and preoptic area.
Tagma: a meaningful higher-level unit of biological structure, comprising segments that share a general character (e.g., the *Drosophila* thorax tagma as opposed to the abdominal tagma).
Telencephalon: a dorsal subdivision of the secondary prosencephalon that forms the pallium and subpallium.
Topography: a system for describing and representing position relative to external references.
Topology: a system for describing the relative position of the components of a structure irrespective of external references and any nondisruptive deformations; topology attends exclusively to the invariant neighborhood relations between the components.

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Keywords: ontology; gene expression; neuromeres; forebrain; midbrain; hindbrain.

0166-2236/$ – see front matter.
 http://dx.doi.org/10.1016/j.tins.2013.06.004

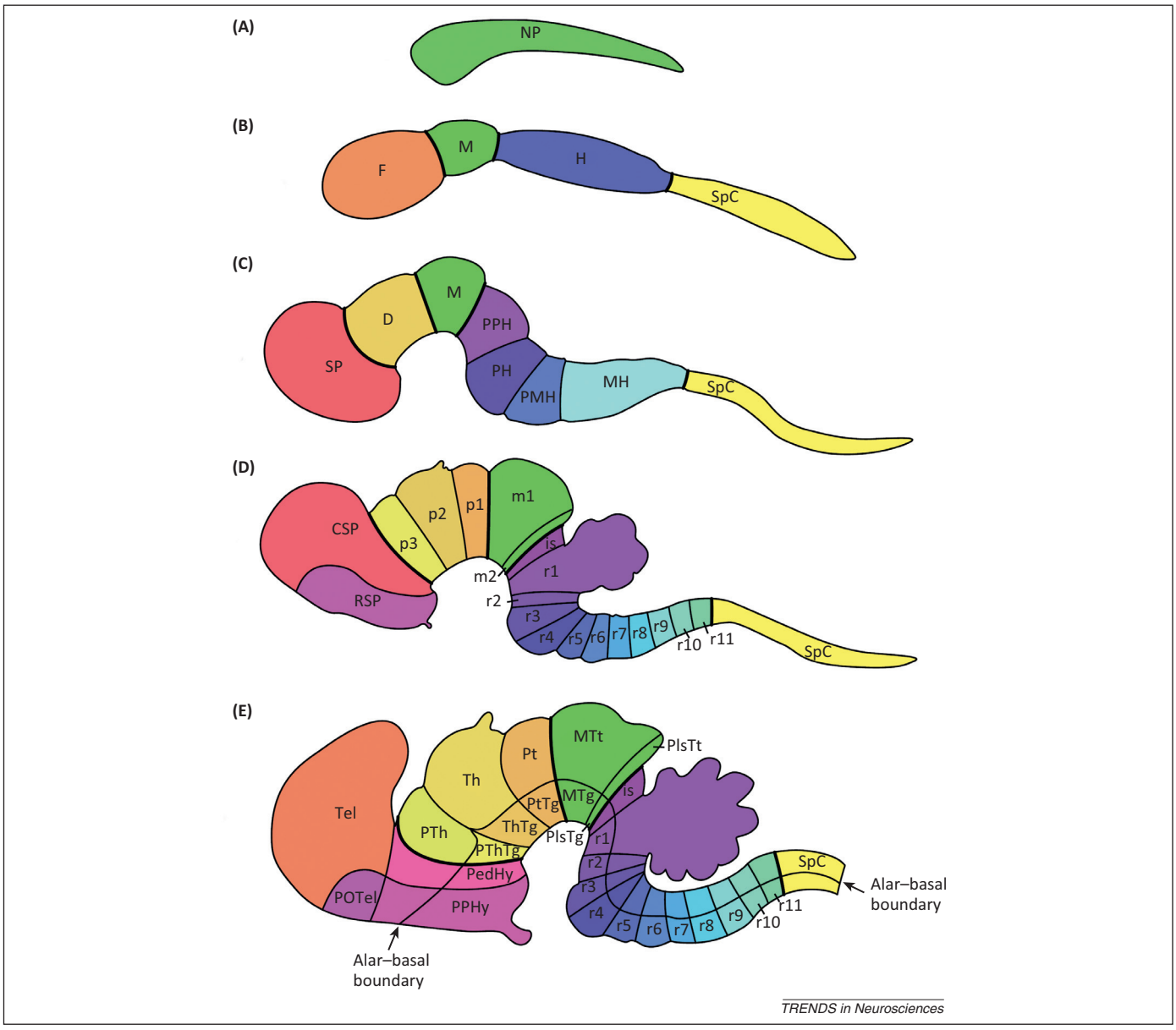

Figure 1. A series of diagrams of lateral views of the developing mouse brain. **(A)** The neural primordium (NP), which is a hollow tube with no subdivisions. In **(B)**, the rostral (left) part of the neural tube shows the appearance of the forebrain (F), midbrain (M), and hindbrain vesicles (H), with the developing spinal cord (SpC) on the right. In **(C)**, the forebrain vesicle has two divisions, the secondary prosencephalon (SP) and the diencephalon (D), and the hindbrain is divided into four regions: the prepontine hindbrain (PPH), the pontine hindbrain (PH), the pontomedullary hindbrain (PMH), and the medullary hindbrain (MH). In **(D)** from the top, more subdivisions appear in the forebrain [caudal secondary prosencephalon (CSP or hp1); rostral secondary prosencephalon (RSP or hp2); and prosomeres 1–3 of the diencephalon (p1, p2, and p3)], midbrain [mesomere 1 and 2 (m1 and m2)], and hindbrain [isthmus (is) and rhombomeres 1–11 (r1 to r11)]. In **(E)**, some parts of the forebrain have become further differentiated: the caudal prosencephalon has formed the main part of the telencephalon; the rostral secondary prosencephalon has formed the preoptic telencephalon (POTel), the terminal hypothalamus (THy), and the peduncular hypothalamus (PedHy)); and prosomeres 1–3 have formed the pretectum (Pt), thalamus (Th), and prethalamus (PTh), respectively. In this diagram, the diencephalon and midbrain are further subdivided by the alar–basal boundary, which bounds distinct tegmental regions [prethalamic tegmentum (PThTg); thalamic tegmentum (ThTg); pretectal tegmentum (PtTg); midbrain tegmentum (MTg); and preisthmic tegmentum (PlsTg)]. The dorsal part of the midbrain is divided into the main midbrain tectum (MTt) and smaller preisthmic tectum (PlsTt). Created by L. Puelles for the Allen Brain Institute (http://developingmouse.brain-map.org).

among vertebrates, as revealed by fate-mapping studies, and is consistent with evolutionarily conserved gene patterns. Because of this, a developmental ontology has the capacity to stimulate insights into causation. Our proposal of a developmental ontology for the adult mouse brain is a simplified version of the extended version designed by L. Puelles for the *Allen Developing Mouse Brain Atlas* (http://developingmouse.brain-map.org). The new ontology is consistent with the most recent version of the prosomeric model [9], a known paradigm for structural and molecular analysis of vertebrate brains (Figure 1). Note that this review centers on the ontology and does not aim to explore the prosomeric model itself.

Comparing traditional and developmental ontologies

All adult brain ontologies start with the recognition of three basic elements: forebrain, midbrain, and hindbrain. Even at this level, the developmental ontology is distinctive, in that it includes the isthmus within the hindbrain, rather than in the midbrain, as found in traditional