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Expansion modes of primate nervous system structures in the light of the Prosomeric Model

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The expansion of human and non-human primate central nervous system structures has been a paramount question for classic and contemporary studies in comparative vertebrate neuroanatomy. These studies can benefit from framing data analysis within the Prosomeric Model, which defines a common Bauplan for all vertebrate species, including mammals. According to this model, the vertebrate nervous system is composed of several Fundamental Morphological Units (FMUs) that are defined and delineated by characteristic gene expression profiles. Thus, the expansion of neural structures can be traced back to heterochronic neurogenesis, cell lineage specification, and axon growth in their corresponding FMUs. In the present article, we exemplify the use of the Prosomeric Model as the proper theoretical framework for analyzing the expansion of the cerebral and cerebellar cortices, the pontine nuclei, the striatum, the nigrostriatal dopaminergic system, the thalamus, and the amygdala in primates compared to rodents. We describe the quantitative (volume and neuron number) and qualitative (cytoarchitectonic and cell type differences) expansion of these structures in primates versus rodents and define different expansion modes. Then, we relate these modes to the developmental primary events of specification and secondary events of histogenesis, like neurogenesis. We conclude that the systematic analysis of the molecular regulation of primary and secondary developmental events in each FMU in rats, primates, and other mammals could provide the necessary insight to identify the causal mechanisms of the expansion modes described in the present article.

KEYWORDS

genoarchitecture, columnar model, field homology, fundamental morphological unit, histogenesis, morphogenesis, cerebral cortex, rhombic lip

1 Introduction

Since the dawn of modern studies on brain structure, comparative neuroanatomists have devoted large efforts to identify similarities and differences in the size, cytoarchitecture, chemical composition, synaptic connections, and cell types across the central nervous system in different vertebrate species [e. g., Ariëns Kappers et al. (1936)]. The preservation of “older” and the appearance and expansion of “newer” vertebrate nervous system parts have been explored, quantified, and conceptualized in different scaling models [e. g., Finlay and Darlington (1995); Yopak et al. (2010)]. These comparative studies are a central core of contemporary neuroscience and have implications that go beyond their own scope; for instance, they can provide sound criteria for defining homology of brain regions in different species, which is key for extrapolating experimental data obtained in laboratory animals to the human brain.

Most of the classic comparative studies of the vertebrate central nervous system were performed within the theoretical framework of the Columnar Model of Charles Judson Herrick (1910; 1933; 1948) and Hartwig Kuhlenbeck (1967–1978), a model that has been proved incompatible with the spatiotemporal expression profiles of morphogenetic genes across vertebrate embryos (Puelles and Rubenstein, 2015). On the contrary, molecular developmental data have provided sound foundations for the Prosomeric Model of Luis Puelles and his coworkers. This model defines a vertebrate nervous system Bauplan (or blueprint) composed of several Fundamental Morphological Units (FMUs), each of them defined and delineated by characteristic gene expression profiles (García-Calero and Puelles, 2020). More important, the topological neighborhood relationships among FMUs are invariant across vertebrates species (Nieuwenhuys and Puelles, 2016). Thus, Bauplan FMUs seem to have been conserved across all vertebrates and allow for advancing sound homology hypotheses: two brain structures in two different species should be homologous if they are originated in the same FMU of the Bauplan defined by the Prosomeric Model (Puelles and Medina, 2002).

Besides homology criteria, the Prosomeric Model has also proved its efficacy for making predictions on brain connectivity based on the causal mechanisms of development (Puelles, 2022) and explaining malformations (Diaz and Puelles, 2020). Thus, this model could provide a fruitful theoretical framework for comparative neuroanatomical studies in search of evolutionary principles. In our opinion, defining principles does not consist only in identifying regularities, like those represented in scaling models. A principle in evolutionary biology also requires a causal mechanism for the identified regularity; and causal mechanisms of nervous system evolution must be searched for in the genetic regulation of embryonic development.

In the present article, we compare the expansion of several central nervous system regions in primates compared to rodents in the light of the Prosomeric Model. Our aim is to exemplify the use of this model for defining different expansion modes of neural structures and propose potential causal mechanisms for such modes. First, we summarize the historical development and major

concepts of the Columnar and Prosomeric Models to identify the model that can better explain the differential expansion of primate nervous system parts. Then, we compare the quantitative (volume and neuron number) and qualitative (cytoarchitectonic and cell type differences) expansion of the cerebral and cerebellar cortices, the pontine nuclei, the striatum, the dopaminergic nigrostriatal system, the amygdala, and the thalamus in human and non-human primates compared to rodents. Also, we identify the corresponding FMUs of these structures and compare between rodents and primates the data (when available) on neuron number of each structure. Finally, we define five expansion modes of primate nervous system structures and relate them to the primary events of specification and secondary events of histogenesis in the corresponding FMUs to identify their potential developmental and phylogenetic causal mechanisms.

2 Models of neural tube development and evolution

2.1 The Columnar Model of the vertebrate nervous system

Our current understanding of central nervous system development is rooted in the seminal works of the Swiss embryologist Wilhelm His (1831–1904), who, during the second half of the XIXth century, carried on systematic descriptions of the developing nervous system in human and other vertebrate embryos. His obtained complete series of sections through *in toto* embedded-in-paraffin embryos, stained the sections with Nissl technique, and used them for 3D reconstructions (Richardson and Keuck, 2022). The illustrations and drawing produced by His are still reproduced in contemporary textbooks of embryology and anatomy [e. g., Mancall et al. (2011)].

His described in the neural plate and early neural tube several longitudinal zones, called plates (floor, basal, alar, and roof plates), that extended rostro-caudally along the prospective prosencephalon, mesencephalon, rhombencephalon, and spinal cord [His (1897; 1904); Figure 1A]. He could distinguish the alar and basal plates based on differences in neurogenesis time-course (earlier in the basal than in the alar plate). His model was later rejected in favor of an alternative interpretation that assumed that the notochord, and, thus, the basal plate, did not extend to the anterior end of the neural plate and was present only in the spinal cord, the rhombencephalon, and the mesencephalon [Kingsbury (1920); Figure 1B]. Simultaneously, Charles Judson Herrick (1868–1960) described four longitudinal zones, called columns, abutting on the ventricular surface of the diencephalon. These columns were, from dorsal to ventral, the epithalamus (gives rise to the habenula and the pineal gland), the dorsal thalamus (gives rise to all the thalamic nuclei, except the reticular nucleus), the ventral thalamus (gives rise to the thalamic reticular nucleus, the *zona incerta*, and the Forel fields), and the hypothalamus. The diencephalic columns showed different neurogenesis time-courses (Reinoso Suárez, 1966) and were outlined by three sulci (dorsal, middle, and ventral

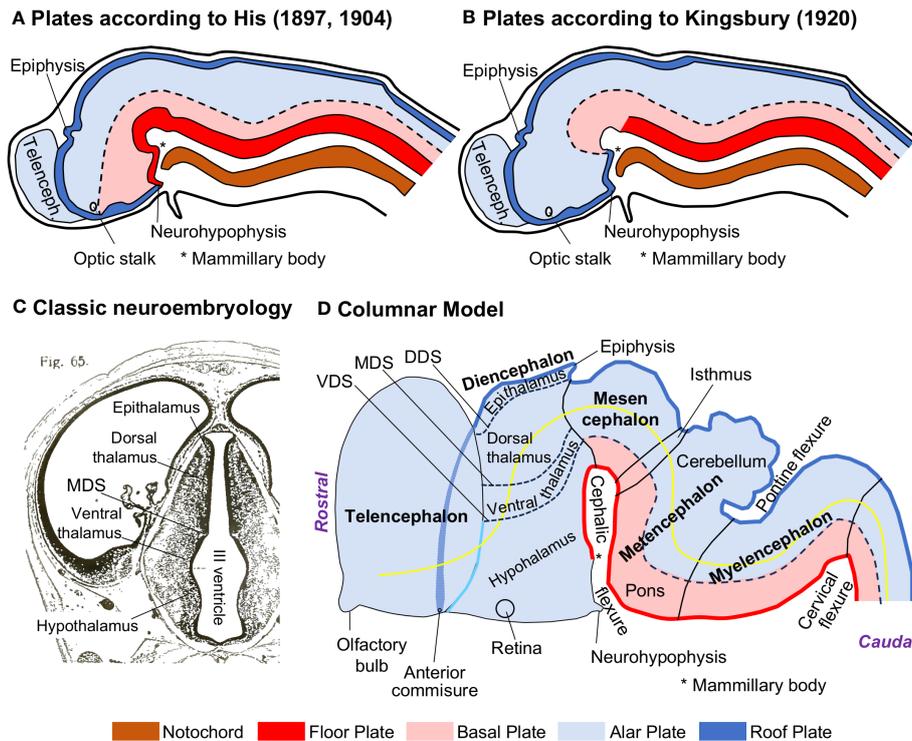


FIGURE 1

The Columnar Model of the vertebrate central nervous system. (A), Scheme that shows the medial view of a parasagittally cut mammalian neural tube; the basal plate (pink) extends from the spinal cord to the diencephalon according to [His \(1897; 1904\)](#). (B), Scheme that shows the medial view of a parasagittally cut mammalian neural tube; the basal plate (pink) extends from the spinal cord to the mesencephalon according to [Kingsbury \(1920\)](#). (C), Coronal section stained with Nissl through the diencephalon of a human embryo (Crown-rump length = 25.1 mm); the four diencephalic columns and the middle diencephalic sulcus (MDS) are indicated on the wall of the III ventricle. (D), Scheme of a mammalian neural tube (left lateral view) showing plates (floor, basal, alar, and roof plates), the four diencephalic columns (Epithalamus, Dorsal thalamus, Ventral thalamus, and Hypothalamus) the three diencephalic sulci (dorsal, middle, and ventral), and the axis (yellow line) of the central nervous system according to [Herrick \(1910; 1933; 1948\)](#) and [Kuhlenbeck \(1967–1978\)](#). (A, B) have been modified from Figure 440 in [Arey \(1965\)](#); note that the roof plate is represented as in contact with the floor plate (A) or the basal plate (B), which now we know that are incorrect topological relations [see Figure 1 in [Puelles \(2018\)](#)]. (C) has been modified from Figure 65 in [Hochstetter \(1919\)](#). The floor plate is colored in red, the basal plate in pink, the alar plate in light blue, the roof plate in dark blue, and the notochord in brown. The Microsoft PowerPoint program was used to prepare Figure 1 (and all the other figures); drawings were delineated with “shape” tools and colored with “shape fill”. DDS, dorsal diencephalic sulcus; MDS, middle diencephalic sulcus; Telenceph., telencephalon; VDS, ventral diencephalic sulcus.

diencephalic sulci) that could be identified at different developmental stages [[Herrick \(1910; 1933\)](#); [Figure 1C](#)]. The four columns in a devoid of basal plate diencephalon were the touchstone of the Columnar Model ([Figure 1D](#)) that was further elaborated by [Kuhlenbeck \(1967–1978\)](#) and incorporated to most textbooks of embryology and neuroanatomy [e.g., [Kahle et al. \(1986\)](#); [Langman and Sadler \(1990\)](#)].

It is important to consider that the Columnar Model is an interpretation of the development of the neural tube and its constituents that is based on observations of vertebrate embryos stained for classic neuroanatomical techniques, like Nissl-staining ([Figure 1C](#)). These techniques, in combination with serial sectioning and 3D reconstruction, allow for identifying sulci on the pial and ventricular surfaces of the neural tube (like the diencephalic sulci), bulges on the ventricular surface (like the diencephalic columns), and flexures (like the cephalic and pontine flexures) and dilations (like the diencephalic vesicle) along the neural tube ([Figure 1D](#)). In the literature of the Columnar Model [e.g., [Kuhlenbeck \(1967–1978\)](#)], the parts of the developing nervous system delineated by sulci, like the diencephalic columns, are

considered fundamental constituents of a vertebrate nervous system Bauplan. Another important tenet of the Columnar Model is the definition of the telencephalon as the most rostral part of the neural tube; thus, the rostro-caudal axis of the neural tube (yellow line in [Figure 1D](#)) passes, from rostral to caudal, through the telencephalon, the diencephalon, the mesencephalon, the metencephalon, the myelencephalon, and the spinal cord.

2.2 The Prosomeric Model of the vertebrate nervous system

In parallel to the alar and basal plates, classic developmental studies also described transient transverse structures that were called neuromeres. In the rhombencephalon, several rhombomeres were delineated by obvious sulci between them, but in other neural tube regions the neuromeric organization was less obvious. In spite of this, several neuromeric models were proposed along the XXth century based on classic neuroanatomical techniques [e.g., [von Kupffer \(1906\)](#); [Rendahl \(1924\)](#); [Bergquist and Kallen \(1954\)](#)]; reviewed in

Nieuwenhuys and Puelles (2016) and Puelles (2021)]. Some of these models identified neuromeric boundaries according to differences in neurogenesis time-course (Bergquist and Kallen, 1954). Importantly, the neuromeric boundaries did not coincide with the sulci between the diencephalic columns, but Kuhlenbeck considered that the initial neuromeric structure was later substituted by the diencephalic columns (Kuhlenbeck, 1967–1978).

A new neuromeric model, the Prosomeric Model, was proposed by Luis Puelles (1948–) and his coworkers based on the analysis of *in toto* chick embryos stained for acetylcholinesterase. This technique stains all the newborn neurons and revealed transverse patterns of neurogenesis that did not coincide with the diencephalic columns (Puelles et al., 1987a). In the last decade of the XXth century, the use of *in situ* hybridization to color the expression of morphogenetic genes in vertebrate embryos was instrumental to confirm the neuromeric organization of the vertebrate neural tube

(Puelles and Rubenstein, 1993; Rubenstein et al., 1994). These studies also showed that Sonic hedgehog (Shh), the morphogenetic determinant of the basal plate, was expressed in the ventral part of the diencephalon (Figure 2A), supporting the presence of a basal plate component in this vesicle as advanced by His (1897; 1904). Puelles and his coworkers also experimentally demonstrated that the most rostral part of the neural tube was the prospective anterior commissure (Puelles et al., 1987b) and defined the Natural axis of the nervous system (yellow line in Figure 2B), which roughly matches the alar-basal plate boundary; also, they have demonstrated that the entire neural tube is epichordal (Puelles and Rubenstein, 2015).

The Prosomeric Model defines the components of the vertebrate central nervous system based on abundant genoarchitectonic data obtained from *in situ* hybridization experiments performed on vertebrate embryos (Puelles and

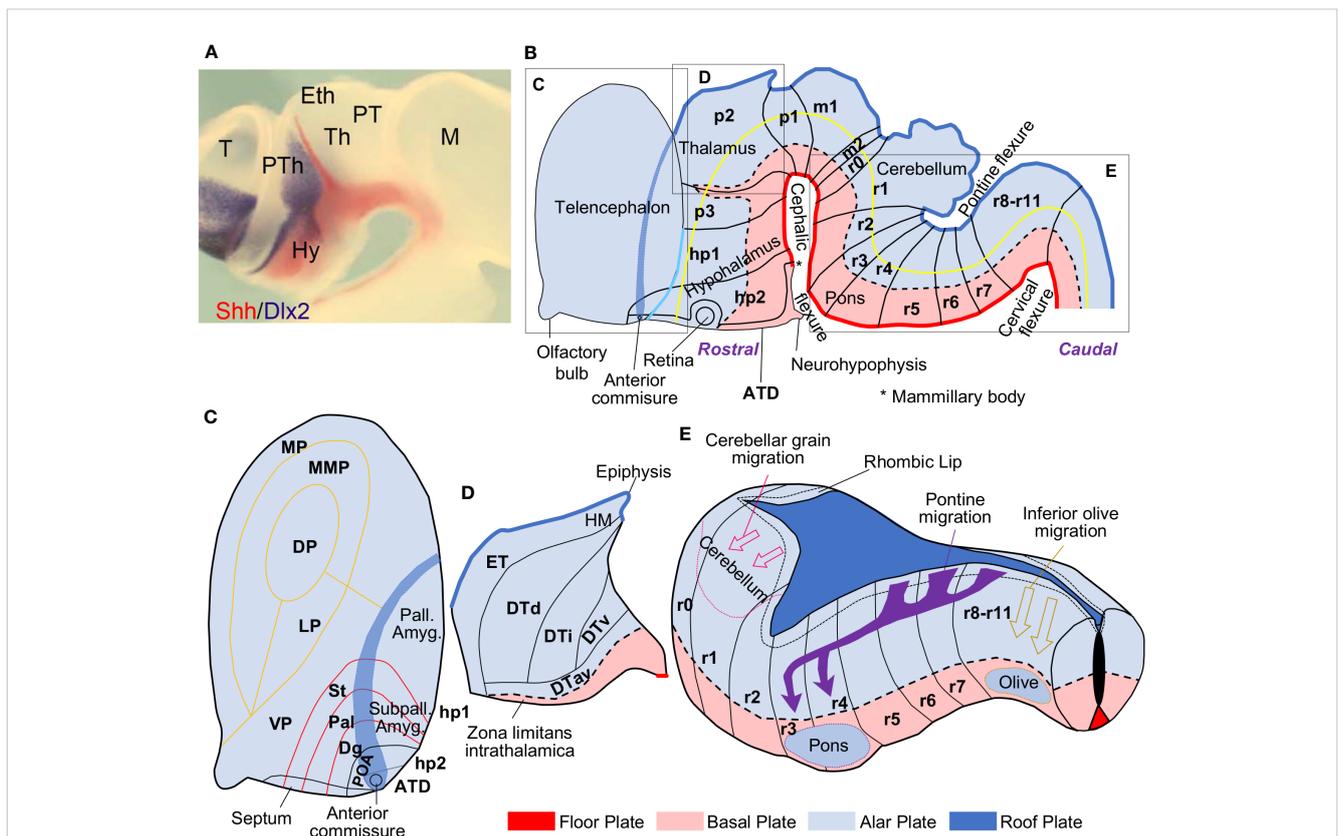


FIGURE 2

The Prosomeric Model of the vertebrate central nervous system. (A), Expression of Sonic hedgehog (Shh; reddish) and Distal-Less Homeobox 2 (Dlx2; gray) genes colored by *in situ* hybridization in the diencephalon of a hole mount chick embryo; Shh labels the basal plate. This photography is reproduced from Figure 2B in [Martinez-Ferre and Martinez \(2012\)](#). (B), Scheme of a mammalian neural tube (left lateral view) showing neuromeres (from caudal to rostral: r11–r0, m2–m1, p1–p3, hp1, hp2, ATD), plates (from ventral to dorsal: floor, basal, alar, and roof plates), and the axis (yellow line) of the central nervous system according to [Puelles et al. \(1987b\)](#); [Puelles et al. \(2008\)](#); [Puelles and Rubenstein \(2015\)](#); [Nieuwenhuys and Puelles \(2016\)](#); and [Puelles \(2018\)](#). (C), Magnification of the telencephalic region in B; the pallial (MP, MMP, DP, LP, VP, pallial amygdala; yellow boundaries) and subpallial (St, Pal, Dg, POA; red boundaries) FMUs are represented. (D), Magnification of the prosomere p2 in B; the thalamic FMUs (ET, DTd, DTi, DTav) are represented in the alar plate. (E), Magnification of the rhombencephalon in B; the rhombic lip is delineated by a short-dashed black line in the alar plate adjacent to the roof plate; tangential migrations that give rise to the cerebellum (pink arrows), the pontine nuclei (purple arrows), and the inferior olive (mustard arrows) are represented. The floor plate is colored in red, the basal plate in pink, the alar plate in light blue, and the roof plate, in dark blue. ATD, acroterminal domain; Dlx2, Distal-Less Homeobox 2 gene; Dg, diagonal subpallial domain; DP, dorsal pallium; DTav, dorsal thalamus, anteroventral subdivision; DTd, dorsal thalamus, dorsal subdivision; DTi, dorsal thalamus, intermediate subdivision; DTv, dorsal thalamus, ventral subdivision; ET, epithalamus; Eth, epithalamus; HM, medial habenula; hp1–2, hypothalamic prosomeres 1–2; Hy, hypothalamus; LP, lateral pallium; m1–2, mesomeres 1–2; M, mesencephalon; MP, medial pallium; MMP, mesomedial pallium; p1–3, prosomeres 1–3; Pal, pallial subpallial domain; Pall. Amyg., amygdalar pallium; POA, preoptic subpallial domain; PT, pretectum; PTh, prethalamus; r0–11, rhombomeres 0–11; Shh, Sonic hedgehog; St, striatal subpallial domain; Subpall. Amyg., subpallial amygdala; T, telencephalon; Th, thalamus; VP, ventral pallium.

Ferran, 2012). Genoarchitectonic data has served to identify and delineate several FMUs that constitute the “building bricks” of a common nervous system Bauplan for all vertebrates, including primates. FMUs are patterned during primary events of specification under the induction of several organizers. The notochord and the lateral ectoderm specify the longitudinal floor, basal, alar, and roof plates. The isthmus, the *zona limitans intrathalamica* (ZLI), and the acroterminal domain (ATD) specify the transverse neuromeres, which are segments of neural tube comprising a representation of the four plates; from caudal to rostral there are twelve rhombomeres (r11-r0; r0 corresponds to the isthmus), two mesomeres (m2-1), and six prosomeres (p1-3, hp1-2, and the ATD). The intersection of longitudinal plates and transverse neuromeres in the neural plate creates a checkboard of histogenetic units, each of them characterized by a specific gene expression profile detected by genoarchitectonic techniques. Further molecular processes within the histogenetic units specify progenitor domains which constitute the FMUs that will give rise to adult brain structures (Figure 2B). The Bauplan formed by the FMUs is conceptualized in the Prosomeric Model [for a review of the Prosomeric Model see Puelles et al. (2013); Nieuwenhuys and Puelles (2016); Nieuwenhuys (2017); García-Calero and Puelles (2020); Puelles (2021)] and takes into account the Natural axis of the central nervous system, which corresponds to the rostro-caudal axis of the early neural tube before it folds [yellow line in Figure 2B; see also Figure 2 in Nieuwenhuys (2017)]. Thus, anatomical descriptors, like rostral, caudal, ventral, and dorsal can be used in a topological sense in relation to this axis; for example, the hypothalamus in the adult brain is topographically ventral to the thalamus but, from the point of view of the Prosomeric Model is topologically rostral to the thalamus. It is important to note that the topological position of each FMU in relation to the others is invariant across vertebrate species. Such invariance allows to propose homology hypothesis based on Field homology: two nervous system structures in two different vertebrate species are homologues if they originate in the same FMU (Puelles and Medina, 2002).

According to the Prosomeric Model, the hypothalamus is a derivative of the floor, basal, and alar plates of hp1, hp2, and the ATD and the telencephalon is a topologically dorsal extension of the alar plate of prosomere hp1, with a small contribution from hp2 (Puelles and Rubenstein, 2015). Four subpallial and six pallial FMUs are specified in the telencephalon. The subpallial FMUs are Striatum (St, gives rise to the striatum), Pallidum (Pal, gives rise to the globus pallidus and the lateral part of the bed nucleus of the stria terminalis), Diagonal (Dg, gives rise to basal prosencephalic structures and the medial part of the bed nucleus of the stria terminalis), and Preoptic (POA, the only part of the telencephalon originated in the alar plate of hp2; gives rise to the preoptic region) (García-López et al., 2008; Medina et al., 2011). The pallial FMUs are the medial pallium (gives rise to the hippocampal allocortex and the entorhinal cortex), the ventral pallium (gives rise to the primary olfactory cortex and the olfactory bulb), the lateral pallium (gives rise to paraolfactory mesocortices), the mesomedial pallium (a hypothetical pallial sector that should give rise to the parahippocampal mesocortices), the dorsal pallium (gives rise to

the isocortex), and the amygdalar pallial sector (Puelles et al., 2019; García-Cabezas et al., 2023a). Amygdalar nuclei are originated in the amygdalar pallial sector but also in the four subpallial FMUs [García-López et al. (2008); Puelles et al. (2019); Figure 2C]. Several smaller FMUs have been identified within the amygdalar pallial sector (García-Calero et al., 2020).

The thalamus was considered a diencephalic column in the Columnar Model of Herrick (1910; 1933; 1948) and Kuhlbeck (1967–1978), but genoarchitectonic data show that it is originated in the alar plate of p2, with the exception of the thalamic reticular nucleus, which is originated in the alar plate of p3. Five smaller FMUs have been identified in the alar plate of p2 [Martinez-Ferre and Martinez (2012); Redies et al. (2000); Figure 2D].

In the rhombencephalon, twelve rhombomeres have been identified based on cytoarchitectonic boundaries and gene expression profiles (Nieuwenhuys, 2011). The rhombic lip is a region of the alar plate adjacent to the floor plate that extends from r0 to r10. This region is specialized in producing neurons that will tangentially migrate long distances, like the inferior olive, the pontine nuclei, and the cerebellum. The inferior olive originates from tangential migrations starting at the rhombic lip from r10 to r8 and ending in the basal plate of these same rhombomeres (Tomas-Roca et al., 2016). The pontine nuclei are originated by massive tangential migrations starting at the rhombic lip from r8 to r6; these migrations transverse several rhombomeric boundaries and invade the basal plate of r3 and r4 (Tomas-Roca et al., 2016; Kratochwil et al., 2017). The rhombic lip also contributes to form the cerebellum, which has a dual origin. First, excitatory cerebellar neurons are originated in the rhombic lip at r1 and tangentially migrate to populate the prospective cerebellar cortex and the deep cerebellar nuclei. Second, GABAergic inhibitory cerebellar neurons originate in a different sector of the ventricular zone in the alar plate of r1 and radially migrate to the prospective cerebellar cortex and the deep cerebellar nuclei [Martinez et al. (2013); Figure 2E].

2.3 The Columnar and the Prosomeric Models face to face

The Columnar and the Prosomeric Models propose two different Bauplans for the vertebrate nervous system from two different epistemological and ontological frameworks (Table 1). The Columnar Model is based on the microscopic examination and 3D reconstruction of embryos that are cut and stained with classic techniques, like Nissl staining (Figure 1C). These techniques allow for identifying sulci, bulges, and columns produced by differential growth of some parts of the neural tube over others. Finally, the Columnar Model describes an axis of the neural tube that considers the telencephalon as its most rostral part.

In contrast, the Prosomeric Model is based on the microscopic examination of embryos that are stained with *in situ* hybridization and immunohistochemistry to color the expression of morphogenetic genes, like Shh. These techniques allow for identifying boundaries between parts of the embryo that express a given gene and other parts that do not express it; for instance, Shh is expressed in the basal plate, but not in the alar plate (Figure 2A).

TABLE 1 Epistemological differences between the Columnar and the Prosomeric Models.

	Columnar Model	Prosomeric Model
Basic references	Herrick (1910); Herrick (1933); Herrick (1948); Kuhlenbeck (1954); Kuhlenbeck (1967–1978)	Puelles et al. (1987a); Puelles and Rubenstein (1993); Nieuwenhuys and Puelles (2016); Nieuwenhuys (2017)
Anatomical techniques used	Classical stains	Genoarchitecture
Definition of boundaries	Sulci	Gene expression boundaries
Axis of the central nervous system	Adult nervous system Central axis	Natural axis (alar-basal plate boundary)

Finally, the Prosomeric model uses the Natural axis of the neural tube that roughly matches the alar-basal plate boundary and considers that the entire neural tube is epichordal.

The use of different staining techniques provides each model with different ontological power because the classic stains of the Columnar Model and the genoarchitectonic stains of the Prosomeric Model detect different events of development. In embryos, we can define three types of events [Nieuwenhuys and Puelles (2016); Table 2]. First, the *primary events of specification* are the result of induction processes directed by organizers like the notochord or the isthmus; there are several levels of specification, from the specification of the neural plate by the hypoblast and the primitive node (Echevarria et al., 2003) to the specification of histogenetic units and FMUs. Second, the *secondary events of histogenesis* comprise all the cellular processes, like neurogenesis, cell migration, or axon growth, that lead to circuit formation after FMUs are specified. Finally, the *tertiary events of morphogenesis* consist in the appearance of sulci in the ventricular and pial surfaces of the neural tube, in the deformation of the neural tube like and accordion, and in the enlargement of vesicles, columns, and eminences due to the differential growth of some FMUs over others; the tertiary events of morphogenesis also comprise the formation of grisea (thalamic nuclei, cortical layers, etc.) after secondary events finalize. Thus, the Columnar Model uses tertiary events of morphogenesis (like the diencephalic columns separated by the diencephalic sulci) to define the constituents of the neural tube. In contrast, the Prosomeric Model defines FMUs of the nervous system according to the primary events of specification.

In comparative and evolutionary neuroanatomy, the choice of one Bauplan model over another is not a trivial question. Specifically, the genetic mechanisms that underlie changes in the relative dimension of nervous system parts [“mosaic” evolution; Barton and Harvey (2000)] could be searched for in the constituent units of the Columnar or the Prosomeric Model Bauplans. We consider that the Prosomeric Model, with FMUs defined by the primary events of specification, provides a better framework for investigating differential expansion of nervous system parts across species than the Columnar Model. For instance, the expansion of

TABLE 2 Types of events during embryological development.

Primary events (Specification)	1 st level Specification of the neural plate
	2 nd level Specification of floor, alar, basal, and roof plates Specification of neuromeres The intersection of plates and neuromeres produces a checkboard of histogenetic units
	3 rd level Specification of FMUs in the histogenetic units
	4 th level Further lineage specification in the FMUs
Secondary events (Histogenesis)	Neurogenesis
	Cell migration
	Axon navigation and growth
	Dendrite growth
	Cytoplasmic differentiation
	Cell nucleus differentiation
	Synapse formation
Synapse pruning	
Tertiary events (Morphogenesis)	Myelination
	Sulci
	Flexures
	Vesicles
	Eminences
	Columns
Formation of nuclei and layers	

the pontine nuclei in primates should be studied in the rhombic lip of rhombomeres r6-8, two of which are cryptorhombomeres that are identified using genoarchitectonic techniques [Tomas-Roca et al. (2016); Figure 2E]. Regarding the diencephalon, one FMU corresponds to the epithalamus column of Herrick, but other four FMUs have been identified in the alar plate of p2, which corresponds to the dorsal thalamus column [Martinez-Ferre and Martinez (2012); Figure 2D]; each of these thalamic FMUs is differentially expanded in vertebrates [see Figure 5 in Puelles (2001)]. Finally, in the telencephalon the subpallial ganglionic eminences, which are bulges on the ventricular surface due to tertiary events of morphogenesis, are composed of four FMUs, each of them with specific contributions to subpallial nuclei [Puelles et al. (2016); Figure 2C]; on the other hand, the pallium is composed of six FMUs [five of them give rise to the cerebral cortex and one to the pallial amygdala, Puelles et al. (2019); Figure 2C] that are differentially expanded in primates compared to rodents (García-Cabezas et al., 2023a).

In summary, the Prosomeric Model provides an ontology of central nervous system parts based on the primary events of

specification, which are mediated by the action of gene regulatory networks that direct and coordinate the development of the vertebrate nervous system. Also, the Prosomeric Model Bauplan allows to propose homology hypothesis based on Field homology. Therefore, the FMU-based ontology provides a framework for meaningful interspecies comparison and searching for causal mechanisms of nervous system part expansion in phylogeny.

3 Expanded nervous system structures in humans compared to rats

A first look at the rat and human central nervous systems brings to light quantitative differences. Figure 3 shows several adult rat central nervous system regions around a micrograph of a parasagittal section stained with Nissl. Figure 3A represents a fate map of the early pallium from a rat embryo with the six pallial FMUs, Figure 3B represents the cortical gradient of laminar complexity with its different cortical types (allocortex, mesocortex, eulaminate), Figure 3C represents in grayscale these cortical types on the fate map of the early pallium, and Figure 3D shows higher magnifications of representative cortical regions with different grade of laminar complexity. Other regions, like the dorsal (Figure 3E) and ventral striatum (Figure 3F), the thalamus (Figure 3G), and the cerebellar cortex (Figure 3H), are showed in higher magnification.

In contrast, Figure 4 shows schemes of several adult human central nervous system regions on top of and on a parasagittal section drawing [from the Atlas of Marburg (1904)]. Figure 4A represents the cortical gradient of laminar complexity with its different cortical types (allocortex, mesocortex, eulaminate I, eulaminate II, eulaminate III, konicocortex), Figure 4B represents in grayscale these cortical types on the fate map of the early pallium, and Figure 4C represents the same cortical types on the surface of the left hemisphere. Other brain regions, like the thalamus, the pons, the inferior olive, and the cerebellum, are highlighted on the parasagittal section drawing (Figure 4D).

The expansion of the cerebral cortex, the pons, and the cerebellum in the human compared to the rat nervous system stands out at first sight when comparing Figures 3 and 4. In the following sections, we will analyze the quantitative (volume and neuron number) and qualitative (cytoarchitectonic and cell type differences) expansion of the cerebral and cerebellar cortices, the pontine nuclei, the striatum, the dopaminergic nigrostriatal system, the amygdala, and the thalamus in human and non-human primates compared to rodents. We will define several expansion modes and trace them back to the developmental primary events of specification and the secondary events of histogenesis, like neurogenesis and axon growth, in their corresponding prosomeric FMU.

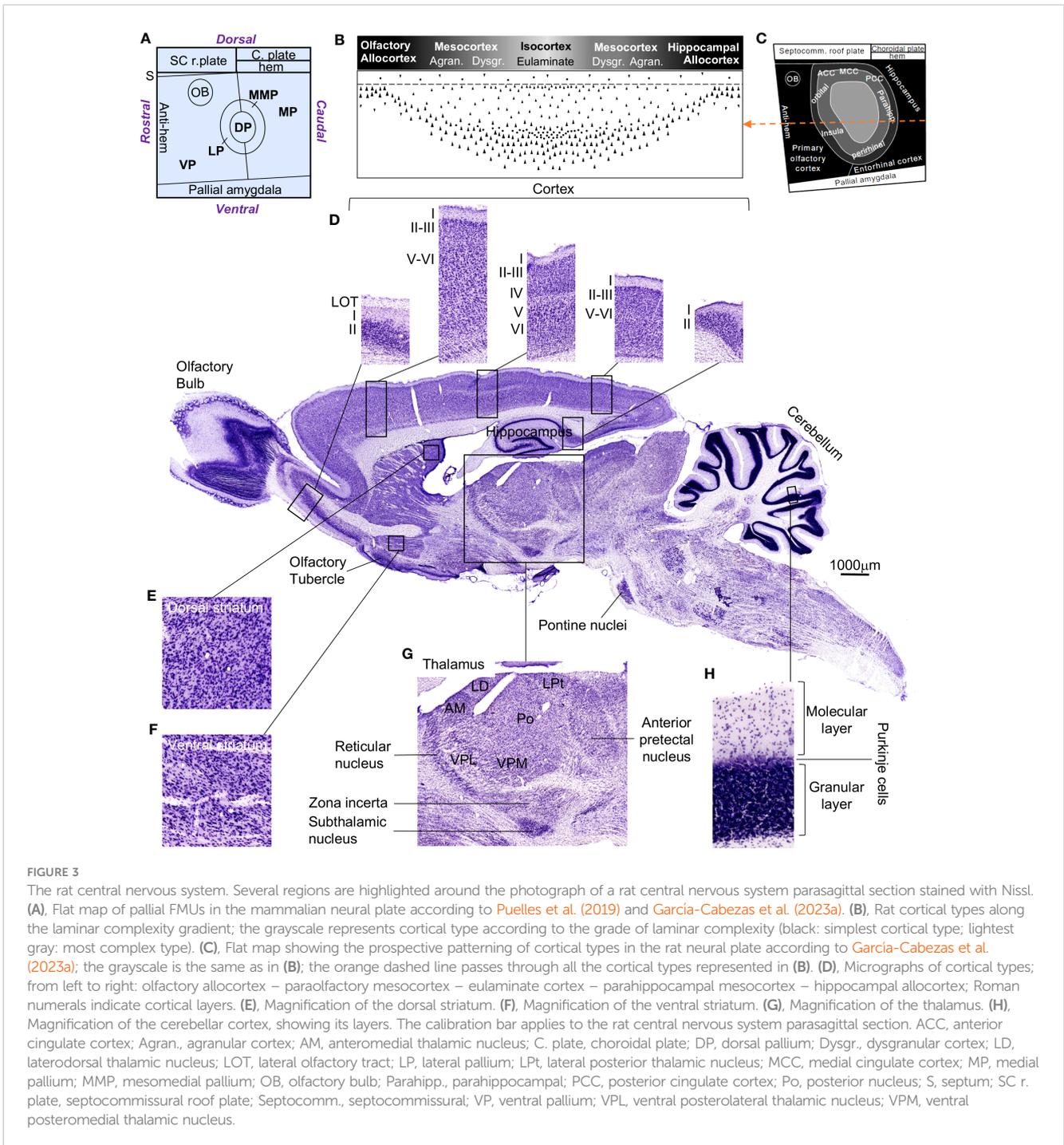
3.1 Tangential expansion of the primate cerebral cortex: “quantitative and qualitative expansion”

The primate cerebral cortex is significantly expanded compared to rodents. This expansion is not merely a quantitative extension of

cortical surface by the addition of more cortical columns with comparable laminar composition. On the contrary, new cortical types of higher laminar complexity that are absent in the rat cortex appear in the primate (García-Cabezas et al., 2023a). The appearance of new isocortical types (Eulaminate II, Eulaminate III, and Konicocortex; Figure 4A), was first observed in the human cortex by Friedrich Sanides (1962) and is at the base of the Hypothesis on the Dual Origin of the Neocortex (Sanides, 1970; García-Cabezas et al., 2023a). This hypothesis is supported, at least partially, by genoarchitectonic data obtained in mammalian embryos that suggest that the tangential expansion of the human and non-human primate cerebral cortex seems to have been directed by molecular signalling form developmental organizers like the hem, the anti-hem, and the septocommissural roof plate (Puelles et al., 2019). Primate cortical expansion seems to involve the specification of new isocortical (eulaminate) types in the dorsal pallium FMU (Figure 4B), as suggested by García-Cabezas et al. (2023a).

We have described previously in detail the cytoarchitecture of cortical types along the gradients of laminar complexity in rat, macaque, and human cerebral cortices (García-Cabezas et al., 2019; García-Cabezas et al., 2020; John et al., 2022; Aparicio-Rodríguez and García-Cabezas, 2023; García-Cabezas et al., 2023a). We have also described the differences in the embryonic cortical layers of rats and humans, highlighting the absence of intermediate progenitors in the rat cortex and in prospective human mesocortical areas and their abundance in prospective human eulaminate areas (Barbas and García-Cabezas, 2016; García-Cabezas et al., 2019). Briefly, the tangentially expanded part of the primate cerebral cortex (eulaminate II, eulaminate III, and konicocortical areas) requires an expanded germinal zone composed of ventricular and well-developed subventricular (including outer subventricular) zones (Reillo et al., 2011); the latter, which is underdeveloped in the rat embryonic cortex and in prospective mesocortical human areas, contains intermediate progenitors that produce the abundant granular neurons in layer IV and the projection neurons in layers II and III. It is important to recall that eulaminate II, eulaminate III, and konicocortical areas in the primate cortex have higher neuron density at the expenses of their layers II, III, and IV than mesocortical areas (O’Kusky and Colonnier, 1982; Dombrowski et al., 2001; García-Cabezas et al., 2017). Also, the expanded primate cerebral cortex contains more GABAergic interneurons than the rodent cortex [25% and 15% of the total neuron population, respectively; DeFelipe (2011)]; in the latter species cortical GABAergic interneurons are originated in subpallial domains and tangentially migrate to the cortical plate (Marin and Muller, 2014), but in primates they are also originated in pallial sectors (Letinic and Rakic, 2001; Fertuzinhos et al., 2009; Delgado et al., 2022) and probably migrate guided by radial glia, like cortical excitatory neurons do.

In summary, the tangential expansion of the human cerebral cortex (Figure 4A) consisted in the addition of cortical types that do not exist in rodents (Figure 3B). These new types are probably specified in concentric rings within the dorsal pallial FMU (Figure 4B) and contain a well develop subventricular zone with abundant intermediate progenitors. The new cortical types in primates have more excitatory neurons in layers II–IV than in layers V–VI and more GABAergic interneurons across all layers from both pallial and subpallial origin.



Thus, we describe the expansion mode of the human cerebral cortex as “Quantitative and qualitative expansion”.

3.2 Primate pontine nuclei, cerebellum, and striatum expansion: “general quantitative expansion”

Several circuits involving the cerebellum and pontine nuclei support different aspects of cortical function [[Caligiore et al. \(2017\)](#); [Figure 5](#)]. Extensive cortical regions project to the pontine nuclei,

which in turn project to the contralateral cerebellar cortex. Then, Purkinje neurons in the cerebellar cortex project to the deep cerebellar nuclei, which in turn project to the contralateral thalamus. Thalamocortical neurons in the cerebellar thalamic territory close the loop projecting back to frontal cortical areas ([Schmahmann and Pandya, 2008](#)). The development of these circuits involves the specification of cerebral cortex, pontine, cerebellar, and thalamic neurons in the alar plate of neuromeres hp1, r6-8, r1, and p2, respectively ([Figures 2C–E](#)). Pontine neurons are originated in the alar plate (rhombic lip) of r6-8. Excitatory cerebellar neurons (granule cells in the cerebellar cortex and

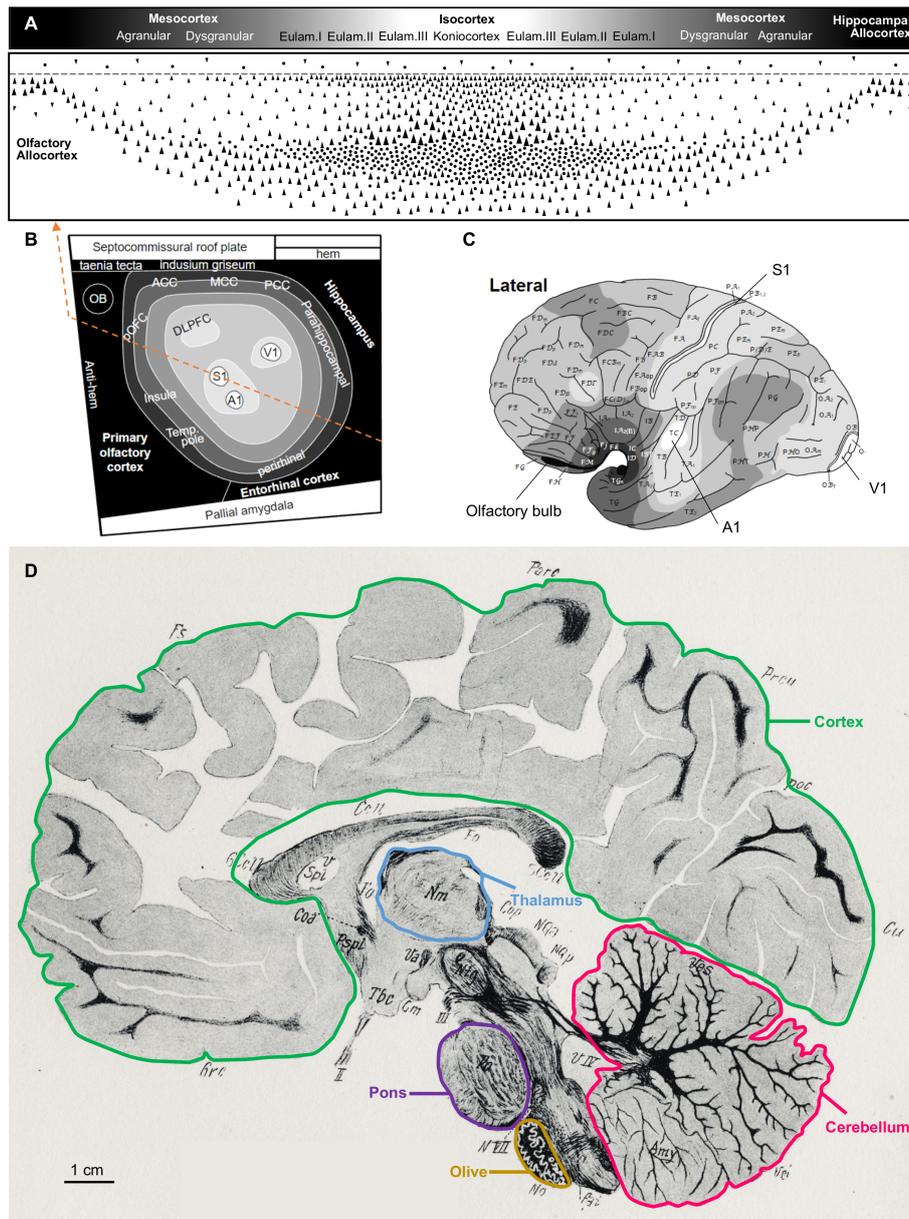


FIGURE 4

The human central nervous system. Several regions are highlighted on top and on a drawing of a human central nervous system parasagittal section stained for myelin [reproduced from Figure 80 in the atlas of Marburg (1904)]. (A), Human cortical types along the gradient of laminar complexity; the grayscale represents cortical types according to the grade of laminar complexity (black: simplest cortical type; white: most complex type). (B), Flat map showing the prospective patterning of cortical types in the primate neural plate according to García-Cabezas et al. (2023a); the grayscale is the same as in A; the orange dashed line passes through all the cortical types represented in (A). (C), Drawing of the lateral view of a left adult human brain hemisphere showing the distribution of cortical types [modified from García-Cabezas et al. (2020), licensed under CC-BY 4.0]; the grayscale is the same as in (A). (D), Drawing of a parasagittal section of the human brain stained for myelin. The cortex (green contour), thalamus (blue contour), pons (purple contour), olive (mustard contour), and cerebellum (pink contour) are delineated. The calibration bar applies to the human central nervous system parasagittal drawing. A1, primary auditory area; ACC, anterior cingulate cortex; DLDFC, dorsolateral prefrontal cortex; Eulam., eulaminate cortex; MCC, middle cingulate cortex; OB, olfactory bulb; PCC, posterior cingulate cortex; pOFC, posterior orbitofrontal cortex; S1, primary somesthetic area; Temp. pole, temporal pole; V1, primary visual area.

neurons in the deep cerebellar nuclei) are originated in the rhombic lip of r1, while GABAergic cerebellar neurons (like Purkinje cells) are originated in another sector of the alar plate in r1 (Leto et al., 2016). The thalamic nuclei that receive the deep cerebellar nuclei projection, like the ventral posterior lateral nucleus–oral part (Asanuma et al., 1983), are originated in the Dorsal Thalamus dorsal tier (DTd; in the alar plate of p2) FMU (Puelles, 2001).

Finally, the frontal areas that receive projections originated in the cerebellar thalamic territory are originated in the mesomedial pallium (mesocortical cingulate motor areas) and the dorsal pallium (isocortical frontal areas) (Puelles et al., 2019; García-Cabezas et al., 2023a).

Contrary to the cerebral cortex, there is not significant variation in the neuron types that constitute the cerebellum and the pontine

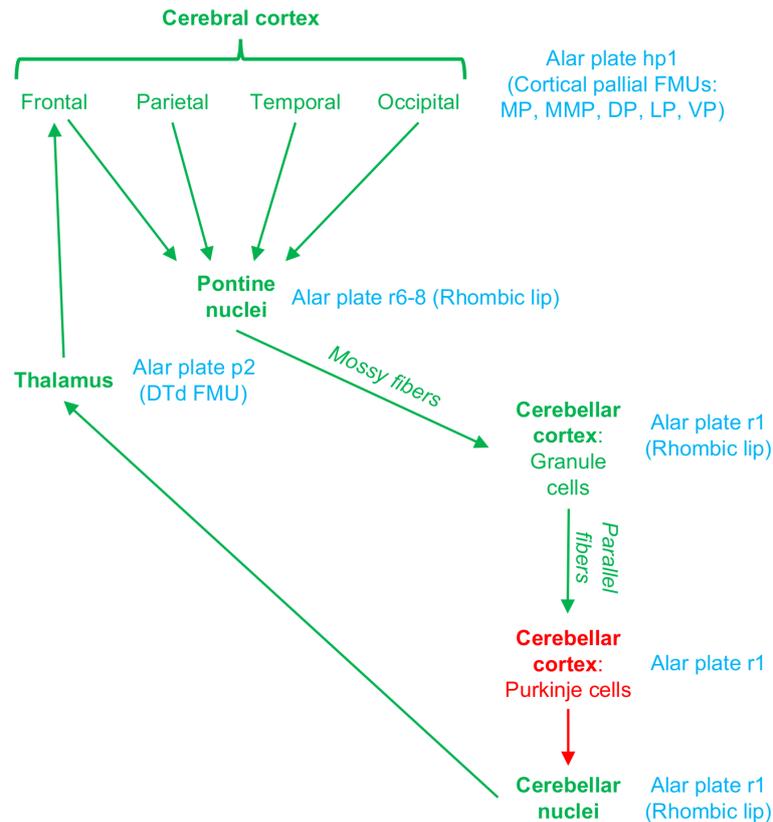


FIGURE 5

Circuits connecting the cerebral cortex with the pontine nuclei and the cerebellum. Excitatory pathways are colored in green and inhibitory (GABAergic) in red. The corresponding plate, neuromere, and FMU of each circuit station is indicated in blue. Note that all the neurons that form these cortico-pontine, ponto-cerebellar, cerebellar-thalamic, and thalamo-cortical pathways are originated in alar plate FMUs from six different neuromeres. For abbreviations see Figure 2.

nuclei in primates compared to rodents. Actually, the cerebellar cytoarchitecture and cellular composition does not change significantly in primates compared to rodents (Larsell and Jansen, 1967; Baizer, 2014), but the human cerebellar cortex has a much higher index of gyrification than the rat cerebellar cortex (compare Figures 3, 4). Regarding the pontine nuclei, it seems that the differences between rodents and primates are quantitative (with a significant expansion of these nuclei in the human brainstem as showed in Figure 4D) without the addition of new neuron types (Mihailoff et al., 1981; Schmahmann and Pandya, 1997). In summary, the expansion of the primate cerebellum and pontine nuclei does not involve major cytoarchitectonic modifications and probably “just” consists in the addition of more neurons of basically the same types as in rodents. Therefore, we describe the expansion mode of these structures as “General quantitative expansion”.

Besides ponto-cerebellar circuits, the basal ganglia also support cortical function. The striatum is the most important input nuclei of the basal ganglia, and its sectors [olfactory tubercule (TOL), nucleus accumbens (NAc), putamen (Put), and caudate (Cd); originated from the St subpallial FMU; reviewed in Del Rey and García-Cabezas (2023)] receive projections from the entire cerebral cortex. Synaptic tract-tracing studies in primates show that corticostriatal projections are arranged topographically in parallel to cortical type; thus, hippocampal and olfactory allocortices project to TOL and

NAc, mesocortical areas project mostly to NAc, and isocortical eulaminate areas project to Put and Cd (Figures 6A, B). In rats, corticostriatal projections are also arranged in parallel to cortical type (Figures 7A, B), but the cortical gradient of laminar complexity in these species does not include highly eulaminate isocortical types (Figures 3B, 7A). Therefore, the pattern of corticostriatal projections in primates and rats is compatible with a striatal expansion in parallel to the tangential cortical expansion [see Del Rey and García-Cabezas (2023)]. Contrary to the cortex, the overall cytoarchitecture and neuron composition of the rat and primate striatum does not vary significantly across striatal nuclei or species, with medium spiny neurons constituting over 80% of the entire neuron population in the striatum of rodents and primates (Del Rey et al., 2022). We can conclude that the expansion of the striatum in primates, like the cerebellum and the pontine nuclei, follows a “General quantitative expansion”.

3.3 Primate dopaminergic nigrostriatal pathways: “telodendron expansion”

Besides corticostriatal pathways, the striatum receives dopaminergic projections from the substantia nigra *pars compacta* (SNc) and the ventral tegmental area (VTA). These

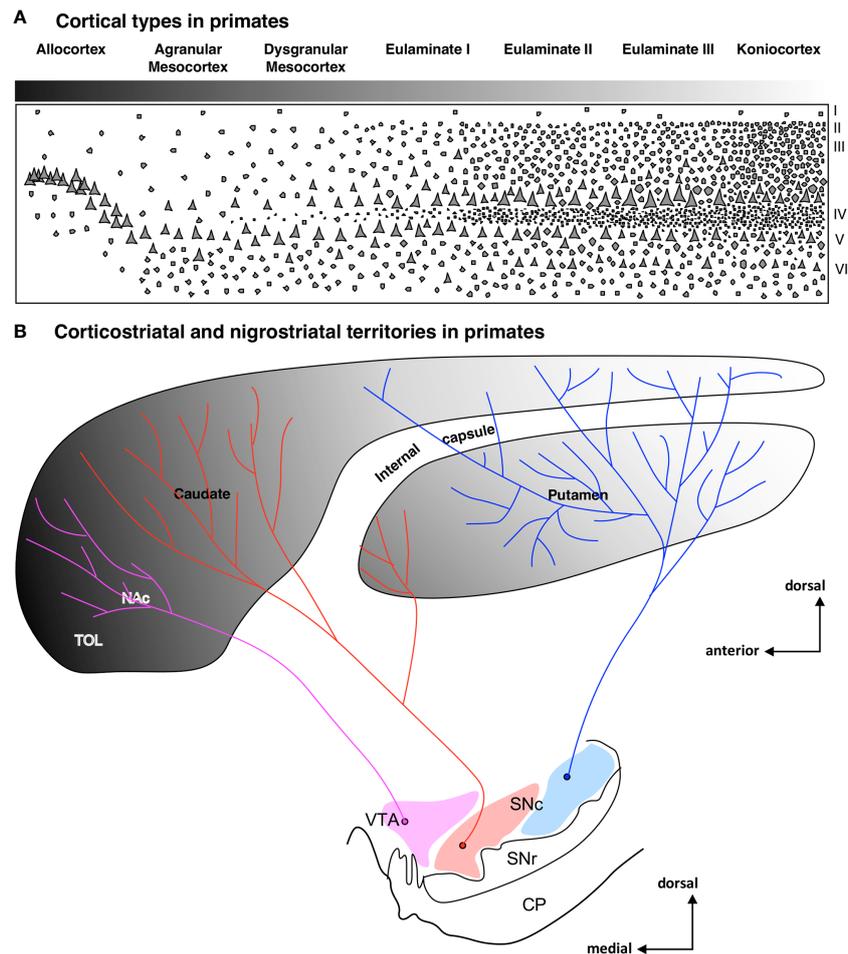


FIGURE 6

Corticostriatal and nigrostriatal territories in primates. (A), Laminar complexity gradient in the primate cerebral cortex. The grayscale represents cortical types according to the grade of laminar complexity (black: simplest cortical type; white: most complex type); Roman numerals indicate cortical layers. (B), Scheme of the striatum showing the distribution of corticostriatal [according to Yeterian and Pandya (1991); Yeterian and Pandya (1993); Yeterian and Pandya (1995); Yeterian and Pandya (1998); reviewed in Del Rey and García-Cabezas (2023)] and nigrostriatal [according to Lynd-Balta and Haber (1994)] territories. The grayscale represents the corticostriatal territories according to the corresponding cortical type of the projecting areas. Pink represents the ventral tegmental area (VTA), red represents the medial part of the substantia nigra *pars compacta* (SNc), and blue represents the lateral part of SNc. CP, cerebral peduncle; NAc, nucleus accumbens; SNc, substantia nigra *pars compacta*; SNr, substantia nigra *pars reticulata*; TOL, olfactory tubercle; VTA, ventral tegmental area.

projections are key for motor and cognitive functions and are disrupted in neuropsychiatric disorders like Parkinson's disease [reviewed in Del Rey and García-Cabezas (2023)]. The macaque striatum volume increases one order of magnitude compared to rodents and the human striatum is nearly 10 times larger than the macaque striatum (Figure 8A). Thus, the striatum volume in humans compared to rodents increases in a logarithmic scale (Figure 8B). In contrast, the number of dopaminergic SNc neurons increases only in one order of magnitude in humans compared to rodents (Figure 8C). Thus, each dopaminergic neuron in the human SNc must provide innervation to four times more striatal volume than equivalent macaque neurons and ten times more striatal volume than equivalent rodent neurons (Figure 8D). It is important to note that the striatal volume occupied by neuropil compared to the volume occupied by neuron bodies also increases in humans compared to rodents. This is evidenced by microscopic examination of the striatum in

Nissl-stained sections (Figures 8E–H); Nissl technique stains neuron bodies and the nuclei of neurons, glial, and endothelial cells, but leaves the neuropil (dendrites, spines, axons, axon terminals, and synapses) unstained. Thus, human dopaminergic SNc neurons must innervate not only larger striatal volumes than those innervated by macaques and rodents, but also enriched-in-synapses volumes. We hypothesize that, in order to provide dopaminergic innervation to their corresponding enriched-in-neuropil larger striatal volumes, human dopaminergic SNc neurons may have significantly longer telodendria (Figure 6B) than those of rodent nigral neurons (Figure 7B). The increase in body size of SNc neurons in primates compared to rodents (Figures 8I–K), especially in humans (Figure 8L), may reflect larger metabolic burdens of human dopaminergic SNc neurons due to their longer telodendria and higher number of synapses, which, as has been suggested (Bolam and Pissadaki, 2012), may render human SNc neurons vulnerable to Parkinson's disease. In

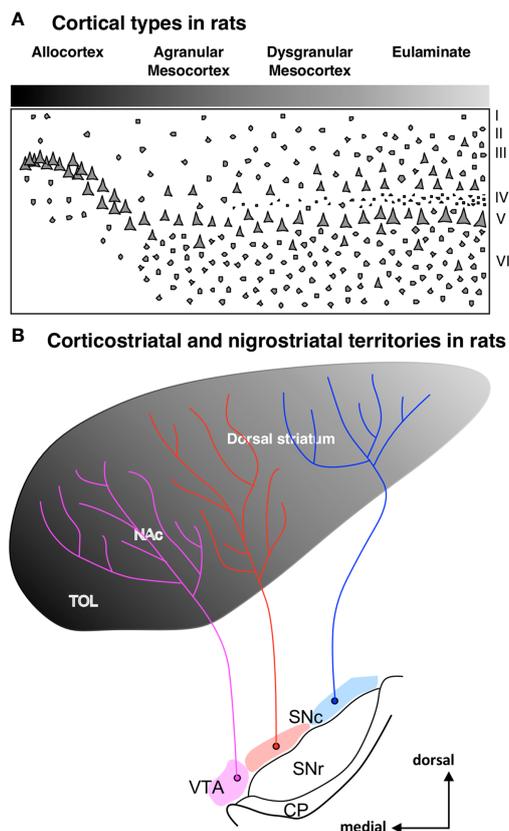


FIGURE 7

Corticostriatal and nigrostriatal territories in rats. **(A)**, Laminar complexity gradient in the rat cerebral cortex. The grayscale represents cortical types according to the grade of laminar complexity (black: simplest cortical type; lightest gray: most complex type); Roman numerals indicate cortical layers. **(B)**, Scheme of the striatum showing the distribution of corticostriatal [according to Heimer (2008)] and nigrostriatal [according to Beckstead et al. (1979)] territories. The grayscale represents the corticostriatal territories according to the corresponding cortical type of the projecting areas. Pink represents the ventral tegmental area (VTA), red represents the medial part of the substantia nigra *pars compacta* (SNc), and blue represents the lateral part of SNc. CP, cerebral peduncle; NAc, nucleus accumbens; SNc, substantia nigra *pars compacta*; SNr, substantia nigra *pars reticulata*; TOL, olfactory tubercle; VTA, ventral tegmental area.

summary, we describe the expansion mode of the primate dopaminergic nigrostriatal system as “Telodendron expansion”.

3.4 The primate vs rat amygdala: “focal quantitative expansion”

The amygdala is composed of pallial and subpallial nuclei. Cytoarchitectonic studies in rat, macaque, and human amygdala have identified a comparable set of nuclei, with the only probable exception of the primate paralaminar nucleus, as showed in Figure 9. Some amygdalar nuclei originate in the four subpallial FMUs [García-López et al. (2008); red, Figures 9A–C] and others originate in several FMUs within the pallial amygdalar sector [García-Calero et al. (2020); yellow, Figures 9A–C]. Subpallial amygdalar nuclei are composed mostly of GABAergic neurons and issue inhibitory projections (red pathways, Figure 9C) to effector autonomic nuclei in the hypothalamus and the brainstem. On the other hand, pallial amygdalar nuclei are composed mostly of

excitatory neurons (green pathways, Figure 9C) and have reciprocal connections with mesocortical limbic and isocortical multimodal and unimodal associative areas.

The amygdalar volume in macaques (Figure 9C) and humans (Figure 9B) increases compared to rats (Figure 9A). But this volume expansion is not homogeneous, because the relative size of the subpallial and the cortical pallial nuclei is not preserved. Actually, the Lateral (L), Basolateral (BL), and Basomedial (BM) nuclei are significantly expanded in macaques compared to rats and in humans compared to macaques (Figure 9). The expanded primate amygdalar nuclei are connected to mesocortical and isocortical areas (Barbas and de Olmos, 1990; Hoistad and Barbas, 2008; Timbie et al., 2020), suggesting that they expand in parallel to the isocortex. The expansion of pallial amygdalar nuclei does not seem to have involved the appearance of different neuron types, because the amygdala in rodents (Millhouse and DeOlmos, 1983; Millhouse, 1986) and primates (Ulfig et al., 2003; Zikopoulos et al., 2016) is composed of comparable neuron types. Therefore, we describe the expansion mode of the primate amygdala as “Focal quantitative expansion”.

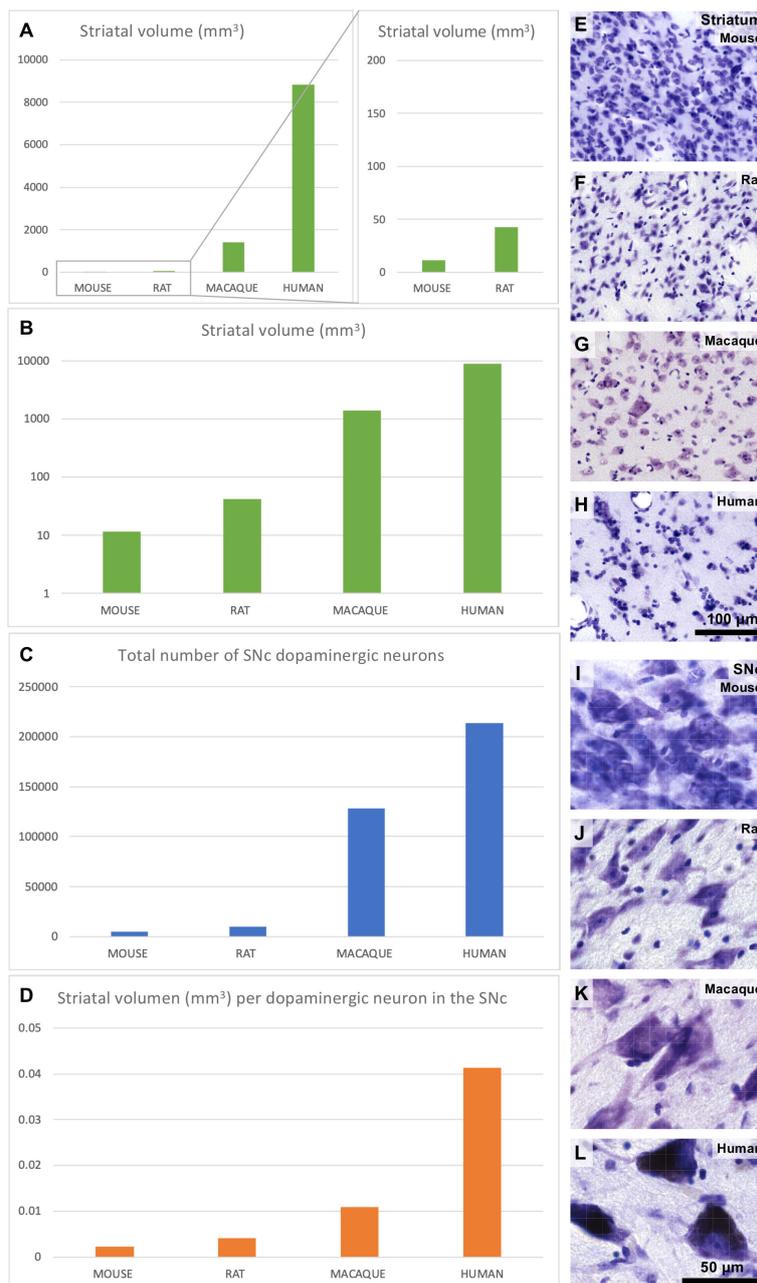


FIGURE 8

Striatal and nigral expansion in primates compared to rodents. (A), Mouse, rat, macaque, and human unilateral striatal volume. (B), Mouse, rat, macaque, and human unilateral striatal volume in logarithmic scale. (C), Unilateral number of dopaminergic neurons in the mouse, rat, macaque, and human substantia nigra *pars compacta* (SNc). (D), Striatal volume per dopaminergic SNc neuron in mice, rats, macaques, and humans. (E–H), Micrographs of the mouse, rat, macaque, and human striatum from Nissl-stained sections. (I–L), Micrographs of the mouse, rat, macaque, and human SNc from Nissl-stained sections. Calibration bar in H applies to (E–H) and in L applies to (I–L). Striatal volume data used in this Figure were obtained from Hajek et al. (2009); Yin et al. (2009); Park et al. (2011); Li et al. (2015); Crum et al. (2017); Hamezah et al. (2017) and Nguyen et al. (2020). SNc dopaminergic neuron numbers used in this Figure were obtained from Oorschot (1996); Emborg et al. (1998); Baquet et al. (2009); Omelchenko et al. (2016); Smeyne et al. (2016); Alam et al. (2017); Ip et al. (2017); Vidyadhara et al. (2017); Selemon and Begovic (2020) and Belliveau et al. (2021). See also Supplementary Data File.

3.5 The primate thalamus: “focal quantitative and cell lineage expansion”

The human thalamus (Figure 4D) is larger than the rat thalamus (Figure 3G), but, contrary to the amygdala, there are also qualitative differences in the cytoarchitectonic parcellation of

thalamic nuclei across these species. Comparable functional nuclear groups are identified in the rat and human thalamus according to their synaptic connections (Figures 10A–H), but some of them, like the pulvinar complex and the ventral motor nuclei, are expanded and include further subdivisions in humans that are not identified in rats.

The developmental origin of thalamic nuclei has been traced to four FMUs in the alar plate of p2, with the exception of the thalamic reticular nucleus, which is originated in the alar plate of p3 (Figure 2D). This FMUs are the Epithalamus, the Dorsal Thalamus dorsal tier (DTd), the Dorsal Thalamus intermediate tier (DTi), the Dorsal Thalamus ventral tier (DTv), and the Dorsal Thalamus anteroventral tier (DTav) (Redies et al., 2000; Puelles, 2001; Martínez-Ferre and Martínez, 2012; Botella-Lopez et al., 2019). The thalamic nuclei originated in each of these FMUs are represented in Figures 10I–L for the rat thalamus and in Figures 10M–P for the human thalamus. Most nuclei in the rat and human thalamus originate from DTd, which rises the following question: Are smaller FMUs specified within DTd that would give rise to specific sets of thalamic nuclei, like pulvinar or ventral motor nuclei? Further developmental studies may identify smaller thalamic FMUs like those recently described in the pallial amygdala (García-Calero et al., 2020).

Regarding neuron composition, there is a significant difference between the rat and human thalamus. It has been known since the studies of Ramón y Cajal (1903; 1966) that the human thalamus is enriched in interneurons, which are scarce in the rodent thalamus. These interneurons, like the thalamic reticular neurons, are GABAergic (Arcelli et al., 1997) and in the rat thalamus are mostly restricted to the dorsal lateral geniculate nucleus (Figures 10Q–T); in contrast, in the primate thalamus there are GABAergic interneurons across all nuclei (Hunt et al., 1991) (Figures 10U–X). Thus, in the primate thalamus there are more GABAergic interneurons than in the rodent thalamus. In addition, thalamic GABAergic interneurons also have an outstanding feature that makes them a “game changer” for primate thalamic circuits. They have dendrites endowed with flat and pleomorphic GABA-containing vesicles that can be the presynaptic element in symmetric (GABAergic) synapses with other dendrites (Peters et al., 1991; Tai et al., 1995). Presynaptic inhibitory dendrites in the primate thalamus contribute to the formation of complex synaptic arrangements (Kultas-Ilinsky and Ilinsky, 1991; Timbie et al., 2020) that increase the complexity of thalamic circuits compared to rodents. Therefore, we describe the expansion mode of the primate thalamus as “Focal quantitative and cell lineage expansion”.

4 Potential causal mechanisms of expansion modes in the primate nervous system

In the previous sections we have defined several expansion modes according to differences in the cytoarchitecture and cell type composition of several expanded nervous system regions in primates compared to rodents. In Table 3 we summarize these expanded structures, their corresponding FMU, and the expansion modes features. In the following sections, we discuss the potential developmental causal mechanisms underlying the expansion modes in relation to the primary and secondary developmental events in the corresponding FMUs.

4.1 Neurogenetic heterochrony across species

The different expansion modes of nervous system structures in human and non-human primates compared to rodents described in the previous sections (Table 3) have been quantified volumetrically in several scaling models [e. g., Finlay and Darlington (1995); Yopak et al. (2010)]. Differences in volume can be due to differences in several cellular factors like the total neuron number, the extension of dendritic arborizations, the length of telodendria, or the amount of myelin. Of all these cellular factors, which are the result of secondary events of histogenesis (Table 2), the total neuron number is the most comparable across species because it can be unbiasedly quantified using stereological methods (Figure 11). The total encephalic, the total cerebral cortex, and the cerebellum neuron number in humans are nearly one order of magnitude higher than in macaques and two orders of magnitude higher than in rodents (Figures 11A–C; the data summarized in this figure were obtained from studies that used unbiased stereological methods – see figure legend and Supplementary Material File). This raises the question of whether the human brain expansion is “concerted” (isometric expansion of all human brain parts) or “mosaic” [some parts expand more than other; Barton and Harvey (2000); Charvet et al. (2011)]. In general, it is acknowledged that, in vertebrates, some brain parts expand more than others [e. g., birds have larger optic tectum, which develops in the alar plate of neuromere m1 (Puelles, 2016; Puelles, 2018), than mammals; Charvet et al. (2010)] and such differential expansions have been related to differential neurogenesis in the prospective expanded regions compared to the non-expanded [e. g., zebra finches -Passerines- have larger telencephalon and thicker proliferative pallial and subpallial subventricular zone than quails -Galliformes-; Charvet and Striedter (2009a)]. A recent study compared neurogenesis in lizard, chicken, and rat embryos and concluded that relative size differences of nervous system parts must result from developmental proliferative heterochrony (Amat et al., 2022). In fact, the vast number of neurons that are generated during human prenatal development implies longer neurogenetic periods, especially in the most expanded regions like the cerebral and cerebellar cortices. The classic article of Kahle (1951), who performed a semi quantitative description of the germinal matrix across developing neural structures in human embryos (Figure 12A), showed that alar plate derivatives (like the cerebral cortex, the striatum, the thalamus, or the spinal cord posterior horn) start and finalize their neurogenetic period later than basal plate derivatives (like the spinal cord anterior horn) resulting in longer neurogenetic periods. Actually, some of the alar plate derivatives have extended periods of neurogenesis in human embryos: in the cerebral cortex and the striatum neurogenesis ends by gestational week 26 (Kostovic et al., 2019; Kostovic et al., 2022) and in the cerebellum there is neurogenesis until the first years of postnatal life (Ten Donkelaar and Lammens, 2009; Iskusnykh and Chizhikov, 2022); in contrast, other alar plate derivatives, like the thalamus, finalized their neurogenesis by gestational week 10.

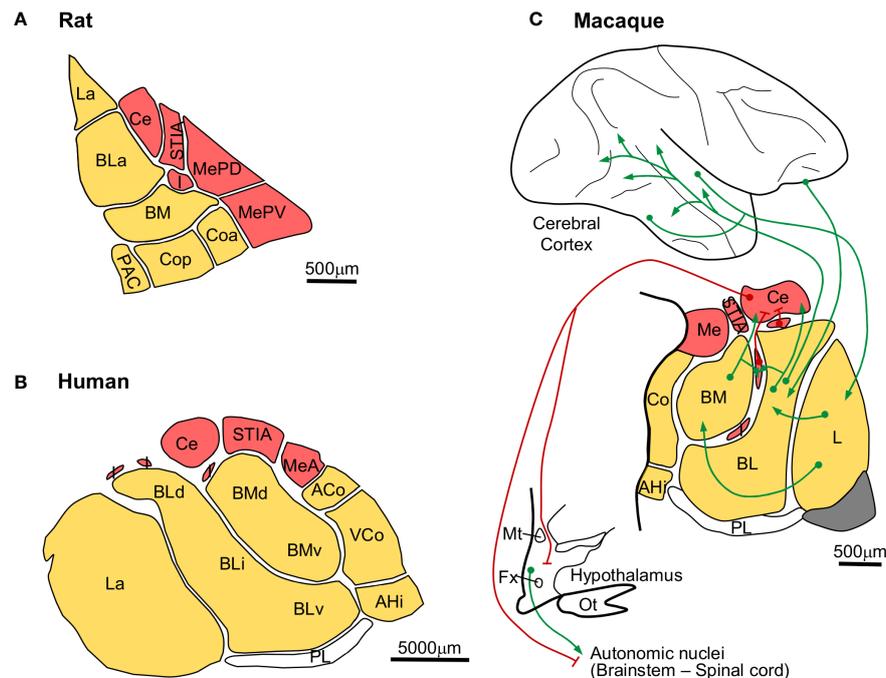


FIGURE 9

Expansion of pallial amygdalar nuclei in primates. (A), Rat amygdalar nuclei cytoarchitectonic parcellation in coronal section [according to Paxinos and Watson (2007)]. (B), Human amygdalar nuclei cytoarchitectonic parcellation in coronal section [according to de Olmos (1990)]. (C), Scheme of the macaque amygdalar cortical and subcortical synaptic connections [nuclear parcellation in coronal section according to Barbas and de Olmos (1990); synaptic connections according to Freese and Amaral (2009)]; red lines represent GABAergic inhibitory projections; green lines represent excitatory projections. Pallial amygdalar nuclei are colored in yellow; subpallial amygdalar nuclei are colored in red. The calibration bar in C applies only to the amygdala. ACo, anterior cortical nucleus; AHl, amygdalo-hippocampal area; BL, basolateral nucleus; BLd, dorsal subdivision of the basolateral nucleus; BLi, intermediate subdivision of the basolateral nucleus; BLv, ventral subdivision of the basolateral nucleus; BM, basomedial nucleus; BMd, dorsal subdivision of the basomedial nucleus; BMv, ventral subdivision of the basomedial nucleus; Ce, central nucleus; Co, cortical nucleus; Coa, anterior subdivision of the cortical nucleus; Cop, posterior subdivision of the cortical nucleus; L, lateral nucleus; La, lateral nucleus; Me, medial nucleus; MeA, anterior subdivision of the medial nucleus; MePD, posterodorsal subdivision of the medial nucleus; MePV, posteroventral subdivision of the medial nucleus; Mt, mammillothalamic tract; Ot, optic tract; PAC, periamygdaloid cortex; PL, paralaminal nucleus; STIA, intra-amygdaloid subdivision of the stria terminalis; VCo, ventral subdivision of the cortical nucleus.

The study of Kahle suggest that embryonic plates have intrinsic different neurogenetic capacity. All the expanded human nervous system structures analyzed in the present article are alar plate derivatives, except the SNc. Why the logarithmic volumetric increase of the primate striatum along phylogeny has not been paralleled by logarithmic increase in the number of dopaminergic SNc neurons? The answer may be in the developmental constrains of the FMUs that give rise to the SNc, which is a plurisegmental nucleus whose neurons are originated in the paramedian subdomain of the floor plate and in the adjacent medial sector of the basal plate along neuromeres p1-3 and m1-2; later, SNc neurons tangentially migrate to the superficial stratum of the basal plate in the neuromere where they were originated (Puelles and Verney, 1998; Verney et al., 2001; Marin et al., 2005). Importantly, the neurogenetic period that gives rise to the SNc in macaques lasts from embryonic day 36 (E36) to E43 (Levitt and Rakic, 1982), a much shorter neurogenesis period compared to macaque alar plate derivatives like the thalamus [from E25 to E50; Spadory et al. (2022)], the striatum [from E36 to E80; Brand and Rakic (1979); Brand and Rakic (1980)], the mesocortex [from E40 to E70; Granger et al. (1995)], and the koniocortex [from E45 to E102; Rakic (1974)]. This points to a severe constrain in the neurogenetic

capacity of the floor and basal plates, whose shorter periods of neurogenesis and earlier maturation compared to the alar plate (Charvet and Finlay, 2014) were already observed by Wilhelm His (1897; 1904).

In summary, some FMUs, like those in the floor and basal plates, have developmental constrains that impede their phylogenetic expansion. In contrast, alar FMUs seem to have higher phylogenetic flexibility and differentially expand across vertebrates (e.g., the optic tectum in birds, the cerebral cortex in mammals, the pontine nuclei in primates). These different developmental constrains would explain “mosaic” expansion of some nervous system parts over others.

4.2 Genetic regulation of primary and secondary developmental events

Some studies have addressed neurogenetic heterochrony in different vertebrate species [e.g., Charvet and Striedter (2008); Striedter and Charvet (2008); Charvet and Striedter (2009a); Charvet and Striedter (2010)] and related those differences with genetic regulation of primary events of specification and secondary

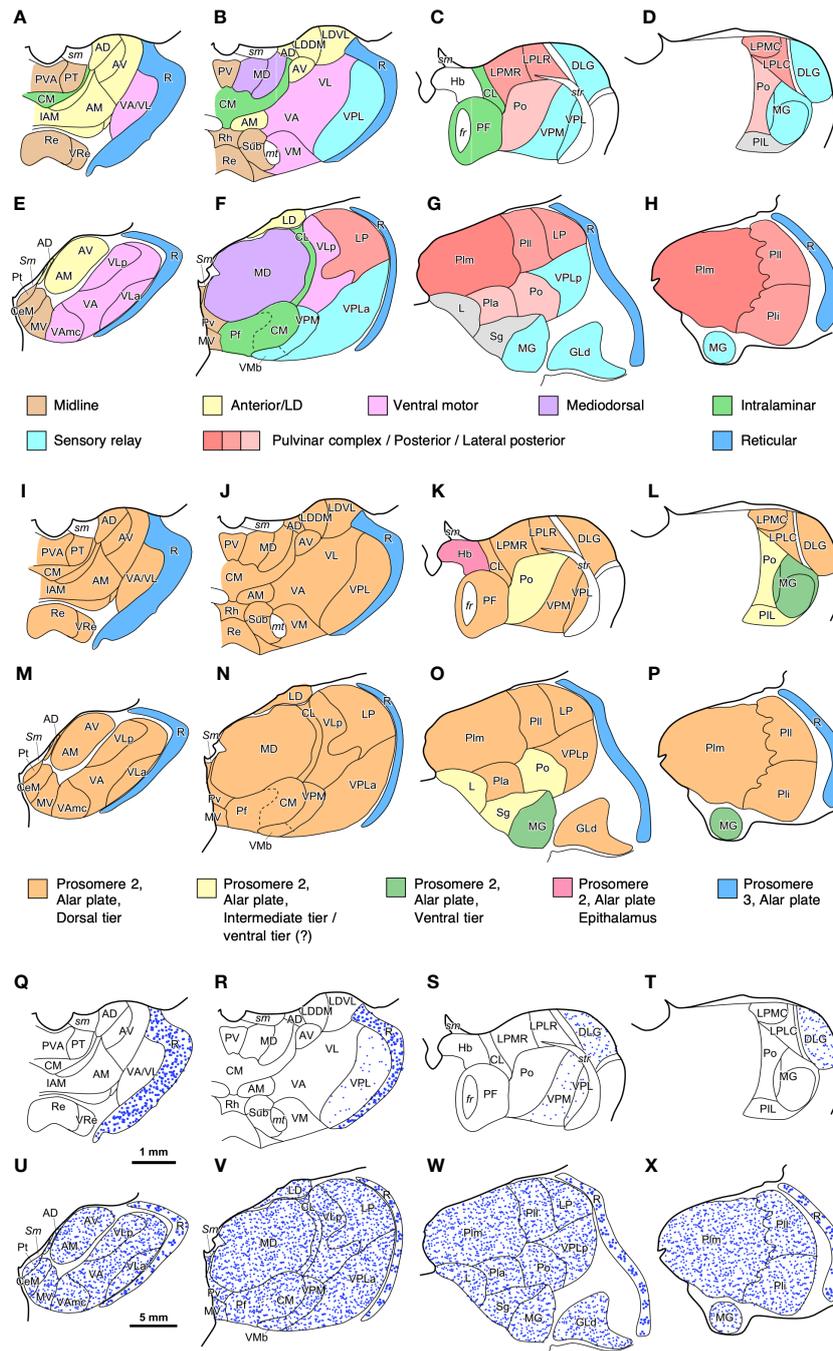


FIGURE 10

Maps of thalamic nuclei drawn from rat and human brain coronal sections. (A–D), Maps of rat [according to Paxinos and Watson (2007)] and (E–H) human thalamic nuclei [according to Hirai and Jones (1989) and García-Cabezas et al. (2023b)] colored according to their synaptic connections/functions (Jones, 2007). Note how the relative size of some nuclear groups, like anterior or midline nuclei is similar in both species; while the relative size of other nuclear groups, such as Pulvinar complex/Posterior/Lateral posterior is notably increased. (I–L), Maps of rat and (M–P) human thalamic nuclei colored according to their probable FMU (Redies et al., 2000; Puelles, 2001); note that most thalamic nuclei are originated from one FMU (Dorsal Thalamus dorsal tier) in the alar plate of prosomere 2. (Q–T), Distribution of GABAergic interneurons in the rat and (U–X) human thalamus. In the rat thalamus (Q–T), GABAergic interneurons are almost restricted to the reticular thalamic nucleus (R) and the lateral geniculate (DLG) nucleus. In the human thalamus (U–X), GABAergic neurons are present in the reticular thalamic nucleus (R) and in all the other thalamic nuclei. Note the lower density of neurons in the human reticular thalamic nucleus, as compared to the rat reticular thalamic nucleus. GABAergic interneurons in the human dorsal thalamus are represented homogeneously distributed due to lack of precise description of their distribution; probably, these neurons are not equally distributed across the different human thalamic nuclei, as happens in the macaque thalamus (Hunt et al., 1991). Scale bar in (Q) applies to (A–D), (I–L), and (Q–T); Scale bar in (U) applies to (E–H), (M–P), and (U–X). For abbreviations of the rat thalamus see Paxinos and Watson (2007), for the human thalamus see Hirai and Jones (1989) and García-Cabezas et al. (2023b).

TABLE 3 Expansion modes of human nervous system structures.

Structure	FMU	Expansion mode		
		Mode	Cytoarchitectonic expansion	Cell type expansion
Cerebral cortex	Alar plate hp1 (MP, MMP, DP, LP, VP; St, Pall, Dg)	Quantitative and qualitative expansion	New cytoarchitectonic cortical types	More excitatory projection neurons and interneurons for layers II–IV More GABAergic interneurons of pallial and subpallial origin
Pontine nuclei	Alar plate r6-8 (Rhombic lip)	General quantitative expansion	Same basic cytoarchitecture	Same basic cell types
Cerebellar cortex	Alar plate r1 (Rhombic lip and adjacent matrix)	General quantitative expansion	Same basic cytoarchitecture	Same basic cell types
Striatum	Alar plate hp1 (St)	General quantitative expansion	Same basic cytoarchitecture	Same basic cell types
Nigrostriatal system	Floor and basal plates p1-3, m1-2	Telodendrion expansion	Same basic cytoarchitecture	Same basic cell types
Amygdala	Alar plate hp1 (Pallial amygdala)	Focal quantitative expansion	Same basic cytoarchitecture with expansion of some pallial nuclei	Same basic cell types
Thalamus	Alar plate p2 (DTd)	Focal quantitative and cell lineage expansion	New cytoarchitectonic nuclei and expansion of other nuclei	More GABAergic interneurons

For abbreviations see [Figure 3](#).

events of histogenesis [summarized in [Charvet et al. \(2011\)](#) and [Montgomery et al. \(2016\)](#)]. Several mechanisms have been described to account for nervous system “mosaic” expansion. First, the gene expression boundaries (primary events of specification) can vary in different species ([Menuet et al., 2007](#); [Sylvester et al., 2010](#)) and, thus, modify the FMU limits resulting in larger or smaller progenitor populations. Second, the neurogenetic period in a given FMU can last longer in different species ([Striedter and Charvet, 2009](#); [Amat et al., 2022](#)). Finally, cell rate-division can be shorter ([Charvet and Striedter, 2009b](#)). Of these three developmental mechanisms for “mosaic” expansion the first one (primary event modification) is probably the less frequent because the Prosomeric Bauplan and its gene regulatory networks ([Figures 12B–D](#)) seem to be strongly conserved across vertebrates. The other two mechanisms can explain larger production of neurons, which would account for some of the expansion modes described in the present article. Thus, most, but not all, differences in nervous system structure across vertebrates must be due to the time-course and magnitude of secondary events of histogenesis in already specified FMUs.

The tangential expansion of the primate cerebral cortex shows the most complex expansion mode (“Quantitative and qualitative”) described in the present article. The primate cerebral cortex is larger, has new cytoarchitectonic cortical types, more excitatory neurons, and more GABAergic interneurons compared to the rodent cerebral cortex. This expansion may imply changes in the primary events of specification in the early primate pallium that may specify novel FMUs (compare [Figure 3C](#) with [Figure 4B](#)) with more intermediate progenitors in the outer subventricular zone, as

suggested by [García-Cabezas et al. \(2023a\)](#). Also, the expanded primate cortex has significantly increased neurogenesis probably by longer neurogenetic periods in the pallial FMUs, whose neuroblasts radially migrate to the cortical plate. Finally, more GABAergic interneurons are produced both in pallial and subpallial FMUs; those produced in the latter tangentially migrate to their cortical destination. Importantly, primate cortical GABAergic interneurons do have different morphology [as already noted by [Ramón y Cajal et al. \(1988\)](#)] and are classified in different biochemical subclasses ([DeFelipe, 1997](#)) than rodent cortical GABAergic interneurons [reviewed in [Barbas et al. \(2018\)](#)], which may imply the specification of new cell lineages. Altogether, the “Quantitative and qualitative” expansion mode of the primate cerebral cortex may be due to variations in the primary events of specification in the pallium together with variations in the secondary events of histogenesis of pallial and subpallial FMUs.

In contrast to the cerebral cortex, other primate alar plate derivatives, like the cerebellar cortex, the pontine nuclei, and the striatum, show “General quantitative expansion” without significant cytoarchitectonic modification or new cell types compared to rodents. Contrary to the cerebral cortex, the expansion modes of these other alar plate derivatives may not involve the specification of novel FMUs and are probably due to variations in the secondary events of histogenesis, like neurogenesis, in the corresponding FMUs. These differences in secondary events should be regulated by the morphogenetic genes that specify the FMUs ([Figures 12C, D](#)). For instance, the transcription factor *Gbx2* is expressed in prospective cerebellar granule cell neurons ([Hagan et al., 2017](#)) and restricts the expression of *her5*, a repressor of

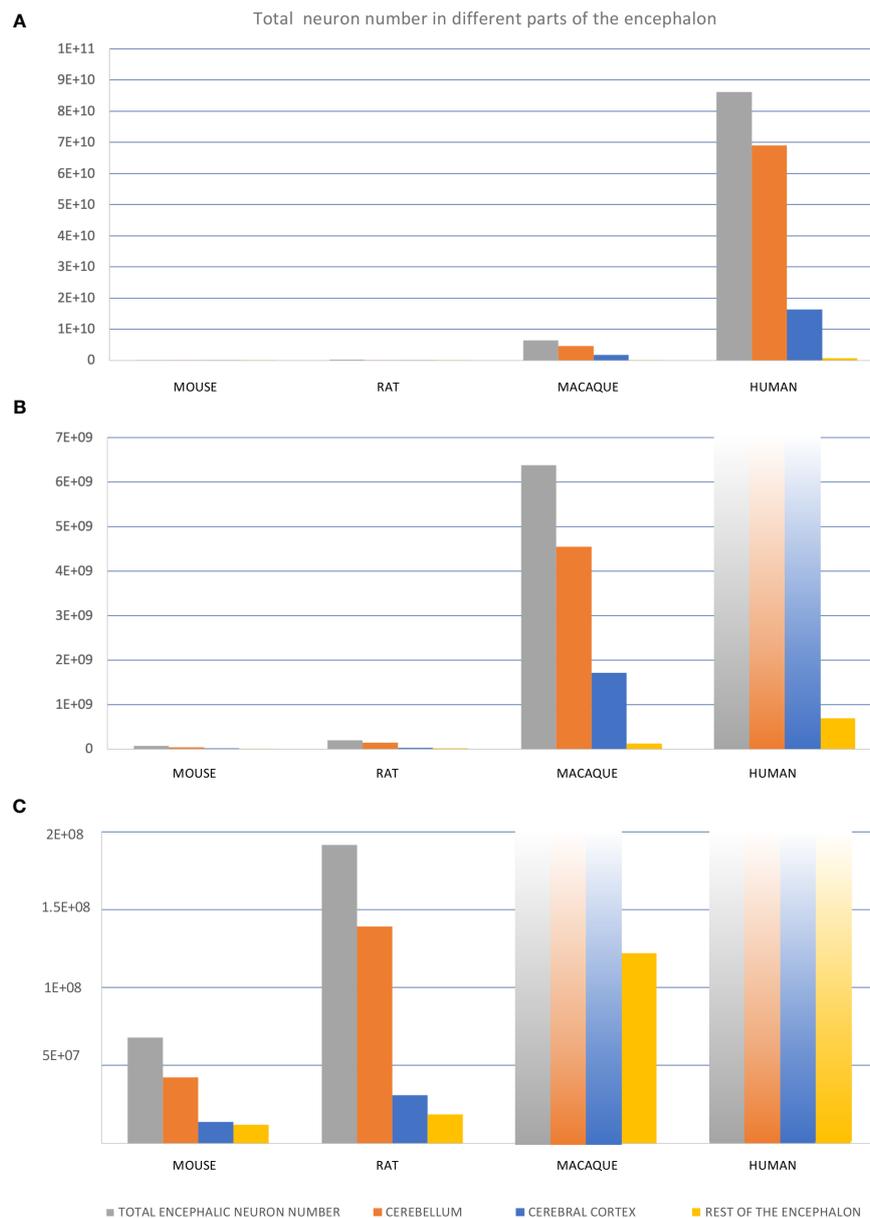


FIGURE 11

Total neuron number in different regions of mouse, rat, macaque, and human encephalon. (A–C), Three graphics containing the same information but represented in different scales to permit visualization of different orders of magnitude: from tens of billions (A) to tens/hundreds of millions (C). Total number of neurons for “total encephalic neuron number”, “cerebellum”, “cerebral cortex”, and “rest of the encephalon” were obtained from Herculano-Houzel et al. (2015); see also Supplementary Data File.

neurogenesis (Nakayama et al., 2017). Thus, different modulation of *Gbx2* in the primate cerebellum compared to other species could direct the expansion of the granule cell progenitor pool.

The primate amygdala shows “Focal quantitative expansion” in some pallial nuclei, without the addition of new cytoarchitectonic nuclei, with the only probable exception of the paralamina nucleus (Figure 9). The most expanded nuclei are originated in several small FMUs identified in the pallial amygdalar sector; interestingly, these small FMUs also give rise to pallial nuclei that do not significantly expand, like the cortical amygdalar nuclei (García-Calero et al., 2020).

The primate thalamus shows “Focal quantitative expansion” in some nuclei, but, contrary to the amygdala, it also shows the appearance of new nuclei (like some ventral and the pulvinar nuclei) that are not identified in rodents; further genoarchitectonic studies may identify novel FMUs in the primate p2 alar plate that may give rise to the “newer” thalamic nuclei. The primate thalamus also shows a significant “cell lineage expansion” of GABAergic interneurons. In rodents, these neurons are originated in the midbrain and the forebrain (Jager et al., 2021), but they have not been traced to specific FMUs. Thus, the thalamic expansion in primates compared to rodents may involve the

alar plate derivatives regulated? Developmental gene regulatory networks are hierarchical (Peter and Davidson, 2015). This means that the generation of spatial gene expression profiles during the early pre- and postgastrular embryos is encoded at the highest level of the networks (1st specification level in Table 2); in a lower level are encoded the spatial gene expression profiles that specify FMUs (2nd and 3rd specification level in Table 2); and, finally, in the lowest level are encoded the gene expression profiles that specify cell types and other secondary events of histogenesis (4th specification level in Table 2). The primate alar plate derivative expansion could be coded in the lower level by coincident independent modifications in the regulation of each alar FMU; alternatively, there could be an intermediate level where regulatory modifications could impact downstream the regulation of secondary events in several alar FMUs.

5 Conclusions

In the present article we have described five different expansion modes of human and non-human primate nervous system parts and traced them back to their corresponding Prosomeric Model FMUs. These modes confirm that neural structures originated in the alar plate can significantly expand in the primate nervous system both quantitatively, by the production of more neurons, and qualitatively, by the expansion of some cell types and, maybe, the specification of novel FMUs. The human cerebral cortex shows a large tangential quantitative (volume and number of neurons) expansion but also a significant qualitative expansion with the appearance of new cytoarchitectonic cortical types; the new types have more neurons in layers II–IV and more GABAergic interneurons originated in pallial and subpallial FMUs. Some alar plate derivatives, like the pontine nuclei, the cerebellar cortex, and the striatum, are “just” quantitatively expanded by the addition of more neurons. Other alar plate derivatives, like the amygdala and the thalamus, show volume expansion in some nuclei and, in the case of the thalamus, the appearance of new nuclei together with an extraordinary expansion of the GABAergic interneuron population. Our analysis also confirms that neural structures originated in the floor and basal plates have severe developmental constraints that do not allow for significant phylogenetic neuron number expansion; thus, the nigrostriatal system is expanded by “Telodendrion expansion” to provide dopaminergic innervation to the enlarged primate striatum. The expansion and branching of telodendria also probably plays major roles in the diversification and specialization of alar plate neural circuit in primates compared to rodents, as showed for the thalamus (Parent and Parent, 2005).

The expansion modes in primate nervous system structures can be traced back to variations in the primary events of specification (like the specification of novel FMUs) and secondary events of histogenesis (like longer neurogenetic periods, expansion of cell lineages, or axon growth disinhibition) in the corresponding FMUs. Variation in primary events should be encoded in the intermediate level of gene regulatory networks; on the other hand, variation in secondary events should be encoded in the lower levels of gene regulatory networks, although some modifications in intermediate regulatory levels could account for the concerted expansion of primate alar plate derivatives. It must be

acknowledged that the speculations advanced in the present article are based on the comparative analysis of primate and rodent adult brains (thus, after the tertiary events of morphogenesis are finalized) and lack experimental confirmation from developmental studies in primate embryos. Such confirmation may be obtained in future studies of the gene regulatory networks of primary and secondary developmental events in each Prosomeric Model FMU in primates and other mammals. These studies could provide the necessary insight to identify the developmental and phylogenetic causal mechanisms of the expansion modes described in the present article.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Materials. Further inquiries can be directed to the corresponding author.

Author contributions

MG-C developed the study conception and design. MG-C, SR-C, JZ-D, and IP-S reviewed the literature cited in the text and the figures. SR-C, JZ-D, IP-S, and MG-C assembled the figures. MG-C secured funding. JZ-D contributed to the data curation, formal analysis, visualization, and writing - review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author MAG-C declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fmamm.2023.1241573/full#supplementary-material>

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