Deep Homology of Arthropod Central Complex and Vertebrate Basal Ganglia

Nicholas J. Strausfeld[1]* and Frank Hirth[2]*

The arthropod central complex and vertebrate basal ganglia derive from embryonic basal forebrain lineages that are specified by an evolutionarily conserved genetic program leading to interconnected neuropils and nuclei that populate the midline of the forebrain-midbrain boundary region. In the substructures of both the central complex and basal ganglia, network connectivity and neuronal activity mediate control mechanisms in which inhibitory (GABAergic) and modulatory (dopaminergic) circuits facilitate the regulation and release of adaptive behaviors. Both basal ganglia and central complex dysfunction result in behavioral defects including motor abnormalities, impaired memory formation, attention deficits, affective disorders, and sleep disturbances. The observed multitude of similarities suggests deep homology of arthropod central complex and vertebrate basal ganglia circuitries underlying the selection and maintenance of behavioral actions.

Vertebrate basal ganglia are evolutionarily conserved interconnected nuclei traceable to stem group taxa (*1*). Their ground pattern comprises four principal volumes: the striatum, the internal and external domains of the globus pallidus, the subthalamic nucleus, and the substantia nigra. Basal ganglia play a key role in selecting and maintaining adaptive behavior by conveying sensorimotor, limbic, and associative information corresponding to action selection among behavioral modules that are competing for the control of a limited set of motor programs (*2*). Focal lesions and dysfunction of the basal ganglia are associated with movement disorders, such as parkinsonism, dystonia, and abulia, as well as neuropsychiatric disorders (*3*), essentially affecting goal-directed behavior and habitual control (*4*).

[1]Department of Neuroscience, School of Mind, Brain and Behavior, University of Arizona, Tucson, AZ 85721, USA. [2]MRC Centre for Neurodegeneration Research, Department of Neuroscience, Institute of Psychiatry, King's College London, London SE5 8AF, UK.

*Corresponding author. E-mail: flybrain@neurobio.arizona.edu (N.J.S.); frank.hirth@kcl.ac.uk (F.H.)

Similar behavioral manifestations have been attributed to the arthropod central complex (*5*, *6*), which in insects and crustaceans comprises three interconnected midline centers: the protocerebral bridge, fan-shaped body, and ellipsoid body leading to the paired lateral accessory lobes (fig. S1). Central complexes can be traced to related arthropods, including Onychophora, and to Lophotrochozoa represented by polychaete annelids (*5*). Here, we review multiple lines of evidence suggesting deep homology of the vertebrate basal ganglia and the arthropod central complex in the selection and maintenance of adaptive behavior.

Basal Forebrain Origin and Developmental Genetics

Nuclei of the basal ganglia derive from precursor cells of the ventral telencephalon, with neural stem cells from the ganglionic eminences giving rise to striatum and pallidum to become located at the segmental border between the prosencephalon and mesencephalon, where they populate the midline of the basal forebrain (*7*). In insects, specific embryonic and larval neural stem cells in the basal forebrain give rise to components of the central complex that populate the midline of the posterior protocerebrum (*6*). Thus, the vertebrate basal ganglia and arthropod central complex share comparable embryological derivation and topography.

In mice, forebrain patterning, prosencephalic and mesencephalic boundary formation, and genesis and specification of the ventral telencephalon (especially the ganglionic eminences) are under

Table 1. Genetic programs underlying the formation of vertebrate basal ganglia and insect central complex. Abbreviations: FB, fan-shaped body; EB, ellipsoid body; DA, dopaminergic.

Vertebrate basal ganglia	Gene homologs	Insect central complex
Patterning of forebrain/midbrain and ventral telencephalon (*9*, *62*, *63*)	*Otx2/otd* *FGF8/pyramus, thisbe* *SHH/hh* *BMP/dpp*	Patterning of forebrain and basal protocerebrum (*71*)
Patterning of ventral telencephalon and formation of striatum and pallidum (*7*, *8*)	*Six3/Tc-Six3* *SHH/hh*	Patterning of anterior neuroectoderm and formation of FB+EB (*13*)
Formation and specification of striatum and pallidum (*7*, *64*, *65*)	*Dlx1,2/Dll* *Tlx/tll* *Nkx2.1/vnd*	Formation and specification of basal protocerebrum (*13*, *71*)
Specification of striatum and pallidum (*9*, *65*–*67*)	*Otx2/otd* *Pax6/eyeless* *Emx2/ems* *Gsh1,2/ind* *Lhx6,7/–*	Specification of protocerebral bridge, FB, and EB (*13*, *14*, *16*)
Specification and maintenance of DA neurons (substantia nigra) (*10*, *68*)	*Otx2/otd* *En1,2/en* *FGF8/pyramus, thisbe* *SHH/hh* *LRRK2/lrrk2*	Specification and maintenance of DA neurons (PPM3, PPL1) (*15*)
Formation of subthalamic nucleus (*69*, *70*)	*Pitx2/Pitx1*	?
Nigropallidal projections (*10*), EtOH-induced reward/addiction (*52*)	*AUTS2/tay-bridge*	PPL1-FB projections, EtOH-induced reward/addiction (*40*, *43*, *52*, *72*)

the control of signals including fibroblast growth factor 8 (FGF8), sonic-hedgehog (SHH), and members of the bone morphogenetic protein (BMP) family; FGF8 and SHH play essential roles in the neurogenesis of dopaminergic cells of the substantia nigra (*7*). The *Six3* gene interacts and is required with SHH for early ventral telencephalon formation (*8*), and *Otx2* is required for early forebrain and midbrain development (*9*). Later in development, *Otx2* is involved in the genesis of substantia nigra dopaminergic neurons and the formation of the dopaminergic nigrostriatal pathway (*10*). *Dlx1/2*, *Tlx*, *Nkx2.1*, *Pax6*, *Emx2*, *Gsh1/2*, and *Lhx6/7* play essential roles in the development and specification of the striatum and pallidum; *Engrailed1/2* (*En1/2*) genes are required for substantia nigra formation; and *Pitx2* is required for the formation of the subthalamic nucleus (Table 1).

In *Drosophila* and the beetle *Tribolium*, homologs of FGF8, SHH, BMP, *Otx2*, *Dlx1/2*, *Tlx*, *Nkx2.1*, *Pax6*, *Emx2*, *Gsh1/2*, *En1/2*, and *Pitx2* have all been identified. The region-specific gene expression patterns in the developing brain correspond to those in vertebrates (*11*–*13*). For example, the *Drosophila Otx2* homolog *otd* is required for embryonic forebrain development and, later during development, for the formation of the protocerebral bridge (*14*) and the specification of central dopaminergic neuron clusters (*15*). The *Tribolium* homolog of the vertebrate *Six3* gene is required for formation of the fan-shaped body and ellipsoid body; knockdown of *Tc-Six3* leads to early patterning defects in the anterior neuroectoderm and the complete absence of central body lineages (*13*). The *Drosophila Pax6* homolog *eyeless* is required for fan-shaped body and ellipsoid body specification (*16*). Thus, the genesis and specification of the basal ganglia and central complex share underlying developmental genetic programs that extend from homologous gene structure to patterned expression and function (Table 1).

Neural Architectures of Striatum/Fan-Shaped Body and Pallidum/Ellipsoid Body

The adult striatum and fan-shaped body are distinguished by their three-dimensional architectures. A cardinal feature of the striatum, best resolved in mammals, is its differentiation into modular islets, the striosomes, embedded in the surrounding neural matrix, and a system of domains adjacent to striosomes, termed matrisomes (*17*) (Fig. 1, A to C). Matrisomes relate to body parts and their representations in sensory cortices (*17*), whereas striosomes receive relays via the prefrontal cortex from the amygdala, hippocampus, and limbic system (*17*–*19*). Combinatorial interactions among modules provide substrates for associations among the representations of body parts and of their spatial coordinates, with striosomal afferents relating to stored associations and functions that are loosely referred to as motivational levels, reafference, and autonomic functions (*20*).

In the insect central complex, the fan-shaped body comprises an arrangement of successive synaptic layers intersected by a repeated arrangement of modules (Fig. 1, D to F). Each arrangement reflects the clonal organization of uniquely identifiable columnar, tangential, and fan-shaped arborizations of efferent, intrinsic, and afferent neurons (*21*–*24*). Sensory representations at the level of the protocerebral bridge are exemplified by maps of the e-vector of polarized light, which are combinatorially intermingled by a system of chiasmatal projections to modules spanning the underlying fan-shaped body (*25*). Haptic information, also encoding sensory space and provided by mechanosensory appendages, is represented across the protocerebral bridge and fan-shaped body (*26*, *27*). Insects with evolved blindness demonstrate the robustness of such modularity and its independence from a single sensory modality (*28*). Stratifications of the fan-shaped body are further denoted by systems of modulatory peptidergic neurons (*23*) and inputs to it from the protocerebrum carrying information of higher-order visual primitives and learned discrimination of visual cues (*29*–*31*). Thus, distinctive modules representing sensory attributes, and modules provided by afferents from association and modulatory centers, can be identified in both phyla (Fig. 1).

The vertebrate pallidum and the arthropod ellipsoid body share comparable organizational features. In vertebrates, the internal and external globus pallidus (GPi and GPe) are dominated by GABAergic neurons that connect to the subthalamic nucleus and the thalamus, with reciprocal glutamatergic connections from the subthalamic nucleus back to the GPe. Inhibitory outputs from the globus pallidus serve to select specific motor actions by suppressing inhibition of their activating circuits (*2*). In insects, inhibitory GABAergic neurons, which provide dense networks in the fan-shaped body, ellipsoid body, and two satellite centers (noduli), extend their axons laterally from the central complex to the flanking lateral accessory lobe neuropils (*30*, *32*). The identification of metabotropic glutamate receptors at discrete branching processes suggests reciprocal glutamatergic pathways to the ellipsoid and fan-shaped bodies (*33*). Fibrous distributions of monoamines and peptides, as well as their corresponding metabotropic receptors in neural processes, point to the presence of complex modulatory circuits within and between ellipsoid and fan-shaped body neuropils (*34*).

Dopaminergic Neuron and Receptor Distribution

In vertebrates, the substantia nigra provides the primary source of dopaminergic neurons that ascend to the striatum, leading to a dense innervation via the nigrostriatal pathway (*35*). All known G protein–coupled dopamine receptors are expressed in the striatum, with D1 and D2 receptors the most abundant. D1 receptors, together with substance P, are expressed by GABAergic spiny projection neurons (SPNs) constituting 90% of the striatal neurons that project to the GPi and substantia nigra reticulata, thereby defining the direct pathway (*36*). Projections to the GPe, defining the indirect pathway, express D2 dopamine receptor together with enkephalin (*36*).

As evidenced in *Drosophila*, clusters of dopamine-containing neurons identified at the level of single nerve cells have stereotypic anatomical and location-specific projection patterns. Whereas several such clusters are associated with the mushroom bodies (*37*), two clusters termed PPM3 and PPL1, revealed at the single-cell level, provide dense dendritic arborizations within the central complex (*37*–*41*). Thus, individual dopaminergic neurons of the PPM3 cluster target fan-shaped body, ellipsoid body, and lateral accessory lobes (*37*–*39*), and single neurons of the PPL1 cluster target the fan-shaped body, with both PPM3 and PPL1 targeting the mushroom bodies as well (*40*, *41*) (Fig. 2). D1-like dopamine receptor expression and immunoreactivity have been demonstrated for the fan-shaped body, ellipsoid body, and lateral accessory lobes (*42*, *43*). Substance P immunolabeling has been described in the central complex of insects (locusts), chelicerates (*Limulus*), and decapod crustaceans (*Homarus*) (*44*–*46*). In the locust, columnar substance P immunoreactive fibers project to the protocerebral bridge, from which they extend to the lower division of the central body (the locust term for the ellipsoid body); substance P immunoreactive terminals extend out to the central complex's lateral triangle and the lateral accessory lobes (*46*). However, comparative analysis reveals limited evidence for enkephalin and D2 receptor expression. These data suggest the presence of a direct pathway in the arthropod central complex, with substance P and D1 receptor expression linking ellipsoid and fan-shaped bodies (*42*–*46*) and direct GABAergic output to the lateral accessory lobes (*30*, *32*).

Selection and Maintenance of Behavioral Actions

In insects, the central complex is critical in the selection of motor actions and the control of multijoint movement (*47*). Genetic deletion of parts of the central complex, developmental errors that disrupt central complex circuitry, or the misexpression of neuropeptides can all give rise to ataxia, tripping, hesitancy, and other parkinsonism-like defects. In addition, targeted synaptic inactivation of central complex substructures impairs visual orientation and place memory, diminishes startle- or ethanol-induced arousal, and results in attention deficits and sleep disorders (table S1).

The behavioral outcomes of neuronal activity of the central complex are reminiscent of action selection and maintenance mediated by the vertebrate basal ganglia, which includes a raft of functions (table S1). Dysfunction of the basal ganglia caused by injury, viral or bacterial infection, or age-related degeneration of neuronal subpopulations, along with other pathological deficiencies, results in a spectrum of motor system disorders ranging from hypokinesia to hyperkinesia (including ataxias, parkinsonism, Tourette syndrome, chorea, and dystonia) as well as neu-

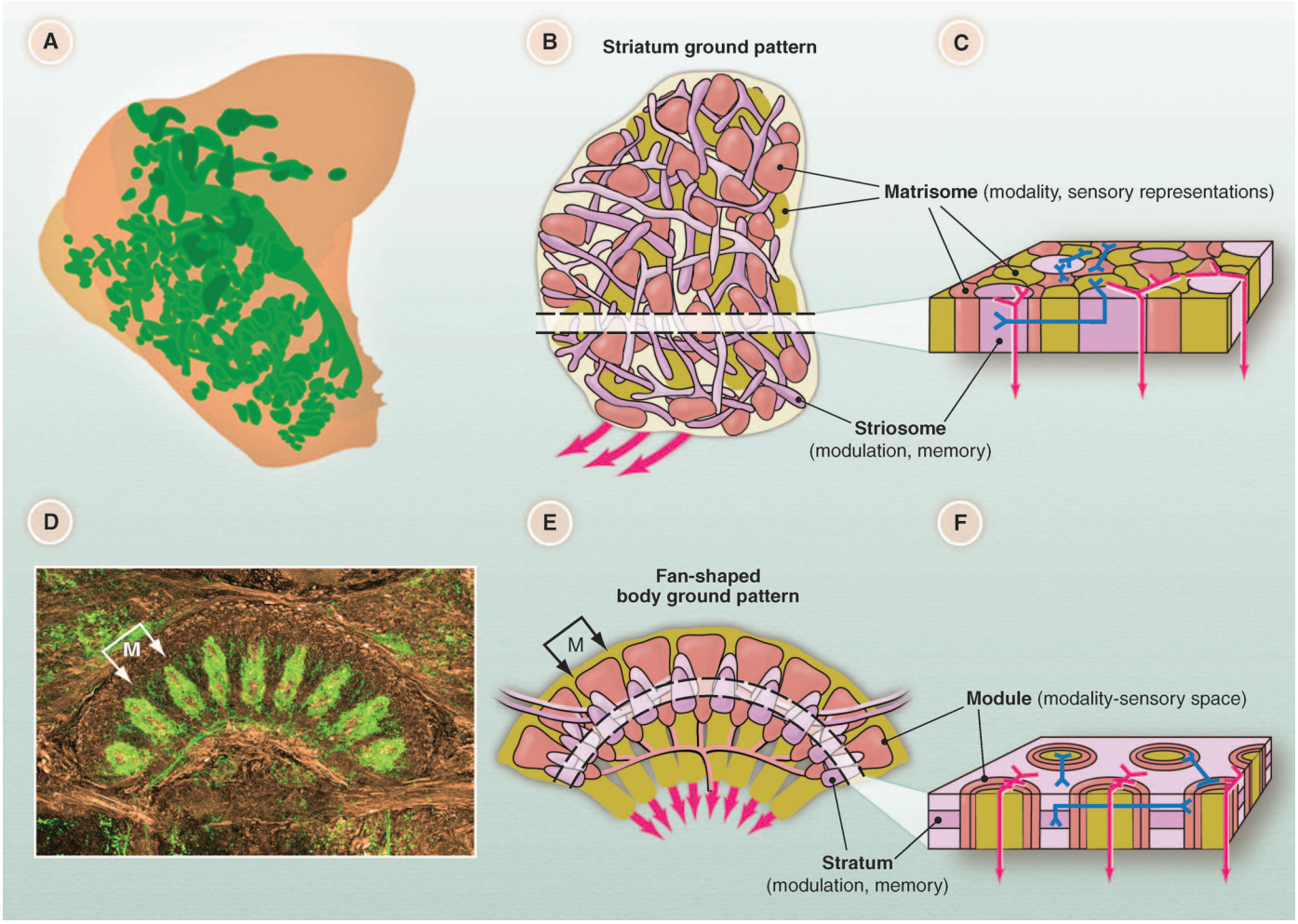

Fig. 1. Ground pattern and modular arrangement of the mammalian striatum and the insect fan-shaped body. (**A** to **C**) The mammalian striatum [(A), modified from (*73*)] consists of two principal subunits. Striosomes [green in (A)] within the matrix of the striatum [schematized in mauve, purple in (B) and (C)] are associated with discrete volumes of the striatal matrix, called matrisomes [brown, yellow in (B) and (C)]. In mammals, striosomes receive inputs from the hippocampus and amygdala via the frontal cortex, among other brain regions, carrying information about internal physiological states (modulations, memories) (*17*, *20*). Matrisomes are supplied by cortical representations of sensory space and sensory modalities (*17*). (C) Interactions and associations among matrisomes, and between matrisomes and striosomes, are mediated by local interneurons (blue) that integrate and provide information to striatal afferents supplying direct and indirect GABAergic pathways (red arrows) to the globus pallidus and subthalamic nucleus [see (*3*, *36*)]. (**D** to **F**) The insect fan-shaped body [(D), from *Mantis religiosa*, labeled with antisera against allatostatin (green) and β-tubulin (ochre)] consists of two principal subunits: tangential stratifications (schematized in mauve, purple) that intersect columnar modules (yellow, brown), one indicated by bracketed arrows M in (D) and (E) [see (*22*, *24*, *32*)]. Columnar modules are supplied by afferents carrying information about sensory modalities and the organization of sensory space (*5*, *25*, *26*). (E) Tangential elements comprise relays mainly from the protocerebrum. These can carry information about higher-order sensory cues, learned sensory associations, and physiological states [modulations, memories (*5*, *25*–*27*, *29*, *30*)]. (F) Cross section of a stratum of the fan-shaped body, showing routes of interactions and associations among columnar elements, and between columnar elements and planar tangentials, that are mediated by local interneurons (blue) at several levels through the fan-shaped body (*5*, *21*). These are assumed to provide integrated information to outgoing GABAergic pathways (red arrows).

ropsychiatric disorders (including impaired memory formation, attention deficits, affective disorders, and sleep disturbances) (*3*). Thus, both central complex substructures and nuclei of the vertebrate basal ganglia mediate sensorimotor integration, motivational and affective behavior, and cognition related to comparable behavioral manifestations (table S1).

Dopaminergic Modulation of Action Selection and Maintenance

In vertebrates, dopamine innervation of the striatum via the nigrostriatal pathway is critical for normal function of the striatum and basal ganglia. Substantia nigra neurons are autonomous pacemakers that provide a tonic release of dopamine onto GABAergic SPNs in the striatum, thereby modulating the tonic inhibitory output of GABAergic SPNs and allowing movements to occur. Depletion of dopamine or its receptors, or dysfunction of the nigrostriatal pathway, can result in a range of pathologies, most of which refer to dysfunction of inhibitory or activation control of motor behaviors (*36*). Progressive loss of dopaminergic neurons in the substantia nigra causes loss of the nigrostriatal pathway, which in turn results in Parkinson's disease characterized by a progressive increase in the brain's inability to suppress motor actions, leading to rigidity, bradykinesia, and nonmotor symptoms including sleep and mood disorders (*3*). The activity of nigrostriatal dopaminergic neurons also modulates motivated behaviors related to aversion and reward. Aversive events transiently decrease the activity of nigrostriatal dopaminergic neurons, whereas reward transiently increases it, thereby providing bidirectional signaling to the striatum. Addiction disorders such as alcohol abuse have been linked to an imbalance or dysfunction of

this system, especially of the striatal nucleus accumbens (*48*). Recent optogenetic and genetic work confirms the modulation of both the direct and indirect pathways by dopamine or dopamine receptor activity; these mediate action selection and reward- or aversion-driven maintenance of behavioral actions (*36*).

Insects show similar dopamine-dependent behaviors and deficits. Dopaminergic neurons and D1 receptor activation in the central complex play crucial roles in behavioral action selection and maintenance. Central nervous system (CNS)–specific depletion of dopamine in *Drosophila* results in reduced activity and locomotor deficits, extended sleep time, and defects in aversive olfactory memory formation, suggesting that arousal and choice require normal dopamine levels (*49*). Age-related degeneration of dopaminergic neuron clusters leads to parkinsonism in *Drosophila* characterized by severely impaired motor behavior (*50*, *51*). Specifically, dopaminergic PPM3 neurons projecting to the central complex (see above) regulate locomotor activity and promote ethanol-induced hyperactivity (*6*, *43*). Expression of the D1-like receptor DopR in the ellipsoid body is required for locomotor activity elicited by ethanol exposure (*43*) and for the regulation of repetitive startle-induced arousal (table S1). Optogenetic and genetic manipulation of PPL1 dopaminergic neurons that project to both mushroom bodies and the fan-shaped body reveal that these cells are essential for motivated behaviors, including reward- and aversion-driven maintenance of behavioral actions that relate to memory retrieval and reinforcement (table S1).

Thus, in both the central complex and basal ganglia, comparable systems of dopaminergic neurons, their projections, and dopaminergic receptor activities are involved in the modulation and maintenance of normal behavioral actions (table S1). Perturbation of dopaminergic pathway activity or of its modulatory output interferes with the selection and maintenance of behavioral actions. This is further exemplified by nigrostriatal pathway and PPL1/fan-shaped body projections: Both are involved in the modulation of reward behavior that is distorted by abusive alcohol consumption leading to addiction modulated by *tay-bridge* in *Drosophila* and its *AUTS2* homolog in mammals, including humans (*52*); in both cases, parts of the underlying, deregulated neural circuitry have been identified, including dopaminergic innervation of the ellipsoid body (*37*–*39*, *43*) and dopaminergic innervation of the pallidum via nigropallidal projection neurons (*48*).

Deep Homology of Neural Circuitry for Action Selection and Maintenance

The multiplicity of similarities described here identifies a highly conserved structural and functional organization of the arthropod central complex and vertebrate basal ganglia (Fig. 2). Differences, beyond shape and size, suggest that an indirect pathway including a subthalamic nucleus-like structure is either absent or remains to be identified in the arthropod central brain. In mammals, bipartite activity of direct and indirect pathways results in action selection by disinhibition of a selected motor program and the simultaneous inhibition of other competing actions (*2*, *3*). Although there is ample evidence for a direct pathway in the arthropod central complex, it remains to be shown whether a comparable interplay between disinhibitory activity and enhanced inhibition mediates action selection and behavioral output in arthropods. Moreover, the evolved loss of central complex components, as in Branchiopoda (*5*), or loss of a centralized nervous system entirely (*11*) are likewise phylum-specific departures from a corresponding ground pattern.

Similarities of brain structure, function, and behavior have been ascribed to convergent evolution (*53*). However, microRNA and ribosomal RNA data (*54*, *55*) support a common origin of arthropods and vertebrates—a conjecture further corroborated by recent morphological and molecular evidence suggesting that Cnidaria represent a true outgroup to Bilateria (*56*). Monophyly of Bilateria, together with the presence of a midline

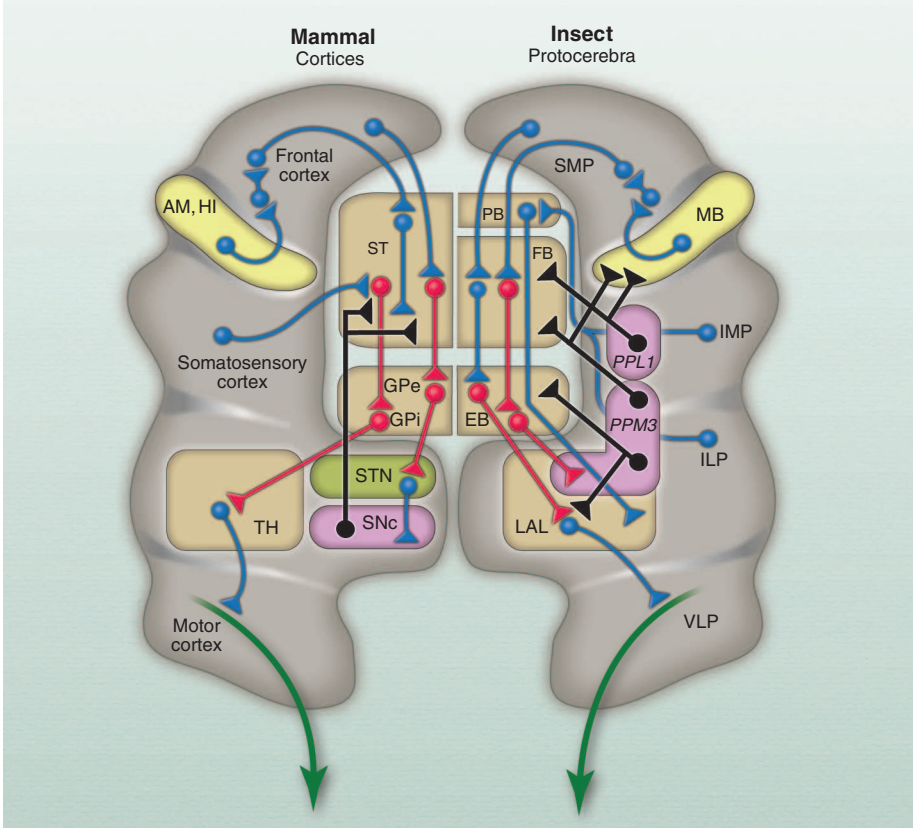

Fig. 2. Proposed correspondences of neural organization of the mammalian basal ganglia and insect central complex. Corresponding regions of the basal ganglia (left) and insect central complex (right) and their associated regions are aligned, as are their relevant connections. Inhibitory pathways are shown in red, dopaminergic pathways in black, and other pathways (excitatory or modulatory) in blue. The striatum (ST = caudate nucleus + putamen) corresponds to the fan-shaped body and protocerebral bridge (FB+PB); the external and internal globus pallidus (GPe, GPi) correspond to the ellipsoid body (EB). There is no center in the insect corresponding to the vertebrate subthalamic nucleus (STN) as an intermediate station between the GP and the dopaminergic substantia nigra pars compacta (SNc). Inputs to the striatum derive from sensory and association cortices (gray), from the hippocampus and amygdala (HI, AM; yellow), and from the limbic system (not shown) via the frontal cortex (*17*, *20*). In insects, inputs to the FB and PB derive from sensory intermediate and inferior lateral protocerebra (IMP, ILP) (*21*, *22*, *25*–*27*, *30*) and associative superior medial protocerebrum (SMP), which receives learned visual cues and outputs from the mushroom bodies (MB) (*29*, *74*), the latter center corresponding to the mammalian hippocampus (*5*, *59*). The PB, FB, and EB are connected by through-going presumably excitatory columnar neurons, many of which also extend to the lateral accessory lobes (LAL) (*21*, *24*, *25*). GABAergic outputs from the insect EB supply the LAL and its associated neuropils (*30*, *32*). The LAL is here equated to the vertebrate thalamus (TH) supplied from the globus pallidus (*2*). Both the TH and LAL supply motor centers [mammal: motor cortices (*2*); insect: inferior and ventrolateral protocerebra (ILP, VLP) (*75*)]. In insects, dopamine pathways extending from PPM3 and PPL1 domains to the FB and EB (*37*–*43*) correspond to dopamine innervation of the striatum from the SNc (*35*, *76*). Descending pathways [vertebrate: from motor cortices to spinal cord; insect: from the ILP, VLP to the ventral cord and ganglia (*77*)] are shown in green.

neuropil in both annelids and arthropods, suggests that a central complex–like midline structure already existed in the common bilaterian ancestor before the split to Protostomia and Deuterostomia, which likely possessed a complex, tripartite brain (*11*, *57*). It follows that genealogical correspondence due to common evolutionary origin (*58*) is the most parsimonious explanation for the observed multitude of similarities between basal ganglia and the central complex, which suggests that homologous circuits mediate comparable behavioral functions across phyla.

There is no a priori reason for rejecting the notion that the selection of an appropriate motor program by a brain is a plesiomorphic trait and that this trait, which is common across phyla, is provided by homologous circuits. Adaptive behaviors, selected by the CNS as responses to one or another environmental challenge, are universal phenotypes of organisms equipped with rostral brains that integrate bilateral sensory input for coordinated behavioral output. The likelihood that such a relationship was present in the ancestor of protostomes and deuterostomes is suggested by trace fossils from the end-Vendian and early Cambrian, which show that organisms accomplished bouts of elaborate searching strategies (*59*, *60*)—that is, complex actions that were switched on and off.

The multitude of commonalities reviewed here suggests deep homology of the arthropod central complex and vertebrate basal ganglia. They indicate that the ancestral bilaterian brain already possessed clusters of midline-associated, interconnected basal forebrain neurons mediating the selection and maintenance of behavioral actions. Together with recent evidence for a common origin of higher brain centers involved in allocentric memory in worms and mice (*61*), these data suggest that the ground pattern of circuits essential for behavioral choice originated very early and have been maintained across phyla throughout evolutionary time.

References and Notes

1. M. Stephenson-Jones, E. Samuelsson, J. Ericsson, B. Robertson, S. Grillner, *Curr. Biol.* **21**, 1081 (2011).
2. S. Grillner, J. Hellgren, A. Ménard, K. Saitoh, M. A. Wikström, *Trends Neurosci.* **28**, 364 (2005).
3. A. M. Graybiel, *Curr. Biol.* **10**, R509 (2000).
4. P. Redgrave *et al*., *Nat. Rev. Neurosci.* **11**, 760 (2010).
5. N. J. Strausfeld, *Arthropod Brains: Evolution, Functional Elegance, and Historical Significance* (Harvard Univ. Press, Cambridge, MA, 2012).
6. K. Furukubo-Tokunaga, Z. N. Ludlow, F. Hirth, in *Memory Mechanisms in Health and Disease*, K. P. Giese, Ed. (World Scientific, Singapore, 2012), pp. 269–306.
7. S. W. Wilson, J. L. Rubenstein, *Neuron* **28**, 641 (2000).
8. D. Carlin *et al*., *Development* **139**, 2614 (2012).
9. A. Simeone, E. Puelles, D. Acampora, *Curr. Opin. Genet. Dev.* **12**, 409 (2002).
10. M. P. Smidt, J. P. Burbach, *Nat. Rev. Neurosci.* **8**, 21 (2007).
11. F. Hirth, *Brain Behav. Evol.* **76**, 3 (2010).
12. R. Urbach, G. M. Technau, *Adv. Exp. Med. Biol.* **628**, 42 (2008).
13. N. Posnien, N. D. Koniszewski, H. J. Hein, G. Bucher, *PLoS Genet.* **7**, e1002416 (2011).
14. F. Hirth *et al*., *Neuron* **15**, 769 (1995).
15. J. Blanco, R. Pandey, M. Wasser, G. Udolph, *Neural Dev.* **6**, 34 (2011).
16. P. Callaerts *et al*., *J. Neurobiol.* **46**, 73 (2001).
17. A. W. Flaherty, A. M. Graybiel, *J. Neurosci.* **14**, 599 (1994).
18. F. Eblen, A. M. Graybiel, *J. Neurosci.* **15**, 5999 (1995).
19. A. M. Graybiel, T. Aosaki, A. W. Flaherty, M. Kimura, *Science* **265**, 1826 (1994).
20. K.-I. Amemori, L. G. Gibb, A. M. Graybiel, *Front. Hum. Neurosci.* **5**, 47 (2011).
21. U. Hanesch, K.-F. Fischbach, M. Heisenberg, *Cell Tissue Res.* **257**, 343 (1989).
22. K. Ito, T. Awasaki, *Adv. Exp. Med. Biol.* **628**, 137 (2008).
23. Z. Herbert *et al*., *J. Morphol.* **271**, 1509 (2010).
24. G. Boyan, L. Williams, *Arthropod Struct. Dev.* **40**, 334 (2011).
25. U. Homberg, S. Heinze, K. Pfeiffer, M. Kinoshita, B. el Jundi, *Philos. Trans. R. Soc. London Ser. B* **366**, 680 (2011).
26. R. E. Ritzmann, A. L. Ridgel, A. J. Pollack, *J. Comp. Physiol. A* **194**, 341 (2008).
27. P. Guo, R. E. Ritzmann, *J. Exp. Biol.* **216**, 992 (2013).
28. H. Ghaffar, J. Larsen, G. Booth, R. Perkes, *Int. J. Insect Morphol. Embryol.* **13**, 357 (1984).
29. G. Liu *et al*., *Nature* **439**, 551 (2006).
30. J. Phillips-Portillo, *J. Comp. Neurol.* **520**, 3088 (2012).
31. S. Kuntz, B. Poeck, M. B. Sokolowski, R. Strauss, *Learn. Mem.* **19**, 337 (2012).
32. U. Homberg, H. Vitzthum, M. Müller, U. Binkle, *J. Comp. Neurol.* **409**, 495 (1999).
33. L. Kahsai, M. A. Carlsson, A. M. Winther, D. R. Nässel, *Neuroscience* **208**, 11 (2012).
34. L. Kahsai, A. M. Winther, *J. Comp. Neurol.* **519**, 290 (2011).
35. J. P. Bolam, J. J. Hanley, P. A. Booth, M. D. Bevan, *J. Anat.* **196**, 527 (2000).
36. C. R. Gerfen, D. J. Surmeier, *Annu. Rev. Neurosci.* **34**, 441 (2011).
37. Z. Mao, R. L. Davis, *Front. Neural Circuits* **3**, 5 (2009).
38. K. E. White, D. M. Humphrey, F. Hirth, *Front Neurosci* **4**, 205 (2010).
39. T. Ueno *et al*., *Nat. Neurosci.* **15**, 1516 (2012).
40. M. J. Krashes *et al*., *Cell* **139**, 416 (2009).
41. Q. Liu, S. Liu, L. Kodama, M. R. Driscoll, M. N. Wu, *Curr. Biol.* **22**, 2114 (2012).
42. Y. C. Kim, H. G. Lee, C. S. Seong, K. A. Han, *Gene Expr. Patterns* **3**, 237 (2003).
43. E. C. Kong *et al*., *PLoS ONE* **5**, e9954 (2010).
44. T. J. Lewandowski, H. K. Lehman, S. C. Chamberlain, *J. Comp. Neurol.* **288**, 136 (1989).
45. K. Langworthy, S. Helluy, J. Benton, B. Beltz, *Cell Tissue Res.* **288**, 191 (1997).
46. H. Vitzthum, U. Homberg, *J. Comp. Neurol.* **390**, 455 (1998).
47. R. Strauss, *Curr. Opin. Neurobiol.* **12**, 633 (2002).
48. E. Tupala, J. Tiihonen, *Prog. Neuropsychopharmacol. Biol. Psychiatry* **28**, 1221 (2004).
49. T. Riemensperger *et al*., *Proc. Natl. Acad. Sci. U.S.A.* **108**, 834 (2011).
50. F. Hirth, *CNS Neurol. Disord. Drug Targets* **9**, 504 (2010).
51. D. M. Humphrey *et al*., *Hum. Mol. Genet.* **21**, 2698 (2012).
52. G. Schumann *et al*., *Proc. Natl. Acad. Sci. U.S.A.* **108**, 7119 (2011).
53. R. G. Northcutt, *Proc. Natl. Acad. Sci. U.S.A.* **109** (suppl. 1), 10626 (2012).
54. F. Christodoulou *et al*., *Nature* **463**, 1084 (2010).
55. J. Mallatt, C. W. Craig, M. J. Yoder, *Mol. Phylogenet. Evol.* **64**, 603 (2012).
56. P. R. Steinmetz *et al*., *Nature* **487**, 231 (2012).
57. X. Ma, X. Hou, G. D. Edgecombe, N. J. Strausfeld, *Nature* **490**, 258 (2012).
58. B. K. Hall, *Biol. Rev. Camb. Philos. Soc.* **78**, 409 (2003).
59. D. M. Raup, A. Seilacher, *Science* **166**, 994 (1969).
60. L. A. Buatois, M. G. Mángano, *J. Paleontol.* **86**, 7 (2012).
61. R. Tomer, A. S. Denes, K. Tessmar-Raible, D. Arendt, *Cell* **142**, 800 (2010).
62. J. L. Rubenstein, K. Shimamura, S. Martinez, L. Puelles, *Annu. Rev. Neurosci.* **21**, 445 (1998).
63. W. Ye, K. Shimamura, J. L. Rubenstein, M. A. Hynes, A. Rosenthal, *Cell* **93**, 755 (1998).
64. L. Sussel, O. Marin, S. Kimura, J. L. Rubenstein, *Development* **126**, 3359 (1999).
65. T. Mueller, M. F. Wullimann, S. Guo, *J. Comp. Neurol.* **507**, 1245 (2008).
66. H. Toresson, K. A. Campbell, *Development* **128**, 4769 (2001).
67. L. Muzio *et al*., *Nat. Neurosci.* **5**, 737 (2002).
68. A. Abeliovich, R. Hammond, *Dev. Biol.* **304**, 447 (2007).
69. S. T. Philips, R. L. Albin, D. M. Martin, *Exp. Neurol.* **192**, 320 (2005).
70. D. M. Martin *et al*., *Dev. Biol.* **267**, 93 (2004).
71. F. Hirth, H. Reichert, in *Evolution of Nervous Systems, Vol. I*, T. H. Bullock *et al*., Eds. (Elsevier, London, 2005), pp. 55–72.
72. B. Poeck, T. Triphan, K. Neuser, R. Strauss, *Dev. Neurobiol.* **68**, 1046 (2008).
73. M. Desban, C. Gauchy, M. L. Kemel, M. J. Besson, J. Glowinski, *Neuroscience* **29**, 551 (1989).
74. K. Ito *et al*., *Learn. Mem.* **5**, 52 (1998).
75. M. Iwano *et al*., *J. Comp. Neurol.* **518**, 366 (2010).
76. M. W. Shiflett, B. W. Balleine, *Prog. Neurobiol.* **95**, 1 (2011).
77. W. Gronenberg, N. J. Strausfeld, *J. Comp. Neurol.* **316**, 87 (1992).

Acknowledgments: Supported by grants from the UK Medical Research Council (G070149), Royal Society (Hirth2007/R2), Parkinson's UK (G-0714), Motor Neurone Disease Association (Hirth/Mar12/6085, Hirth/Oct07/6233), Alzheimer Research UK (Hirth/ARUK/2012), and Fondation Thierry Latran (DrosALS) (to F.H.); the Air Force Research Laboratories (NJS/AFRL FA86511010001) (to N.J.S.); and the Center for Insect Science, University of Arizona, Tucson (to N.J.S.). We thank G. Wolf for the image in Fig. 1D.

Supplementary Materials

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Table S1
Fig. S1
References (*78*–*88*)

10.1126/science.1231828