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The bilaterian forebrain: an evolutionary chimaera

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The insect, annelid and vertebrate forebrains harbour two major centres of output control, a sensory-neurosecretory centre releasing hormones and a primordial locomotor centre that controls the initiation of muscular body movements. In vertebrates, both reside in the hypothalamus. Here, we review recent comparative neurodevelopmental evidence indicating that these centres evolved from separate condensations of neurons on opposite body sides ('apical nervous system' versus 'blastoporal nervous system') and that their developmental specification involved distinct regulatory networks (apical six3 and rx versus mediolateral *nk* and *pax* gene-dependent patterning). In bilaterian ancestors, both systems approached each other and became closely intermingled, physically, functionally and developmentally. Our 'chimeric brain hypothesis' sheds new light on the vast success and rapid diversification of bilaterian animals in the Cambrian and revises our understanding of brain architecture.

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Introduction

Vertebrates, insects and annelid worms share the presence of a centralized nervous system (CNS) with an anterior brain. The brain integrates sensory information to control the animal body through distinct effector systems [1]. First, neurosecretory centres in the brain release hormones that control the general behavioural state, homeostasis and life cycle transitions. Second, the brain is the higher-order control centre for the hierarchically organized somatic motor system, that controls muscular movements. This review proposes a scenario for the evolutionary origin of these fundamentally distinct control centres.

Most instructive in this context is the analysis of regionalization of the brain neuroectoderm, which is generated by the intersection of the 'apical' and 'mediolateral' patterning systems (Figure 1). We will reason that these systems were initially separate, specifying 'apical' (Figure 1a) versus 'blastoporal' (Figure 1b) identities in prebilaterian ancestors, and started to overlap in the bilaterian lineage only. We will then review evidence linking the apical system to the specification of an 'apical nervous system' in several bilaterians, comprising sensory-neurosecretory protoneurons, that perceive light and other stimuli to control the release of neuropeptides and hormones. The circadian and hormonal release centre in the bilaterian forebrain can thus be regarded as the 'legacy' of an ancient apical nervous system. In contrast, the mediolateral system governs the differential specification of various other types of sensory neurons, interneurons and motorneurons that constitute the 'blastoporal nervous system'. The latter is composed of axonal circuits for the control of body movements and referred to as 'blastoporal legacy'.

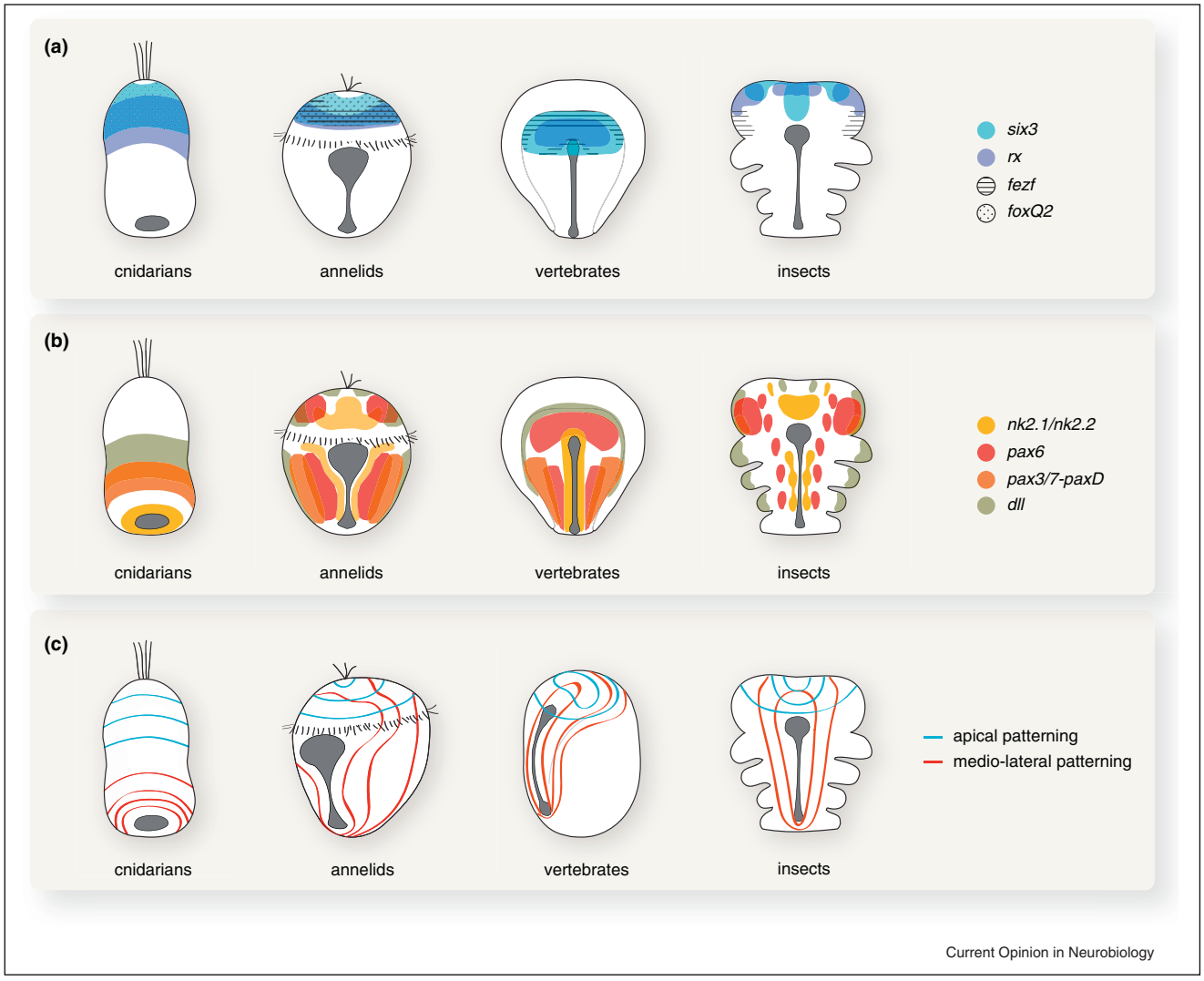
In the course of bilaterian evolution, the most anterior part of the blastoporal nervous system, the primordial locomotor control centre, approached, and finally merged with the sensory-neurosecretory centre of the apical nervous system. This way, an evolutionary chimaera of neural tissues evolved, combining two distinct effector systems of different origin.

A fusion of apical nervous system and anterior blastoporal nervous system components has been previously put forward for the evolution of the protostome brain, based on morphological evidence [2]. Taking into account new molecular data, we propose here that this fusion occurred earlier in animal evolution, predating the bilaterian ancestors.

The apical and mediolateral patterning systems evolved at opposite body sides

The apical system, also referred to as 'head patterning system', involves antagonistic Wnt and FGF signalling. it specifies the tissue around the apical pole (i.e., the non-blastoporal side of the body) in insect [3•,4], annelid [3•,5], brachiopod [6] echinoderm [7], hemichordate, [8,9••], amphioxus [10] and vertebrate development [11] (Figure 1a). The apical system controls the expression of the region-specific transcription factors *six3*, *rx*, *foxQ2* and *fezf* in radial and partially overlapping domains (Figure 1a). Recent data from a bilaterian outgroup, the cnidarians (comprising, e.g. sea anemone and jellyfish), indicates that this patterning system predates bilaterians [12••,13••]. In insects, vertebrates and annelids, the *six3*+ apical region gives rise to the most anterior part of the

Figure 1



The apical and the blastoporal patterning systems. Expression of nervous system regionalization genes in Cnidaria, annelids, vertebrates and insects. **(a)** The apical patterning system comprises concentric expression of *six3*, *rx*, *fezf* and *foxQ2*. **(b)** The blastoporal patterning system establishes the expression of transcription factors centred around the blastopore. *Dll* is expressed at the interface between the two systems. **(c)** The apical (blue) and blastoporal (red) patterning systems are active on opposite body sides in Cnidaria, but they fuse in bilaterians at the level of the anterior forebrain. The expression of *foxA* (grey) demarcates the blastopore in Cnidaria, and the neural midline in Bilateria (plus the blastopore lips in protostomes, see [20]). Cnidaria expression data are drawn from *Nematostella* [12••,13••,95,96] and *Acropora* [97] (lateral views), annelid expression data from *Platynereis* [5,17,98] (blastoporal view in (a) and (b), blastoporal-lateral view in (c)), vertebrate expression data from *Xenopus* [99–103] (blastoporal view in (a) and (b), blastoporal-lateral view in (c)), and insect expression data from *Tribolium* [3•,4,16,104] (blastoporal view). *FoxQ2* expression has never been characterized in vertebrates and insects.

brain [3•]. In vertebrates, this region includes the telencephalon and anterior hypothalamus [14].

The mediolateral system likewise represents ancient bilaterian heritage, involving midline Hedgehog and lateral BMP signalling. In vertebrates, insects and annelids this system controls the staggered expression of medial *foxA*, *sim* and *nk*, and lateral *pax*, *msx* and *dll* genes (Figure 1b) [15–17]. In the vertebrate neuroectoderm, these transcription factors specify the floor, basal, alar and roofplate subdivisions of the folded neural tube that extend into the forebrain [18]. In annelids, the same sequence of genes establishes a bilateral sequence of molecular regions that are centred along the neural midline (Figure 1b). Given that in annelids and other protostomes the neural midline emerges from the median fusion of the blastopore lips [19], it has been suggested that the mediolateral system was originally active alongside the blastopore (and that this spatial connection was lost in vertebrate ancestors due to changes in the mode of

gastrulation) [20]. Recent data from Cnidaria support this hypothesis, revealing that *dll*, *msx*, *pax3/7* and *nk2* genes are expressed in similar sequence around the blastopore [21], together with the medial signal *hedgehog* [22] (Figure 1b). Bilaterian brain patterning thus involves two systems that were initially separate and started to overlap in bilaterian ancestors only (Figure 1c). In the subsequent paragraphs we will reason that both systems play conserved roles in the specification of fundamentally different nervous system components that evolved at opposite body sides. Comparative data allows sorting out the 'original' apical versus mediolateral neural cell fates and thus reconstructing the constituents that were involved in the formation of the chimeric bilaterian brain.

The apical nervous system: an assembly of sensory-neurosecretory protoneurons

Marine invertebrates are particularly useful to understand the apical nervous system component of the bilaterian brain. Their ciliated planktonic larvae develop nervous structures (including an 'apical organ') from the *six3*+ apical plate, downstream of the apical patterning system [3,6]. These larval structures are in place before the blastoporal mediolateral patterning system establishes the axonal circuits for the control of body musculature (that are fully developed only after metamorphosis). In species with a gradual, non-catastrophic metamorphosis, large part of the apical plate remains and becomes incorporated into the adult brain, referred to as cerebral ganglia. That means that in marine ciliated larvae we can study components of the apical nervous system in a more 'puristic' (meaning pre-fusion) form.

In these larvae, the most prevalent apical plate cell types are multimodal sensory-neurosecretory cells, also referred to as protoneurons [23]. These cells usually exhibit a flask-shaped morphology with ciliated dendritic endings [24]. Based on ultrastructural features but also molecular data, these cells closely resemble the cerebrospinal-fluid (CSF)-contacting neurons of the vertebrate brain [23,25] (Figure 2a). Ciliary-type photoreceptors employing c-opsins, orthologs of vertebrate rod and cone opsin, have also been identified in the annelid apical plate [31], where they develop under the control of *rx* (MAT and DA, unpublished). C-opsin expression in the apical plate of brachiopods [32] and echinoderms [33•] confirms that non-visual photoreception is a major task of the larval apical nervous system. Usually, an apical plexus forms underneath the apical organ [24,26], which functions at the same time as a neural integration site and a neuroendocrine release site [24] (Figure 2a). These data suggest that protoneuron-like cells, including ciliary photoreceptors, in conjunction with a neurosecretory plexus represent ancient apical nervous system-derived components. This notion finds support by a comparative survey of six3 and rx-dependent cell types in the adult annelids and vertebrates.

The 'apical legacy' of the bilaterian forebrain: (1) non-visual light perception and the molecular clock

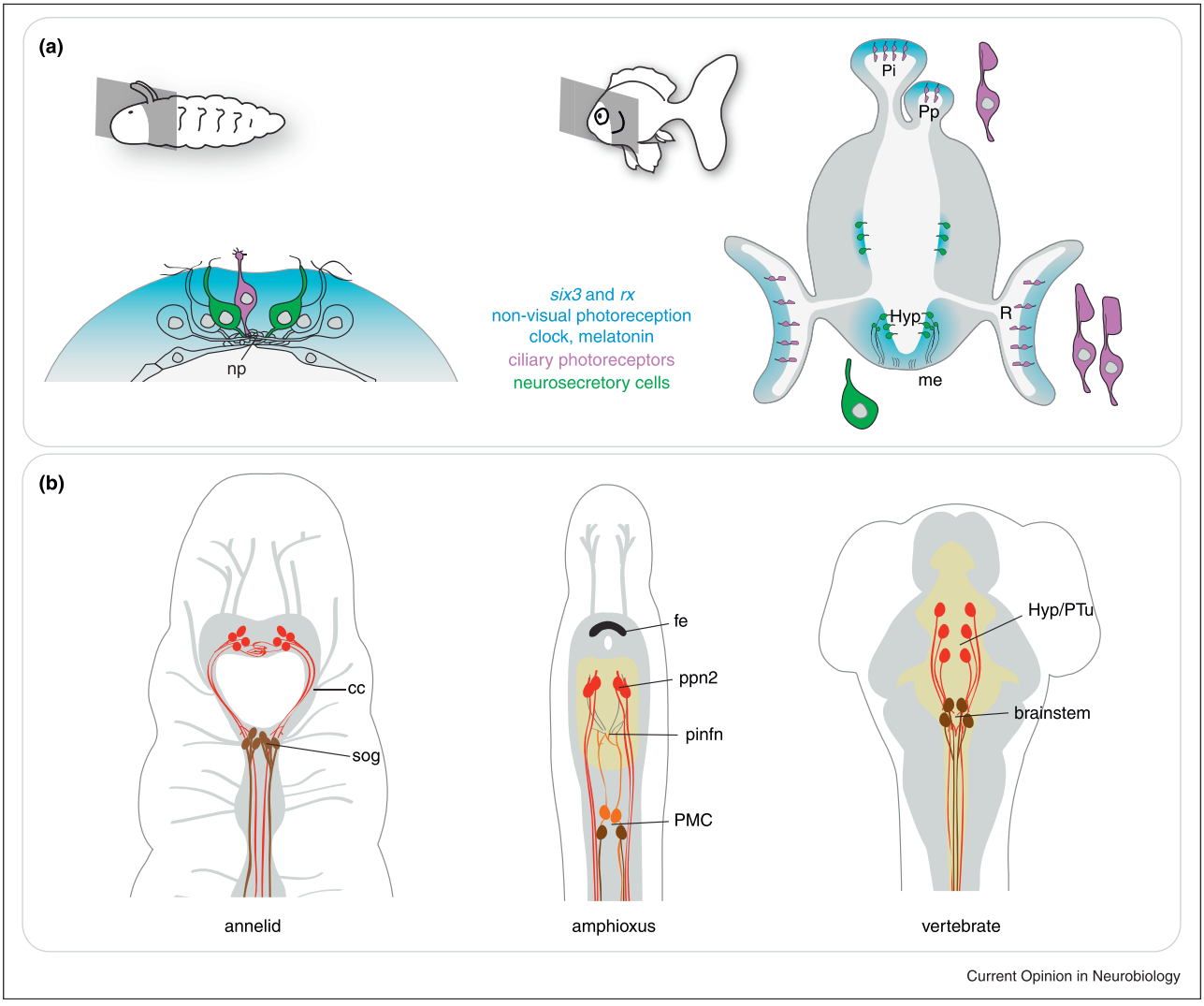
Rx and six3, key transcription factors of the apical patterning system, were initially identified as regulators of retinal development [14,27], but later studies highlighted their essential roles in postmitotic photoreceptors. Rx directly controls the expression of *opsins* and other photoreceptor-specific genes through binding to a photoreceptor-specific regulatory element (PCE-1) [28,29]. Similarly, six3 directly controls *rhodopsin* expression [30]. These data corroborate our notion that six3 and rx played ancient roles in ciliary photoreceptor cell specification and differentiation [31] and suggest that vertebrate rods and cones evolved from apical plate non-visual photoreceptors. Consistently, in amphioxus, the frontal eye, the proposed homolog of vertebrate retina, develops from *rx*+ *six3*+ progenitors; *six3* is expressed in the differentiated row 1 photoreceptors (and *rx* in frontal eye row 3 cells) [34••].

Rx and *six3* are also expressed in the developing vertebrate pineal [35,36], the proposed evolutionary 'sister' of the retina [37,38••]. In non-mammalian vertebrates, the pineal likewise contains ciliary-type photoreceptors employing c-opsins. Also, it entrains an endogenous clock and in all vertebrates produces melatonin, the main output of the circadian system. *Rx* expression in the pineal shows diurnal oscillations in adults, suggesting a possible role in the rhythmic expression of target genes [39]. Both the retina and the pineal represent evaginations of the forebrain and can thus be regarded part of the adult apical nervous system.

Finally, in the anterior hypothalamus the suprachiasmatic nucleus (the master clock that integrates inputs from the retina and the pineal) develops under the control of six3, its paralog six6, and rx, and rhythmically expresses six3 and six6 in adults [41••,42]. These data indicate that the anterior hypothalamus, together with the ciliary photoreceptors of retina and pineal, represents 'apical legacy' of the vertebrate forebrain.

Supporting our notion that luminance detection, the control of physiology and an endogenous central molecular clock were directly coupled in multifunctional cells in the urbilaterian forebrain, we have recently found that rx-dependent ciliary photoreceptor cells in the annelid forebrain (that persist from the larval apical plate) run a circadian clock and release melatonin as an effector. Moreover, specific markers of the vertebrate anterior hypothalamus are also expressed in the annelid apical plate ([25] and MAT and DA, unpublished), corroborating our hypothesis that vertebrate pineal, retina and anterior hypothalamus evolved from apical plate non-visual photoreceptors after 'division of labour' [40].

Figure 2



Apical and blastoporal 'legacies' in bilaterian brains. **(a)** Comparison of the annelid apical plate (left) and the vertebrate diencephalon (right). Annelid drawing based on [5,24,25] and unpublished data; vertebrate scheme redrawn from [105]. Hyp, hypothalamus; me, median eminence; Pi, pineal; Pp, parapineal; R, retina. **(b)** Comparison of the neural architecture that underlies the control of the trunk locomotor pattern generators by descending projections from ventral *nk2*+ forebrain regions (yellow). Based on [76,77,106]. Cc, circumesophageal connectives; sog, subesophageal ganglion; fe, frontal eye; ppn2, preinfundibular projection neuron 2; pinfn, postinfundibular neuropile; PMC, primary motor centre; Hyp/PTu, hypothalamus/posterior tuberculum.

The 'apical legacy' of the bilaterian forebrain: (2) the hormonal release centre

Expression of *rx* in the anterior neural plate also includes prospective neurosecretory areas of the vertebrate hypothalamus. Here, *rx* determines cell fates as *rx* mutant mice fail to develop the posterior pituitary [43] and conditional *rx* elimination under a *Six3::Cre* driver results in the loss of the arcuate and the ventromedial nuclei of the hypothalamus [44••]. Consistently, *rx*+ stem cells are able to generate vasopressinergic and NPY+ neurons *in vitro*, but cannot express posterior hypothalamic markers [45]. In annelids *rx* and *six3* are likewise expressed in neurosecretory cells that project into the apical plexus (see above); and in insects they are expressed in the brain neurosecretory centres (pars intercerebralis and pars lateralis, see [3•,46]). Another apical nervous system marker, *fezf*, also contributes to the specification of neuroendocrine fates: in zebrafish, *fezf* acts upstream of *otp* to control the differentiation of isotocinergic neurons [47]; similarly, vasotocin (the vasopressin/isotocin ortholog) is expressed in *otp*+ flask-shaped cells of the annelid forebrain [25].

The similarity of invertebrate and vertebrate neurohemal sites [48] is highlighted by the conservation of some of the neuropeptides and hormones released in these structures, like the earlier mentioned vasotocin and

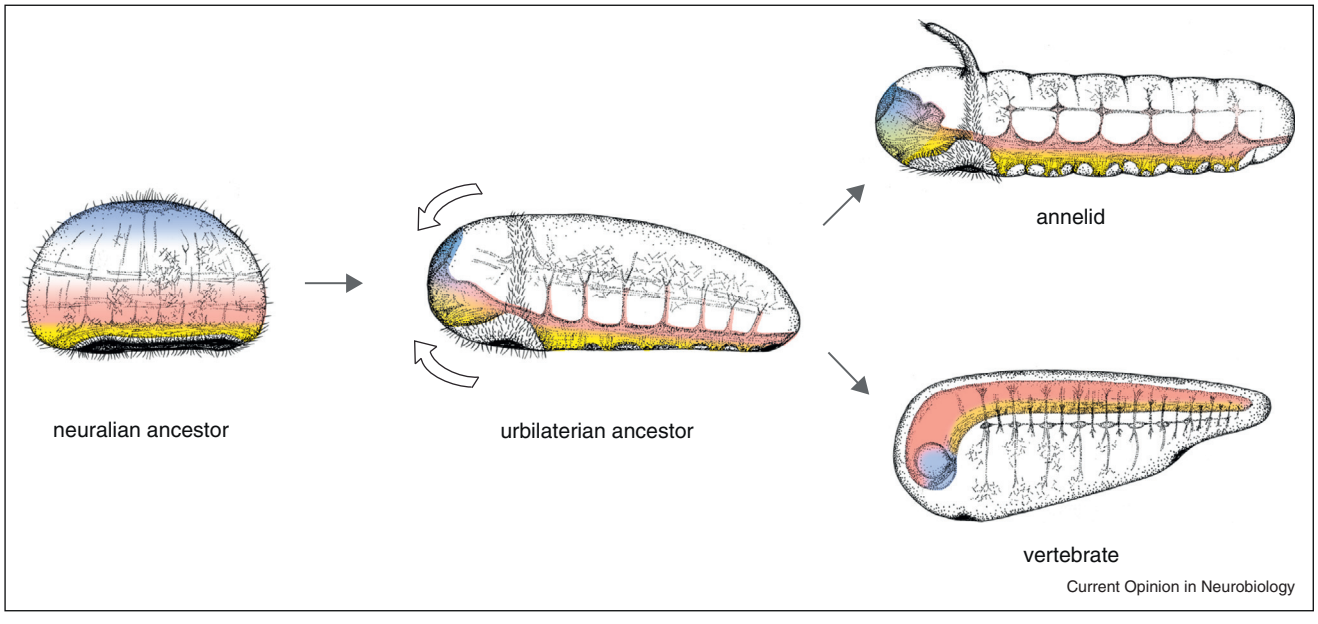
melatonin (the pineal is a neurohemal organ [49]). Moreover, RFamidergic neurons are characteristic of the apical plate and apical plexus of annelids, molluscs, hemichordates and cnidarians [25,50–52], of the insect pars intercerebralis [46] and of the vertebrate hypothalamus [53]. Finally, most of the neurohormones and neuropeptides of the vertebrate arcuate nucleus-median eminence complex, like GnRH, NPY and enkephalins, have ancient evolutionary origins [54] and might be present in the apical plate of various invertebrates, as suggested by cross-reactive antibodies [55,56]. We thus propose that the hormonal release centre represents a characteristic apical nervous system derivative of the bilaterian forebrain.

The blastoporal nervous system: an axonal system comprising lateral sensory-integrative and medial motor regions

In contrast to the apical nervous system, which, in essence, can be traced back to protoneuron-like sensory cells specialized on neurosecretory output, the blastoporal nervous system is functionally based on axonal connections between its components. It is best described as a sensory-contractile system, composed of axonal circuits that integrate sensory information to control body musculature. Across bilaterians, the blastoporal nervous system is specified by the mediolateral patterning system, which establishes a lateral sensory-integrative region comprising sensory neurons and interneurons, and a medial motor region comprising interneurons and motoneurons, in annelids [17] as well as in vertebrates [15]. Importantly, recent comparative data indicate that a medial *foxA*+, *nk2*+ contractile-motor region alongside the blastopore and a more lateral *msx*+, *pax3/7*+, *Dll*+ sensory-integrative region in a distance to the blastopore also exist, albeit in a less centralized form, in the cnidarian outgroup (reviewed in [21]). This would imply that the functional link between mediolateral patterning and neural cell type specification predates the cnidarian-bilaterian ancestor (and that the blastoporal and apical nervous systems indeed evolved on opposite body sides, Figure 3).

Underscoring the essential nature of targeted axonal connections for information transfer in the blastoporal nervous system, transcription factors that play conserved roles in the control of cell fates have proven indispensable for the establishment of axonal connection between postmitotic neurons. For example, foxA, pax6 and nk2 directly control the expression of guidance factors important for axonal outgrowth and the formation of major axonal tracts [57–62,63•,64•]. Also, in mice and fishes mutant for the transcription factor sim, medial neurons are generated correctly but fail to establish proper axonal projections [65,66•]; likewise, Drosophila *sim* is essential for axogenesis [67].

Figure 3



The chimeric brain hypothesis. In the scheme, the apical nervous system is in blue, and the motor and the sensory-integrative components of the blastoporal nervous system are represented in yellow and red, respectively. In the last common ancestor of Cnidaria and Bilateria (neuralian ancestor) the two systems were separate, and concentrated respectively around the apical pole and the blastopore. With the transition to the urbilaterian (the ancestor of all Bilateria) the apical nervous system and anterior side of the blastoporal nervous system merged to form the forebrain, as found in extant annelids and vertebrates.

A 'blastoporal legacy' of the bilaterian forebrain: the primordial locomotor control centre

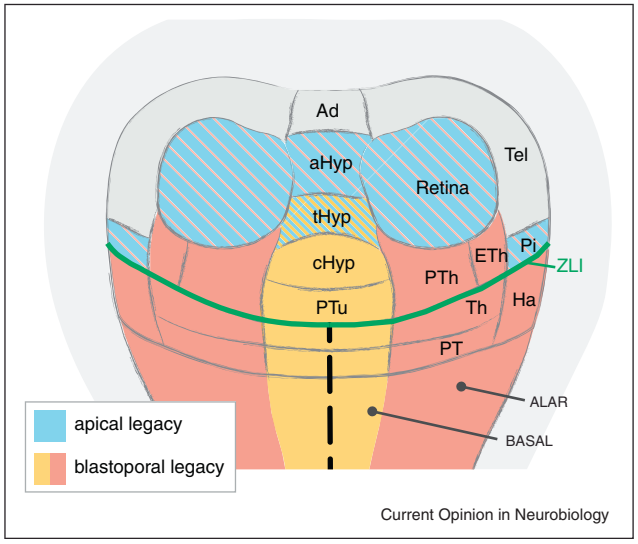
Our focus is on the most anterior extension of the medial motor region that became part of the ventral bilaterian forebrain. The transcription factors nk2.1, nk2.2 and sim demarcate this region in vertebrates, ascidians, amphioxus and annelids [25,68–71]; notably, an anterior ventromedian stripe of *nk2.1* expression is also found in other marine invertebrates including hemichordates, indicating broad evolutionary conservation [6,8,25,72]. In vertebrates, the *nk2+* forebrain region comprises the subprethalamic basal plate and the tuberal and caudal hypothalamus, including the mammillary bodies [70,73,74•] (that are absent in mouse nkx2.1 mutants [1,73]). These regions are known to integrate rostral sensory inputs and initiate and modulate locomotion via axons projecting caudally into the brainstem and the spinal cord [1,75] (Figure 2b). Similarly, in amphioxus the motoneurons and interneurons of the primary motor centre are innervated by preinfundibular projection neurons and by fibres from the tegmental or postinfundibular neuropil (a site of integration of rostral sensory inputs), both located in the nk2.1/nk2.2 region of the cerebral vesicle [76] (Figure 2b). In insects and annelids, large axons descend from the posterior brain to the trunk and contact directly or indirectly trunk motoneurons [77,78•]. In insects, these axons emerge from the central complex, a series of midline neuropils that represents the highest motor control centre. In annelids, the corresponding neurons appear to be part of the nk2.1 domain and their precise molecular identity is currently investigated (MAT, unpublished).

In line with evolutionary conservation of primordial locomotor control centres in the ventromedian bilaterian forebrain, the *nk2.1+* brain regions contain dopaminergic neurons, in vertebrates, amphioxus, ascidians and annelids [79,80]. The role of dopaminergic neurons in locomotor control is well established in vertebrates and invertebrates [81], but further studies are needed to test the homology of these neuromodulatory neuronal circuits throughout Bilateria.

The chimeric brain hypothesis

So far, and for clarity, our effort has been to sort out the 'apical' and 'blastoporal' legacies of the bilaterian forebrain. Figure 4 summarizes and illustrates both hypothetical contributions on a fate map of the anterior vertebrate neural plate. Notably, as a result of the fusion of neurosecretory and locomotor control centres that took place more than six hundred million years ago in prebilaterian ancestors, these components are partially intermingled and closely interconnected in today's brains, to an extent that it becomes sometimes difficult to tell them apart and draw clear boundaries (striped areas in Figure 4).

Figure 4



The apical and blastoporal contributions to the vertebrate forebrain. Generalized fate map of the vertebrate neural plate, illustrating the apical and blastoporal legacies of the vertebrate brain as deduced from the expression of key transcription factors and the comparison of cell types. The fate map is based on [107,108]. *Abbreviations*: Ad, adenohypophysis; aHyp, anterior hypothalamus; cHyp, caudal hypothalamus; ETh, eminentia thalamica; Ha, habenula; Pi/PP, pineal/parapineal; PTu, posterior tuberculum; PT, pretectum; PTh, prethalamus; Tel, telencephalon; Th, thalamus; tHyp, tuberal hypothalamus; ZLI, zona limitans intrathalamica.

In line with this, characteristic apical and mediolateral system genes such as *six3*, *rx* versus *nk2.1*, *pax6* are broadly co-expressed in the developing bilaterian brain. For example, despite being necessary only for the development of the rostral forebrain [82], *six3* expression extends posteriorly into the thalamus and the midbrain during late embryonic development [83] (where deep brain photoreceptors have been described [84]). Also, *nk2.1* expression has expanded anteriorly into the former 'apical' territory. Such expansion might have changed (or complemented) the neurosecretory cell fate towards that of projection neuron, thus contributing to the functional fusion of the two effector systems. Intriguingly, the anterior limits of *nkx2.1* and *nkx2.2* expression are variable and appear to expand even within vertebrates into brain regions that had not expressed them in early vertebrates, insofar as the entire expression domain of *shh* and *nkx2.1* in the ventral telencephalon probably arose *de novo* after the separation of cyclostomes and gnathostomes [74•,85].

To track these variations and to reconstruct ancient brain subdivisions, a systems-level analysis can be more powerful than the analysis of single genes. On the basis of the combinatorial analysis of hundreds of transcription factors, a new interpretation of the vertebrate hypothalamus has been recently proposed [86••], and according to this study, only the caudal hypothalamus (mammillary region

and retromammillary areas) is considered a true basal plate derivative. This new interpretation is in agreement with our evolutionary scenario, which considers the caudal hypothalamus as the anterior part of the blastoporal nervous system basal plate (Figure 4).

Despite the paucity of comparative data, some examples of the chimeric nature of the bilaterian forebrain can be recognized both at the tissue and at the cell type level.

At the tissue level, the fusion of 'apical' and 'blastoporal' legacies would involve the functional integration of cell types of different origin, through the establishment of new synaptic connections. For instance, while the ciliary photoreceptors of the vertebrate retina constitute 'apical' legacy (see above), the ganglion cells appear to be of 'blastoporal' origin, as suggested by their dependence on 'blastoporal' transcription factors such as pax6 and brn3 [87] and by the presence of rhabdomeric photoreceptors along the entire trunk neuroectoderm of protostomes and deuterostomes [88].

At the cell type level, the interesting perspective emerges that neural cells that initially developed under the unique influence of one patterning system, started to receive signals from the other. Such newly received signals might have activated downstream target genes belonging to the respective other system and might have led, at least in part, to 'chimeric' cell fates, according to a cell type neofunctionalization scenario. Indicative of truly chimeric cell fates, neurosecretory and caudally projecting neurons of the same peptidergic type coexist in the tuberal hypothalamus [89,90]. In the same region, *otp* is responsible for the differentiation of caudally projecting dopaminergic neurons of the diencephalospinal tract, that control the maturation of locomotor patterns [90,91]; moreover, light-sensitive *otp*+ neurons have been recently implicated in dark photokinesis [92]. Intriguingly, both 'blastoporal' and 'apical' transcription factors, like sim and fezf, act in parallel with otp to specify these neuronal types [47,90,93], suggesting that different cellular properties, like the neurosecretory fate or establishment of axonal connections, might be controlled by distinct gene regulatory modules acting within neighbouring or even in one and the same cell [94••].

Concluding remarks

If the apical neurosecretory versus blastoporal contractile-motor centres indeed evolved on opposite body sides, what was the driving force to establish contact and finally fuse at the new front end of bilaterian ancestors? We speculate that one selective advantage might have been that the neurosecretory release centre obtained more and more direct control on the newly evolving locomotor control centre. Also, sensory modalities specific of the apical system might have been secondarily recruited for the control of locomotion, via newly evolving direct connections to the muscular motor circuits. It is conceivable that the combination of 'division of labour' and cell type neofunctionalization (with the parallel activation of 'apical' and 'blastoporal' differentiation programmes in the same cell) has boosted cell type diversity in the evolving bilaterian forebrain, and triggered the establishment of new neural circuits between previously non-related parts of the nervous system. These enabled an unprecedented diversification in the divergent bilaterian lineages and led to a true 'Cambrian explosion' for bilaterian brain evolution.

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