

Dispatches

CNS Evolution: New Insight from the Mud

Whether the highly centralised nervous systems of chordates and protostomes arose from a common ancestral precursor or independently has been a long-standing debate. Now, analysis of neural gene expression in an evolutionarily important chordate outgroup — the sand-dwelling, hemichordate acorn worms — reveals the presence of a central and peripheral nervous system, suggesting a common origin of central nervous systems.

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The origin of the chordate central nervous system (CNS) has remained a controversial topic in evolutionary biology. One major unsolved question is how it is related to the CNS of other animal groups (Figure 1). Did the chordate CNS originate independently or from a shared ancestral CNS? Although concentrations of neurons are found in all major animal phyla, there are some basal groups in which the nervous system is only scarcely centralised or not centralised at all. In addition, these neuron concentrations are found at different sites in different animal groups: in chordates, neurons are concentrated at the dorsal side of the body, while in non-chordate invertebrates a strand of centralised neurons is found on the ventral side. This is why many authors believe that the chordate CNS evolved separately in the chordate lineage. One of these authors, Romer [1], proposed that the chordate ancestors were animals with no or only a rudimentary CNS resembling that of today's pterobranchs and ascidians. Another author, Garstang [2], proposed that the chordate neural tube evolved by the dorsal fusion of ciliary bands, like those found in echinoderm or enteropneust larvae. However, there is an alternative view. Inspired by Geoffroy St. Hilaire's 'unité de plan' [3], and despite the opposite locations, comparative anatomist Anton Dohrn [4] proposed that the chordate CNS was homologous to that of protostome annelids and arthropods. He assumed that vertebrates evolved from worm-shaped, annelid-like ancestors that turned upside-down during their evolution such that the dorsal and ventral sides became inverted (DV-axis inversion). In contrast to Romer's

scenario, Dohrn considered ascidians to be secondarily modified forms with a simplified larval CNS. Dohrn's proposed homology between the dorsal and ventral CNS of vertebrates and invertebrates had been abandoned with time, but a paper published by Brunet and collaborators in this issue of *Current Biology* [5] might well yield new perspectives on this old idea.

The revival of Dohrn's ideas could have been already anticipated based on gene expression data from different organisms during neural patterning and neuronal cell-type specification, which revealed striking similarities between the vertebrate, insect and annelid nervous systems. The notion of the DV-axis inversion found great support from this pool of data, particularly after the comparison of DV patterning genes between flies and frogs, most notably BMP, which is expressed ventrally in frogs and dorsally in flies [6–9]. This observation is corroborated by inverted left-right patterning, as revealed by left-sided Pitx and Nodal

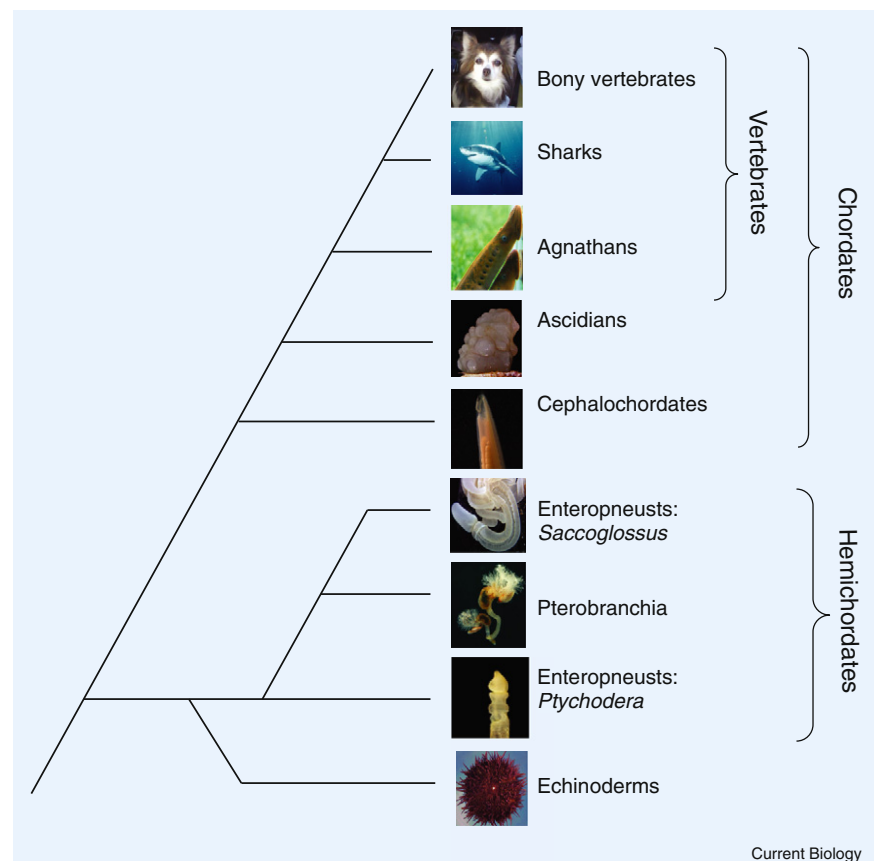


Figure 1. Revised evolutionary tree of deuterostome groups.

This simplified phylogenetic tree of deuterostome groups discussed in the text is based on recent molecular phylogenies [12,13]. One species of each branch has been selected for illustration, except for hemichordates, where the tree has been expanded to illustrate that pterobranchs have evolved within enteropneusts. Note that ascidians are the closest living relatives of the vertebrates.

expression in chordates as opposed to sea urchin and starfish larvae where these genes are expressed on the right side of the body [10,11]. Also, refined deuterostome phylogeny now indicates that ascidians are indeed secondarily simplified [12] and that the sessile pterobranchs stem from free-living acorn worms [13], safely ruling out that pterobranch- or ascidian-like organisms were among the chordate ancestors. These findings eliminated Romer's influential theory from the list of plausible explanations for the origin of chordates.

However, these findings were not enough to stop Dohrn's views being disputed, as there is still a major objection regarding the common origin for the chordate, arthropod and annelid CNS. If they were indeed homologous, strands of centralised neurons that are similar to the chordate CNS should also exist in the more basal deuterostome groups, such as echinoderms or hemichordates (Figure 1). Clearly, the echinoderm CNS is very divergent and bears no resemblance to that of the chordates, but how about that of the hemichordates? In juveniles of the enteropneust worm *Saccoglossus kowalevski* — a hemichordate species commonly known as 'acorn worms' — the scattered epithelial expression of neural markers and nervous system patterning genes seemed to suggest that these worm-shaped animals develop only a diffuse nervous system, with neurons distributed over the entire epidermis instead of being concentrated in a nerve cord [14]. This prompted the idea of ancient 'skin brains' [15], which proposes a non-centralised ancestral nervous system, where scattered neurons within the ectoderm would have evolved into a proper internal CNS independently in the more advanced protostome and deuterostome lineages.

The new work by Brunet and collaborators [5] is now adding a fresh brushstroke to the picture by showing that adult acorn worms — unlike juveniles — actually possess a fully-formed CNS, which features what could be interpreted as a transition between the ventral protostome and the dorsal chordate CNS (Figure 2) [16]. By analysing the expression patterns of genes in the CNS, the authors demonstrate that in adult *Ptychodera flava* and *S. kowalevski* worms a ventral and a dorsal strand of centralised

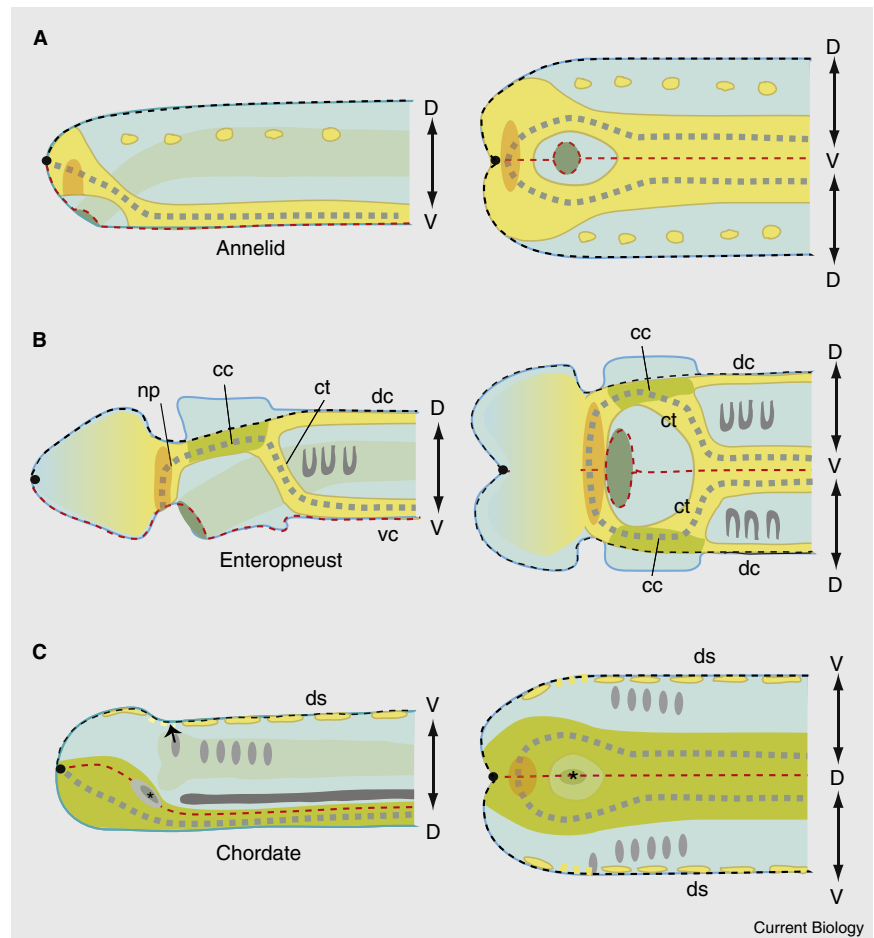


Figure 2. Comparative anatomy of the CNS.

Schematic comparison of centralised nerve cords in an (A) annelid, (B) enteropneust [5] and (C) chordate (note that this schematic is dorsoventrally inverted). Superficial and internalised portions of the CNS are depicted in bright and dark yellow, respectively. Left panels: Lateral views. Right panels: Animals cut open along the midline (black dashed line; dorsal in the annelid and enteropneust, ventral in the chordate) and flattened. Red dashed line indicates the midline on the opposite body side, internalised to form the floorplate of the neural tube in the chordate. A grey dotted line demarcates possibly homologous CNS strands, as initially put forward by Nübler-Jung and Arendt [16]. In the chordate, the asterisks indicate the position of the ancient (now dorsal) mouth at the bottom of the brain and the arrow depicts where a modified gill slit will form the new mouth. Note that the ventral neurogenic strand along the ventral midline will disintegrate (yellow dashed line). cc: collar cord; ct: circumesophageal tract; dc: dorsal cord; np: neural plate; vc: ventral cord; vs: ventral strand.

neurons are present that merge anterior-dorsally at the level of the worm's collar. Both species display a tripartite body that consists of an anterior acorn-shaped proboscis, which they use for burrowing in the sand, followed by a short thick collar and a very long trunk. Further anteriorly, the collar cord extends into a neural plate-like concentration of neurons in the proboscis stem, which harbors the thickest layers of neurons and underlying axons, and which extends ventrally to fully encircle the proboscis stem just behind the proboscis (Figure 2). In other body regions, neurons show a much lower density and

are interpreted as a peripheral nervous system (PNS). In line with a clear separation into a CNS and a PNS, CNS markers such as *hb9* and *Drg*, expressed by somatic motor and sensory neurons of the dorsal root ganglia, or *VACht*, expressed by cholinergic neurons, are only found within the cords. Otherwise, serotonin expressing cells are only found outside the cords. This centralisation of the nervous system is apparent from the earliest stages of metamorphosis between larva and adult. The authors conclude that the previously described 'diffuse' nervous system present at earlier developmental stages in

Saccoglossus is a transitory feature that may correspond to the larval nervous system of other enteropneusts.

This work opens up new avenues of comparative CNS research. Clearly, these data, together with the inverted BMP patterning in acorn worms [17], are consistent with the view that the neural plate of the proboscis stem, the collar cord, the circumesophageal tract and ventral cord together correspond to the chordate CNS as a whole and to the CNS of other invertebrates where inversion has not occurred, as proposed earlier [16]. Yet, a more detailed comparative picture still remains to be drawn. So far, knowledge of neuron types in enteropneusts and of their differential distribution is rather scarce and will require a much closer inspection of a larger number of neuronal markers. Also, a link with the detailed orthologous gene expression data in vertebrates, similar to that described for *Saccoglossus* [14], will have to be established. Only then will it be possible to firmly homologue any portion of the enteropneust CNS with that of chordates or even annelids or arthropods. As a start, the concentration of GABAergic neurons in the proboscis stem, apparently located at the interface between the *six3* and *otx* territory [14], may correspond to GABAergic populations in the vertebrate [18] and in the annelid forebrain (R. Tomer and D.A., unpublished results).

If indeed the CNS represents ancient bilaterian heritage and vertebrates inverted their DV axis, one prominent problem still remains, as discussed by Brunet and colleagues [5] (Figure 2): The dorsal portions of the enteropneust CNS are located exactly where the chordates would have evolved their (new) mouth — on their new ventral (formerly dorsal) body side now facing the substrate. How can we reconcile this? Dohrn [4] had suggested that the new chordate mouth evolved from the ventral relocation of gill slits (Figure 2), as is suggested by the amphioxus mouth, which is thought to represent a ventrally shifted gill slit [19] — hence the name *Branchiostoma*, meaning ‘gill slit mouth’. Interestingly, a strand of neurogenic tissue has recently been discovered along the amphioxus ventral midline giving rise to scattered neuronal precursors that further migrate dorsally [20] before the mouth takes its place. Future molecular comparisons of the neuronal cell types involved will reveal whether this

transitory neurogenic ventral strand in amphioxus might be related to the dorsal strand of neurons in acorn worms or rather represents an independent acquisition that either could be an apomorphy or could be related to a second wave of centralisation: namely the dorsal reunion of a primitive neuronal population with placode-neural crest characteristics. With these new insights derived from mud- and sand-living acorn worms, comparative research on chordate nervous system evolution appears more exciting than ever.

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Cancer: CINful Centrosomes

The regulation of centrosome number is lost in many tumors and the presence of extra centrosomes correlates with chromosomal instability. Recent work now reveals how extra centrosomes cause chromosome mis-segregation in tumor cells.

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Centrosomes are pivotal organizers of the microtubule cytoskeleton and their duplication and inheritance is strictly controlled during the cell cycle in a manner that parallels genome duplication [1]. This control is lost

in many cancer cells, making the presence of extra centrosomes a discernible feature of many tumors [2]. This defect has long been associated with aneuploidy in cancer and it is postulated that additional centrosomes induce chromosome mis-segregation, which then contributes to tumorigenesis [3–6].