How ‘Basal’ Are the Basal Ganglia?

Commentary on Strausfeld NJ and Hirth F (2013a): Deep homology of arthropod central complex and vertebrate basal ganglia. *Science* 340:157–161

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Of the roughly 35 metazoan phyla alive today, only 4 possess nervous tissue that is concentrated and elaborate enough to be called a ‘brain’, suggesting that brains evolved independently in these lineages [Holland, 2003; Northcutt, 2012]. However, growing knowledge of developmental genetics, particularly in vertebrates and insects, has revealed remarkable conservation in the genetic regulatory networks that pattern the developing embryo, including the developing nervous system [Carroll, 1995; Hirth and Reichert, 1999]. This has led to the hypothesis that chordates and arthropods inherited a tripartite rostral brain from their last common ancestor, which would make possession of such a brain the ancestral condition for the entire superclade of bilaterally symmetric animals (Bilateria); the many bilaterian phyla that lack such a brain would have lost it secondarily [Hirth et al., 2003]. A recent review by Strausfeld and Hirth [2013a] takes this a step further by arguing that arthropods have a homolog of the vertebrate basal ganglia, one of the major subdivisions of the telencephalon. Together with claims of a pallium homolog in annelids [Tomer et al., 2010] and suggestions of homology between the vertebrate olfactory bulb and the arthropod antennal lobe [Strausfeld, 2012], this implies that the common ancestor of all Bilateria, living more than 600 million

years ago [Erwin et al., 2011], did not merely have a substantial rostral brain, but specifically a telencephalon, an elaborate set of forebrain structures hitherto recognized only in vertebrates.

The set of structures that Strausfeld and Hirth [2013a] identify as the arthropod homolog of the basal ganglia is the central complex, a group of median neuropils located in the posterior part of the protocerebrum, the rostral-most major division of the arthropod brain. Their hypothesis is based on similarities in function, topological position, anatomical organization, neurotransmitter content and developmental genetics. Strong similarities in all these categories would indeed make a good case for homology between the central complex and basal ganglia, although the absence of these structures in the great majority of Bilaterian taxa would still pose serious problems. To usefully compare such manifestly (if perhaps superficially) different brains, one must not let differences in detail obscure deep parallels nor focus exclusively on similarities, i.e. one must chart a course between nit-picking and cherry-picking. This task is complicated by the fact that most of what we know about the ‘vertebrate’ basal ganglia is derived from the study of a handful of mammalian species. For example, what seems to be a ‘cardinal feature of the striatum’, the

embedding of ‘modular islets’ (striosomes) in a surrounding matrix [Strausfeld and Hirth, 2013a], may look more like a contingent feature when one discovers that the avian striatum appears to lack striosomes [Reiner et al., 1989; Person et al., 2008].

The broadest organizational criteria for basal ganglia circuitry that apply to all vertebrate taxa studied to date would include an input structure (the striatum) that receives excitatory input from other parts of the forebrain (especially the thalamus and pallium/cortex) and an output structure (the globus pallidus or substantia nigra) that receives inhibitory input from striatal cells and makes inhibitory projections to structures outside the basal ganglia [Reiner et al., 1998; Endepols et al., 2004; Stephenson-Jones et al., 2012]. The cellular elements of striatum and pallidum may co-mingle in one structure [Farries and Perkel, 2002] and exhibit a variety of other connections [Parent and Hazrati, 1995], but a two-step striatopallidal inhibitory circuit is probably the minimal criterion that could distinguish the basal ganglia from other motor-related structures like the cerebellum, midbrain tectum or motor cortex. Strausfeld and Hirth [2013a] associate two central complex neuropils with the striatum – the protocerebral bridge (PB) and the fan-shaped body (FB) – while identifying the ellipsoid body (EB) with pallidal/

nigral output. The nearby lateral accessory lobes (LAL) are equated to the pallido/nigrorecipient thalamus. A 'basal ganglia' pattern of organization in this context would include cells with postsynaptic arborizations in the PB and/or FB collecting excitatory input and exhibiting GABAergic presynaptic arbors in the EB. Another set of cells would receive that inhibition on their postsynaptic EB arbors while projecting to targets outside of the central complex (e.g. the LAL) where they in turn release GABA. The first set of cells would represent the striatum while the second set would be equivalent to pallidal neurons.

As noted by Strausfeld and Hirth [2013a], the EB and parts of the LAL exhibit dense GABA-like immunoreactivity [Hanesch et al., 1989; Homberg et al., 1999; Kahsai and Winther, 2011]; this is consistent with their hypothesis. However, most of the GABAergic innervation of the EB is derived from cells that have what appear to be postsynaptic arbors in specific regions of the LAL and presynaptic arbors in the EB [Hanesch et al., 1989; Müller et al., 1997; Homberg et al., 1999; Young and Armstrong, 2010; Phillips-Portillo, 2012]. In other words, these cells, a subset of what are called 'ring cells' in flies and 'tangential cells' in locusts, appear to represent a GABAergic projection from the 'thalamus' to the 'pallidum'. The less intense GABA-like immunoreactivity found in the FB is also derived, at least in part, from cells providing connections from the LAL to the central complex [Homberg et al., 1999], while the PB seems devoid of GABA-like immunoreactivity [Hanesch et al., 1989; Homberg et al., 1999]. There are some cells with postsynaptic arbors in the hypothetical striatum (PB, FB) and presynaptic arbors in the proposed pallidum (EB) and some that appear postsynaptic in EB and presynaptic in the LAL, but they do not appear to be GABAergic and they are outnumbered by cells whose projection patterns are at odds with the striatopallidal ground plan [Hanesch et al., 1989; Müller et al., 1997; Young and Armstrong, 2010].

Although the central complex is not organized like the basal ganglia as currently understood, they may be homologous structures with similar functions that have diverged structurally over the >600 million years since the arthropod and vertebrate lineages diverged, and their correspondence might still be recognized in their topological position and shared developmental mechanisms. Strausfeld and Hirth

[2013a] assert that both the central complex and the basal ganglia are derived from the 'midline of the forebrain-midbrain boundary region', apparently equating the arthropod protocerebrum-deutocerebrum boundary with the forebrain-midbrain boundary. In this context, their description is apt for the central complex, and the vertebrate substantia nigra does at least lie near the forebrain-midbrain interface. But the bulk of the basal ganglia (including striatum and pallidum) are derived from the rostral edge of the neural plate and, although their anlagen are rostromedial to other parts of the telencephalon, they are not midline structures [Eagleson and Harris, 1990; Inoue et al., 2000; Cobos et al., 2001]. In the current neuromeric model of the prosencephalon, the basal ganglia (along with the rest of the telencephalon) are derived from the three rostral-most prosomeres, separated from the midbrain by three caudal prosomeres encompassing the thalamus and pretectum [Puelles and Rubenstein, 2003]. Most of the basal ganglia are about as far away from the midbrain as it is possible to be without leaving the forebrain.

The strongest part of the case for homologizing the central complex with the basal ganglia rests on the shared genetic circuitry responsible for patterning the brains of arthropods and vertebrates. These genes are generally not specific to the basal ganglia and appear in many different developmental contexts, but it is more instructive to suppose that they are specific and ask what this would imply for the evolutionary relationship between the central complex and the basal ganglia. It is now widely recognized that earlier stages of ontogeny can diverge without necessarily affecting later stages [Butler and Sidel, 2000], so that similarities (or differences) appearing during development do not have incontrovertible implications for the homology of adult structures. Yet some have argued that the highly conserved genetic regulatory networks involved in patterning the body axes occupy a privileged position that allows them to define character identity across disparate taxa despite great variation in character state that might otherwise obscure the homology of the character [Wagner, 2007]. This is a neat solution to the difficult problem of recognizing homologous characters in disparate taxa even as they exhibit, in Owen's famous phrase, 'every variety of form and function'. For example, *Otx* and its insect homolog *otd*

could define, in the appropriate developmental context, the forebrain and midbrain and permit us to recognize this shared character identity in arthropods and vertebrates despite divergent character states [Hirth, 2010].

There is, however, another way to view these highly conserved transcription factors: they establish a 'coordinate system' that organizes subsequent development without any necessary connection to the identity of the characters that use the positional information they provide. In this view, they are highly conserved because the need for their positional information during development is universal, but characters in different taxa appearing at the same 'coordinates' need not share a lineage and hence need not be homologous. Recent studies in an enteropneust hemichordate [Lowe, 2008] seem more consistent with this latter view than with the 'character identity' hypothesis of Wagner [2007]. Enteropneusts have a diffuse basiepithelial nervous system, yet the genes associated with patterning the brains of arthropods and vertebrates are expressed within this diffuse nerve net. Genes that have been proposed to define the character identity of the rostral brain and whose expression is restricted dorsoventrally to the side containing the developing central nervous system (dorsal in vertebrates, ventral in arthropods) are expressed throughout the dorsoventral extent of the enteropneust ectoderm, congruent with their dorsoventrally diffuse nervous system. One could still maintain that certain of these genes define a more abstract character identity that encompasses, for example, the vertebrate forebrain, arthropod protocerebrum and enteropneust rostral ectoderm as disparate character states, but at that point these genes would cease to be useful in establishing meaningful homologies between brains. If a diffuse nerve net is among the possible states for the character 'basal ganglia', then what of functional significance could we conclude from knowing that the arthropod central complex and the vertebrate basal ganglia share *that* identity?

There are similarities linking the central complex and the basal ganglia, including some I have not touched on here, and the hypothesis that they are homologous is not ruled out by the great differences between them. But a fair assessment of those similarities must also consider them within the alternative hypothesis of homoplasy, i.e. that the central complex and basal ganglia

arose by parallel or convergent evolution. Suppose the starting point is a common ancestor bearing a simple rostral brain with access to external sensory data such as the level of light or the chemical environment, and with descending control pathways capable of using those data to regulate simple behaviors. It is easy to imagine that multiple descendant groups could at some point occupy niches that reward a more complicated and flexible behavioral repertoire, creating selection pressure for neural machinery that can help the organism meet homeostatic needs in a more predictive and proactive manner. Where could this novel neural machinery appear if not in the place where the data it needs are already available and where descending control pathways are already in place? How else might the development of this new organ be initiated at the correct embryonic location if not by reference to the conserved genetic regulatory networks that define the body axes? This evolving neural organ would make use

of any neurotransmitters available in the originating species, whether they are inherited from the common ancestor, like dopamine [Kahsai et al., 2012], or appear only in a subset of that ancestor's descendants, like octopamine [Sinakevitch et al., 2005]. Defects in this neural organ, including disruptions in the neurotransmitter systems that it uses, should display malfunctions in the tasks it is supposed to perform, i.e. motor control or the predictive pursuit of homeostatic goals.

The consideration of even very simple constraints imposed by a common starting point and similar selection pressure can explain a host of similarities in structures that evolved independently. To support a claim of homology, the similarities cited must at least extend beyond the ones that are likely – or indeed inescapable – in any plausible homoplasy scenario. Many of the parallels between the arthropod central complex and the vertebrate basal ganglia cited by Strausfeld and Hirth [2013a] are nothing

more than what one would expect with homoplasy, and their work overlooks major differences in anatomical organization and topographic position. The central complex does not resemble the basal ganglia any better than it does virtually any other part of the vertebrate brain associated with sensory integration and motor control. With the common origin of even a simple rostral brain still in doubt [Moroz, 2009; Northcutt, 2012], there is no sufficient reason to abandon the hypothesis that the telencephalon, including the basal ganglia, is a synapomorphy of vertebrates [Lacalli, 1996; Holland and Holland, 1999] in favor of a Precambrian ur-bilaterian telencephalon.¹

¹ For responses to the points raised in this commentary, see Strausfeld NJ and Hirth F (2013b) in this issue.

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