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Review

Evolutionary Development of Neural Systems in Vertebrates and Beyond

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Abstract: The emerging field of "neuro-evo-devo" is beginning to reveal how the molecular and neural substrates that underlie brain function are based on variations in evolutionarily ancient and conserved neurochemical and neural circuit themes. Comparative work across bilaterians is reviewed to highlight how early neural patterning specifies modularity of the embryonic brain, which lays a foundation on which manipulation of neurogenesis creates adjustments in brain size. Small variation within these developmental mechanisms contributes to the evolution of brain diversity. Comparing the specification and spatial distribution of neural phenotypes across bilaterians has also suggested some major brain evolution trends, although much more work on profiling neural connections with neurochemical specificity across a wide diversity of organisms is needed. These comparative approaches investigating the evolution of brain form and function hold great promise for facilitating a mechanistic understanding of how variation in brain morphology, neural phenotypes, and neural networks influences brain function and behavioral diversity across organisms.

Keywords: behavior, brain development, brain evolution, evo-devo, neuroanatomy

INTRODUCTION

Although developmental patterning of central nervous systems is remarkably similar across animal phyla, small variations on developmental themes have produced striking variation in brain morphology. Understanding the evolutionary mechanisms underlying this diversity in brain morphology and function remains a major question in biology. Comparative approaches focused on brain development and organization has greatly increased our understanding of brain function and evolution. Just as the field of evolutionary development ("evo-devo") has shed light on how diversity in animal body plans are variations on a few developmental themes (Carroll, 2008; Goodman & Coughlin, 2000; Toth & Robinson, 2007), so the study of brain evolutionary development ("neuro-evo-devo") is beginning to illuminate how the neural substrates of functional diversity in the brain are variations on conserved neurochemical and neural circuit themes (Arendt et al., 2008; Phelps, 2002; Reiner & Wullimann, 2004; Scharff & Petri, 2011). Here I review an emerging field that uses comparative approaches to study the evolutionary development, conservation, and diversity of brain form and function. This work has identified several neural and molecular substrates on which evolutionary forces could shape the proximate mechanisms of generating brain diversity. Variations in patterning of the developing brain can give rise to divergent regional morphology, whereas the manipulation of neurogenesis can promote diversity in brain size. Moreover, alterations in organization and genetic regulation of conserved neurochemicals can result in diverse neural circuits that ultimately influence brain function and behavior. This emerging field holds great promise for facilitating a greater understanding of how variation in brain morphology, neural phenotypes, and neural networks contributes to behavioral diversity across organisms.

EVOLUTIONARY MANIPULATION OF BRAIN DEVELOPMENT

Cellular and morphological diversity of the brain can greatly influence sensory processing and decision-making, but a mechanistic understanding of how species or lineage differences in brain organization contribute to behavioral diversity as well as how these processes have diverged (or converged) across evolutionary time remain

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fundamental questions in neuroscience. Work in the field of brain evolution has brought forth two interconnected hypotheses regarding brain diversity and evolution: developmental constraint, based on the observation that changes in regional brain volume scale with total brain size, and mosaic evolution, which is based on the observation that specific brain regions can vary in volume relative to total brain size. Most evidence suggests that developmental constraint and mosaic evolution work simultaneously to sculpt brain diversity, although perhaps on slightly different evolutionary time scales. The manipulation of total brain size or region-specific volume employs various mechanisms acting on developmental trajectories that specify brain patterning, size, and neuronal identity.

Perhaps the most obvious feature in comparative neuroanatomy is that of size, where whole brains or specific brain parts differ in volume between species (Finlay & Darlington, 1995). A major example is the enlarged cortex in primates, and especially humans (Barton, 1996; Reader & Laland, 2002). Early in the field of brain evolution, it became apparent that the size of a particular substructure seemed to scale with overall brain size (Finlay & Darlington, 1995). The theory of developmental constraint stems from the observation that total non-olfactory vertebrate brain size accounts for most of the variation in size of particular brain regions (Barton & Harvey, 2000; Finlay & Darlington, 1995; Finlay et al., 2001; Yopak et al., 2010). Thus, brains may respond to selection pressures by growing as a whole, since the brain itself is composed of highly integrated parts with conserved neural networks. Indeed, brain scaling is a conserved pattern found in early vertebrates, suggesting that scaling brain size is favored in response to various ecological demands without compromising basic neural functions (Yopak et al., 2010).

Although developmental constraint seemed a comprehensive property of brain evolution, there was accumulating evidence of positive or negative growth of various brain substructures relative to overall brain size (Barton & Harvey, 2000; Charvet & Striedter, 2010; Clark et al., 2001; de Winter & Oxnard, 2001; Finlay et al., 2001; Yopak et al., 2010). In light of this evidence, the theory of adaptive mosaic evolution was proposed to explain variation in regional volume independent of total brain size (Barton & Harvey, 2000). These findings are often regarded as the brain evolving in response to specific ecological or behavioral selection, although finding causation in these correlations is extremely difficult. Variation in relative brain size has been documented in many vertebrate lineages including mammals (Barton, 1996; Reader & Laland, 2002), birds (Lefebvre et al., 1997; Rehkamper et al., 2008), and teleosts (Gonzalez-Voyer & Kolm, 2010). In many cases, these variations have been linked to specific behavioral adaptations. Adjustments in brain size correlating with behavioral functions have also been documented in *Pheidole* ants where relative sizes of mushroom bodies, central ganglion, and optic and antennel lobes vary with caste duties (Muscedere & Traniello, 2012). These differences do not scale with overall brain size and thus also support mosaic brain evolution within invertebrates. Variation in brain region size can also vary with an individual's experience. In homing pigeons (*Columba livia*), individuals with navigational experience have a larger hippocampus compared with confined birds (Cnotka et al., 2008). Thus, brain size and even regional brain volume is variable across diverse taxa and even within species, representing a substrate on which selection pressures can yield behavioral diversity.

DEVELOPMENTAL MECHANISMS FOR THE MANIPULATION OF BRAIN MORPHOLOGY

There are several developmental mechanisms that can influence brain morphology and size. Two central mechanisms are early patterning of the embryonic brain and the manipulation of the timing and length of neurogenesis. The role of these mechanisms underlying brain form and function is discussed below with examples in vertebrates and invertebrates.

Early Patterning Specifies Modulatory of the Embryonic Brain

The genes that specify brain patterning early in development are highly conserved (Denes et al., 2007; Northcutt, 2001; O'Connell & Hofmann, 2011b; Puelles & Rubenstein, 2003; Rubenstein & Puelles, 1994; Striedter, 2005) and studying developmental trajectories that specify brain patterning within a comparative context can help establish brain region homologies across wide evolutionary distances (Arendt et al., 2008; Medina & Abellan, 2009; Moreno et al., 2009; Puelles et al., 2000; Puelles & Medina, 2002). This "evo-devo" approach to neural development has contributed insights into the early origin of the central nervous system in bilaterians, regional brain homologies in vertebrates and invertebrates, as well as some insight into how small variations on these themes contribute to mosaic brain diversity.

Work comparing very early patterning of the neural tube has contributed intriguing insights into the evolutionary origins of the central nervous system. All known bilaterian nervous systems (except nematodes) are established via transforming growth factor β (TGF-β) family (Bone morphogenic protein (Bmp) and its Drosophila ortholog decapentaplegic (Dpp)) signaling that arranges dorsoventral polarity (Denes et al., 2007; Lowe et al., 2006; Mizutani et al., 2005). The Bmp gradient specifies neural (non-Bmp/Dpp) from non-neural (Bmp/Dpp) tissue and subsequently more complex molecular patterns emerge that specify both anterior-posterior and mediolateral brain

patterning, which is also highly conserved among bilaterians. In both vertebrates and invertebrates, anterior-posterior patterning is in part defined by *otd/otx* (anterior) and *unpg/gbx* (posterior) expression, with *pax2/5/8* expressed at the intersection (Farris, 2008a; Lichtneckert & Reichert, 2005; Schilling & Knight, 2001; Slack, 1993). On the mediolateral axis, patterning is specified by columns of molecular markers, including *nk2.2+*, *gsx+*, *msx+*, and *pax6+*, whose expression pattern is conserved in insects, annelids, and vertebrates (Arendt et al., 2008; Arendt & Nubler-Jung, 1999; Cornell & Ohlen, 2000). Together this work suggests a common origin of the centralized nervous system in bilaterians (although the vertebrate nervous system is dorsoventrally inverted compared with invertebrates). This work also highlights some interesting species differences among animals, such as why early patterning in nematodes seems so different compared with other animals. Clearly more comparative work is needed to better understand not only the similarities bilaterian animals share in their nervous systems, but also how and why developmental differences have evolved.

Comparisons of patterning genes within later developmental stages in the brain (after establishment of the anterior-posterior axis) have been extremely useful in identifying field homologies and evolutionary relationships of these brain regions between very distant taxa (Medina & Abellan, 2009; Moreno et al., 2009). Several highly conserved patterning genes specify regions of the telencephalon, and comparative work has elucidated these telencephalic homologies across very divergent nervous systems (Figure 1). Expression of *pax6* and *emx1* specify the pallial telencephalon, whereas *dlx* and *nkx2.1* specify subpallial regions (Medina & Abellan, 2009; Moreno et al., 2009). Interestingly, comparative developmental work has shown that invertebrate mushroom bodies have similar evolutionary origins to the pallium of vertebrates, as annelid (*Platynereis dumerilii*) mushroom bodies are specified by *pax6* and *emx1* expression, similar to the pallium of vertebrates (Tomer et al., 2010). Comparative work has also utilized genetic techniques to spatially manipulate gene expression in an effort to characterize the evolution of regional volume and novel structures. An excellent example is manipulation of the homeobox gene *nkx2.1*, where knockdown of *nkx2.1* leads to a size reduction of the ventral telencephalon and hypothalamus in both mouse (Mus musculus; Sussel et al., 1999) and the African clawed frog (*Xenopus laevis*; van den Akker et al., 2008). Interestingly, lampreys lack expression of *nkx2.1* in the ventral telencephalon (Osorio et al., 2005). Thus, knockdown of *nkx2.1* in mouse and *X. laevis* represents a phenolog of the lamprey telencephalon developmental pattern, suggesting that the expansion of *nkx2.1* into the ventral telencephalon was involved in the evolution of the ventral pallidum (Figure 1).

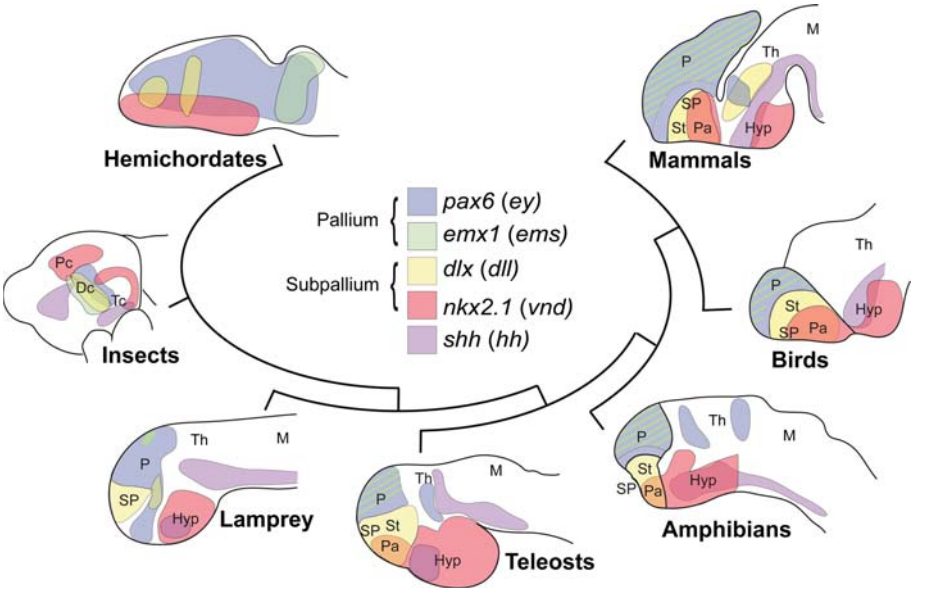

Figure 1. Evolution of early gene patterning that specifies embryonic brain modularity. Expression of patterning genes *pax6* (blue), *emx1* (green), *dlx* (yellow), *nkx2.1* (red), and *shh* (sonic hedgehog; purple) are shown on the lateral-view diagram of developing nervous systems. Orange represents overlap in expression of *dlx* and *nkx2.1*. Gene names in parentheses are *Drosophila* orthologs. Each brain diagram is shown rostral (left) to caudal (right). Dc, deutocerebrum; Hyp, hypothalamus; M, medulla; P, pallium; Pa, pallidum region of the subpallium; Pc, protocerebrum; SP, subpallium; St, striatal region of the subpallium; Tc, tritocerebrum; Th, thalamus. Data gathered from Bachy et al. (2002), Brox et al. (2004), Dominguez et al. (2010), Hauptmann and Gerster (2000), Lowe et al. (2003), Murakami et al. (2002), Murakami and Watanabe (2009), Noveen et al. (2000), Osorio et al. (2005), Puelles et al. (2000), and Urbach and Technau (2003, 2004).

Although the mechanisms of brain patterning have been thoroughly studied (Kiecker & Lumsden, 2012; Sylvester et al., 2011), how these processes vary to promote brain diversity across animals remains a mystery, partly due to the difficultly in genetically manipulating brain development in a comparative context within closely related species. Brain patterning early in development constructs regional boundaries that can serve an important foundation on which neurogenesis and neuronal differentiation mechanisms can build diverse brain structures (Sylvester et al., 2011). Comparative work analyzing expression of patterning genes among closely related species suggests that these early signals establish divergent brain patterns that are elaborated on later in development. The best example to date comes from African cichlids, where behavioral and ecological variation has contributed to a rapid parallel radiation (Kocher, 2004) and a corresponding explosion in brain diversity (Gonzalez-Voyer et al., 2009a, 2009b). Comparative anatomy and gene manipulation work in cichlid brains has shown that variation in the spatial distribution of patterning genes early in development contributes to variation in brain modularity. Specifically, variation in the WNT pathway and sonic hedgehog signaling pathway contributes to brain diversification among closely related species of cichlid fish (Sylvester et al., 2010). Similar findings have also been reported in birds, where spatial distribution of early patterning genes *pax6* and *gbx2* are associated with the telencephalon being proportionally larger in the parakeet (*Melopsittacus undulates*) compared with the bobwhite quail (*Colinus virgianus*; McGowan et al., 2011). These comparative studies have shown that patterning genes can clearly be manipulated to produce a neural phenotypes similar to other closely relates species. However, it is unclear how this variation is specified in the genome or how these modifications affect behavior.

A particularly complex early gene patterning scheme produces mammalian cortical fields, whose somatosensory topography is influenced by both intrinsic (genetic) and extrinsic (experience) forces to create a wide diversity of cortex patterning. These mechanisms have been extensively reviewed (Krubitzer & Kaas, 2005; Krubitzer & Seelke, 2012; O'Leary et al., 2007), but will be discussed here briefly. Primary sensory areas can vary greatly in size between and within species (Airey et al., 2005; Krubitzer & Seelke, 2012) and such size variation has dramatic behavioral consequences. For example, genetically manipulating patterning genes *emx2*, *lhx2*, or *pax6* in mouse development can alter the size of somatosensory and motor areas (Bishop et al., 2000; Monuki et al., 2001; Monuki & Walsh, 2001). These genetic manipulations ultimately lead to behavioral deficiencies, suggesting that cortical areas have reached an optimal size over evolutionary time (Leingartner et al., 2007). Moreover, sensory-dependent plasticity from the thalamocortical axon tract can drastically affect cortical field size in a modality-dependent manner (Sur & Rubenstein, 2005). Manipulations of sensory input have been crucial in determining the causal role of experience in influencing cortical topography by altering expression of brain patterning genes (Dye et al., 2012). A classic example is based on visual input, where animals blinded in development display drastic cortical area changes, including reducing the visual cortex area (Kahn & Krubitzer, 2002). Thus, manipulating both genetic and context-dependent contributions to neural phenotypes can sculpt diversity in brain phenotypes both between and within species (Krubitzer & Kaas, 2005). This comparative work on mammalian cortical fields suggests that both intrinsic and extrinsic factors can manipulate brain form and function, although how this has contributed to the evolution behavioral diversity between species is not well understood. Future investigations into how sensory information contributes to behavioral decision-making within this divergent cortical field framework would greatly facilitate our understanding of these evolutionary processes.

Manipulating Neurogenesis and Adjustments in Brain Size

After brain polarities have been constructed in development, manipulating neurogenesis can promote diversity in brain substructure volume and overall brain size. Initiating and maintaining neurogenesis can have drastic effects on founder cell populations that birth neurons and on the number of neurons that progenitor cells can produce. These mechanisms are altered in the evolution of the expanded cortex in mammals and other brain structures across animal phyla.

In early mammalian brain development, the neural tube closes to form lateral ventricles and two layers of proliferative neuroepithelial cells are formed in a radial fashion along the ventricles (Kriegstein et al., 2006). As cortical neurogenesis proceeds, they migrate radially out of the proliferative zones into what will ultimately form a layered cortex. Delaying neurogenesis leads to an increase in the founder cell population, which can ultimately produce more neurons. Work in rodents has shown that a delay in cell cycle progression results in increased cortical tissue into a more primate-like cortical phenotype (Chenn & Walsh, 2002; Pilaz et al., 2009; Vaccarino et al., 1999). For example, expression of a constitutively active β-catenin, which prolongs progenitor cell proliferation, increases neocortical volume, and generates cortical folds in transgenic mice (Chenn & Walsh, 2002). Similarly, injections of fibroblast growth factor 2 (FGF2) in rats, which delays neocortical cell cycle exit, also result in cortical folds from increasing neocortical volume (Vaccarino et al., 1999). This

delay in neurogenesis may also underlie the relatively enlarged cortex in primates compared with other mammals (Clancy et al., 2001, 2007; Dehay & Kennedy, 2007; Kriegstein et al., 2006; Reep et al., 2007). More recently, this experimental paradigm has been recapitulated in birds, where FGF2 injections increased the size of the chick (*Gallus gallus*) optic tectum and generated cortical-like folds (McGowan et al., 2011). This body of work suggests that manipulating cell cycle of neural progenitors and thus delaying the onset of neurogenesis may be an evolutionary conserved tool to vary brain volume, although little is known about how manipulating brain size of these substructures affects behavior as many of these embryonic manipulations of brain size are lethal.

There have been some attempts to link behavior, the timing of neurogenesis, and evolution of brain substructure size in birds. For example, the telencephalon in parrots and songbirds is much larger relative to overall brain size compared with galliforms (Boire & Baron, 1994; Iwaniuk & Hurd, 2005; Striedter & Charvet, 2008). Charvet and Striedter (2010) have shown that the parakeet (*Melopsittacus undulatus*) and zebra finch (*Taeniopygia guttata*) delay the onset of telencephalic neurogenesis compared with galliforms, whereas timing of neurogenesis in the medulla is similar. In addition to correlations with telencephalic volume, the onset of neurogenesis also corresponds to variation in behavioral development. Galliform chicks are precocial and can forage after hatching, whereas songbird and parrot chicks are altricial. Neurogenesis correlates with the onset of foraging behavior, which led Charvet and Striedter (2011) to propose that behavioral modes in development influences diversity in regional brain size through altering neurodevelopmental mechanisms. Functional manipulations within a comparative context are sorely needed to determine whether neurogenesis does play a functional role of enlarging (or reducing) brain region volume in these species and if this mechanism plays a causal role in the acquisition of songbird behavior.

The length of the neurogenesis period is another mechanism that leads to variation in brain size by extending the time that progenitor cells can divide and thus produce more neurons. For example, the period of cortical neurogenesis is 8-fold longer in primates, with roughly 28 neurogenic cell cycles (Kornack & Rakic, 1998), compared with rodents, with roughly 11 neurogenic cycles (Takahashi et al., 1995). This method of varying the duration of the neurogenic period to produce variation in size of brain substructures has also been observed in scarab beetle (*Coleoptera*: *Scarabaeidae*) mushroom bodies (Farris, 2008b), a brain region that is highly variable in size and analogous to vertebrate higher processing centers. This study showed that *Popillia japonica*, a beetle with large mushroom bodies, have a longer period of neurogenesis compared with another beetle, *Onthophagus hecate*, which has smaller mushroom bodies compared with *P. japonica*. The longer period of neurogenesis in *P. japonica* presumably leads to a larger mushroom body volume. These differences are correlated to foraging tactics where larger mushroom bodies are present in diet-generalist beetles compared with diet-specialist beetles and thus larger mushroom bodies may allow for more broad foraging behavior. Combining evidence from these comparative studies, it appears that either manipulating the timing or length of the period of neurogenesis influences divergence in brain substructure size and can contribute the evolution of different behavioral strategies.

Delaying neurogenesis also delays neuronal differentiation/maturation, and the longer the delay continues into development, the more susceptible these neurodevelopmental processes are to external influences. Thus, behavioral modes both in development (as shown in birds) and in adults (as suggested for African cichlids discussed above) as well as sensory contributions to cortical fields in mammalian development have influenced diversity in regional brain size among closely related species within the same taxa.

EVOLUTION OF NEURONAL PHENOTYPE AND CONNECTIVITY

The contributions of neural development and function to behavior ultimately depend on the cell fate of a neuron and its location and connectivity in the brain. Determining the origins of various neurochemical groups can help us determine what neurons are highly conserved among animals. This will in part help to determine brain region homologies across diverse taxa, but will also shed light on what cell groups have arisen independently to confer new behavioral traits within specific taxa or species. Many neurochemical systems, such as catecholamines and neurosecretory cells, are ancient and date back to at least the evolution of the bilaterian nervous system, although whether these cell types serve the same role in modulating brain function is unknown. Cell specification and migration patterns specify neurochemical phenotypes throughout the brain that play important roles in behavior.

Cell Specification and Migration

Homology between various neurochemical populations can be determined based on developmental origins from progenitor domains. An excellent example of this is the specification of neurosecretory cells involved in nonapeptide synthesis (vasopressin-like and oxytocin-like peptides). It is well established that these nonapeptides play important roles in governing social behavior in vertebrates (Godwin & Thompson, 2012; Goodson, 2008,

2013; Goodson & Bass, 2001; Insel & Young, 2000), but their role in invertebrates is less clear (Stafflinger et al., 2008; Beets et al., 2012). However, determining where the orthologous nonapeptide-producing cells are located in the brains of vertebrates and invertebrates would greatly aid in understanding regional homologies. For example, the nonapeptides are only produced in the hypothalamus of teleosts (vasotocin and isotocin; Godwin & Thompson, 2012), but the number of nonapeptide-producing cell groups jumps to 19 in amphibians (Moore & Lowry, 1998). Invertebrates also produce a variants of the highly conserved nonapeptide family, including annelids (annetocin; Oumi et al., 1994), cephalopods (cephalotocin and octopressin; Takuwa-Kuroda et al., 2003), nematodes (nematocin; Beets et al., 2012; Garrison et al., 2012), and beetles (inotocin; Stafflinger et al., 2008). Interestingly, inotocin is also present in some *Hymenoptera*, but was lost in *Apis* (bees) and *Drosophila*. Developmental work has shown that the nonapeptide populations in teleosts, lampreys, and annelids are all derived from a *nkx2.1+* region in the developing forebrain, thus suggesting a conserved origin and homologous hypothalamic-like regions (Tessmar-Raible et al., 2007). In the red flour beetle (Tribolium castaneum), inotocin is produced solely by a pair of neurons in the subesophageal ganglion. It is currently unknown if this inotocin cell group arises from a nk2.1+ region, although this would be a valuable step towards establishing a hypothalamic homolog between vertebrates and insects. Some functional studies suggest that these homologous nonapeptide groups in vertebrates and invertebrates serve a similar behavioral function, as nonapeptide manipulation induces reproductive behavior in the medicinal leech (*Hirudo* spp.; Wagenaar et al., 2010), nematode (Caenorhabditis elegans; Garrison et al., 2012), and annelid (*Eisenia foetida*; Oumi et al., 1996), similar to vertebrates (Insel et al., 1997). More developmental work examining the origins of these neurosecretory cells as well as functional behavioral manipulations are needed to determine to what extent these nonapeptide cell groups are homologous across taxa.

Another ancient neurochemical present in nearly all bilaterian nervous systems is dopamine, which serves as a neuromodulator in many behavioral processes, including the selection of motor programs (Joshua et al., 2009a; Vidal-Gadea et al., 2011), social behavior (Aragona & Wang, 2009; O'Connell & Hofmann, 2011a), and learning and memory (Hyman et al., 2006; Wise, 2004a). Much effort has been expended to identify the regulatory logic specifying dopaminergic cells through examining conserved motifs of dopamine pathway genes. Flames and Hobert (2009) were the first to propose a conserved "dopamine motif" that appeared to lend regional specificity of dopaminergic cell populations in both *C. elegans* and mammals. Specifically, the Ets-related family of transcription factors appears to determine dopaminergic cell fate in *C. elegans* (via *ast-1*) and mouse olfactory neurons (via *etv1*). However, it appears that mammalian midbrain dopamine neurons may not fall under this regulatory logic, as the Ets variant expressed in the mammalian substantia nigra and ventral tegmental area (*etv5*; Gray et al., 2004) does not appear to influence dopaminergic neurons in mice (Wang & Turner, 2010). Thus, regulatory logic for the specification of these midbrain dopaminergic cell populations in mammals is still a mystery.

Establishing the homologous dopaminergic cell populations between mammals and other vertebrates is difficult, especially in anamniote taxa that do not have a mesencephalic dopamine cell group. Establishing these neural homologies across animals is important for our understanding of behavioral processes that are conserved across animals such as movement (Mogenson et al., 1980; Reiner et al., 1998) and social decision-making (Doya, 2008; O'Connell & Hofmann, 2011a; Rangel et al., 2008; Rilling et al., 2008). The cell specification of dopamine neurons is extensively studied in mammals due to the biomedical relevance of mesencephalic dopamine neurons in Parkinson's disease, which is characterized by the death of dopaminergic neurons in the substantia nigra (Fearnley & Lees, 1991; Shulman et al., 2011), and behaviorally deleterious phenotypes such as addiction, which is attributed to dopamine input from the ventral tegmental area to the forebrain basal ganglia (Corrigall et al., 1994; Schultz, 1997; Schultz et al., 1997). The mammalian substantia nigra and ventral tegmental area share a developmental origin and are remarkably similar in gene expression profiles (Chung et al., 2005; Grimm et al., 2004), which makes identifying homologous populations in other taxa exceedingly difficult. However, functional manipulations and neurochemical profiling during development and into adulthood of dopamine cell populations in both teleosts and mammals has indicated that the posterior tuberculum in teleosts (located in the diencephalon) and the substantia nigra/ventral tegmental area of mammals are putatively homologous. This hypothesis is based on the following developmental evidence. The dopaminergic neurons in the mammalian midbrain and the teleost posterior tuberculum are both derived from the third prosomere (Wullimann & Rink, 2002). There is also some genetic evidence for homology, as knockdown of transcription factor *nr4a2* ablates diencephalic dopamine neurons in zebrafish (Luo et al., 2008) and the midbrain dopamine neurons in mammals (Smidt et al., 1997, 2004). Dopamine neurons in the teleost posterior tuberculum are also neurochemically very similar to the mammalian ventral tegmental area and substantia nigra (O'Connell et al., 2013). Finally, work in the chicken suggests that the amniote midbrain dopaminergic populations originate in the diencephalon during development and then migrate to the midbrain (Klafke, 2008), suggesting that the ancestral state location of the ventral tegmental area and substantia nigra is the diencephalon, similar to the current state of teleosts and amphibians.

The molecular biology of cell specification is difficult to disentangle and is currently achievable only in genetically tractable model systems. A mechanism that has been recently brought to the forefront of neuronal specification by comparative genomics is alternative splicing, which holds promise for understanding how diverse cellular phenotypes evolved across bilaterians. Splicing can vary greatly between species and thus might also functional role in brain evolution. Comparisons within primates have highlighted many human-specific splice variants in brain tissue that is likely regulated by *cis*-regulatory elements (Lin et al., 2010), although this does not necessarily represent a causal mechanism for differential gene expression between humans and chimpanzees (Calarco et al., 2007). Moreover, splicing contributes to neuron cell identity during development (Barash et al., 2010; Calarco et al., 2011), as well as forming synapses in dendrites (Zurner & Schoch, 2009). Thus, divergent developmental profiles of alternative splicing may contribute to the evolution of species-specific differences in cell type distributions or connectivity in the brain, although how this relates to adaptive decision-making has not been addressed.

Evolution of Neurochemical Phenotypes

All animals have evolved flexible strategies allowing them to respond to a social stimulus in an adaptive manner (Krebs & Davies, 1997). Context-appropriate behavioral decisions are critical for an individual's fitness and are carried out by evaluating the salience of external stimuli and integrating this information with internal physiological cues. Remarkably, many of the neurochemicals that facilitate these decision-making processes are conserved across vertebrates and in some cases across bilaterians (O'Connell & Hofmann, 2011a). At least in vertebrates, there are two well-studied neural circuits involved in information processing leading to these adaptive behavioral decisions. The mesolimbic dopamine system is characterized by dopaminergic projections from the ventral tegmental area to the forebrain basal ganglia and is largely studied in mammals due to its biomedical relevance in deleterious behavioral disorders (Hyman et al., 2006; Joshua et al., 2009b; Schultz, 1997; Schultz et al., 1997; Wise, 2004b). Although drugs of abuse hijack the dopamine reward system, its natural function appears to be the evaluation of stimulus valence (Aragona & Wang, 2009; O'Connell & Hofmann, 2011a, 2011b; Reiner et al., 1998; Wise, 2004b). The other neural system involved in social decision-making is the so-called "social behavior network," composed of steroid-sensitive brain regions, mostly located in the hypothalamus. The social behavior network was originally proposed in mammals (Newman, 1999), but has since been expanded to other vertebrate lineages (Crews, 2005; Goodson, 2005; O'Connell & Hofmann, 2011a, 2011b).

As animals must evaluate stimulus valence in addition to physiological cues (such as hormone or reproductive state) to produce an adaptive behavioral response that is context appropriate, the mesolimbic reward system and social behavior network together form a larger social decision-making network (O'Connell & Hofmann, 2011a, 2011b, 2012). The fusion of the mesolimbic dopamine system and social behavior network comprises 13 brain regions that are interconnected and are present in all vertebrates (O'Connell & Hofmann, 2011b). The bases for these neural homologies include similarities in developmental origins during brain patterning (Figure 1), neurochemical profiles, and similarity in hodology (O'Connell & Hofmann, 2011b), although it should be noted that these homologies are tentative and not necessarily one-to-one. Identifying the neural homologies of brain regions involved in adaptive decision-making across vertebrates set a foundation to extend the analysis into evolutionary changes on the neurochemical level.

As homologous neurochemicals play important roles in behavior across animals, much effort has been spent on determining where behaviorally relevant neurochemicals are located in the brain of many different species. To uncover major evolutionary themes across animals within the social decision-making network, information was gathered from decades of neuroanatomical studies to catalog the presence or absence of specific neurochemicals important to social behavior and the main results are summarized here from O'Connell and Hofmann (2012). A focus was placed on nonapeptide systems (oxytocin, vasopressin, and their receptors), steroid hormone systems (aromatase, and the classical androgen, estrogen, and progesterone receptors), and the dopamine system (dopaminergic cell populations and dopamine receptors), as all these systems play established and conserved roles in behavior. When comparing the qualitative differences (total presence or absence of a gene product) in neurochemical profiles across vertebrates, several trends became apparent. First, the neurochemical profiles across vertebrates within the social decision-making network are remarkably conserved over 450 million years of evolution (O'Connell & Hofmann, 2012). Secondly, where there was variation across vertebrates, the location of neurochemical ligand–producing cells (dopaminergic and nonapeptide-producing) was more variable across vertebrates than the receptors (dopamine D1A receptor, steroid hormone receptors, and nonapeptide receptors) (O'Connell & Hofmann, 2012). Finally, there seemed to be different selection pressures on different brain regions. For instance, the preoptic area, which serves many behavioral and physiological functions (Dominguez & Hull, 2005; Gvilia et al., 2006; Ishiwata et al., 2002; Numan, 1974; Wood, 1998), was neurochemically very conserved across vertebrates. However, the striatum, a multimodal receptive structure involved in reward processing and

motor control (Wickens et al., 2007), was the most neurochemically variable across vertebrates.

There are several major evolutionary themes suggested from this work. The spatial location of ligand production seems to be evolutionarily more flexible than their receptors, at least within the neuroendocrine and catecholaminergic genes analyzed in O'Connell and Hofmann (2012). Dopaminergic cell populations are in a few discrete brain regions in mammals, but there are over 20 dopaminergic cell populations in teleosts. On the other hand, nonapeptides are only produced within one brain region in teleosts but are present in over 15 mammalian brain regions (Moore & Lowry, 1998). Thus, in the evolution from teleosts to mammals, there was an expansion of the nonapeptide system and a contraction of the dopamine system (Figure 2). From analyzing neurochemical patterns in brains of over 80 species across vertebrates, it is my impression that receptors are basally expressed throughout the brain so that when shifts in ligand input occurs, whether through the emergence of a new ligand-producing cell group or through seasonal or sex-specific projections, the shift in ligand production would be immediately biologically meaningful. Thus, one of the major trends across vertebrate brains is that there is variation in input, via changes in the spatial distribution of ligand production or neurochemically variable basal ganglia regions that integrate external information, whereas the spatial distribution of neurochemical receptors and the brain regions involved in behavioral output are more conserved across vertebrates (Figure 3). The current hypothesis is that such variation in the spatial distribution of dopaminergic and neurosecretory cells in neurochemically variable brain regions is where species or lineage differences in sensory processing takes place, corresponding to how some animals are evaluating environmental stimuli differently, whereas the conservation of neurochemical receptor locations may be where conserved behavioral output is executed, such as aggression and sexual behavior.

Although the comparative neurochemical profiling across vertebrates was a significant step towards understanding how the neural substrates underlying social decision-making have evolved across vertebrates, there were many limitations that future studies can remedy. First, many more neurochemicals, such as the serotonergic system and other neuropeptide systems, should be evaluated. Unfortunately, the O'Connell and Hofmann (2012) study was limited by comparative data across vertebrates, and although a great deal is known about where various neurochemical systems are located in mammals and birds, information is sorely lacking in other taxa, especially amphibians and reptiles. Secondly, as most of the data were accumulated from decades of published studies using various species and techniques to identify neurochemicals of interest, analyses were limited to qualitative (presence or absence) profiling across vertebrates. This led to the surprising observation that the location of ligand (dopamine and nonapeptide)-producing cells is more variable across vertebrates than their receptors. This was a surprising result, as decades of elegant work in *Microtus* voles has established that quantitative (but not qualitative—total absence or presence) differences in nonapeptide receptors are responsible for species differences in social systems (Insel et al., 1994; Leung et al., 2011). Thus, it appears that within vertebrate taxa, behavioral differences between species are likely implemented by microevolutionary changes in receptor abundance,

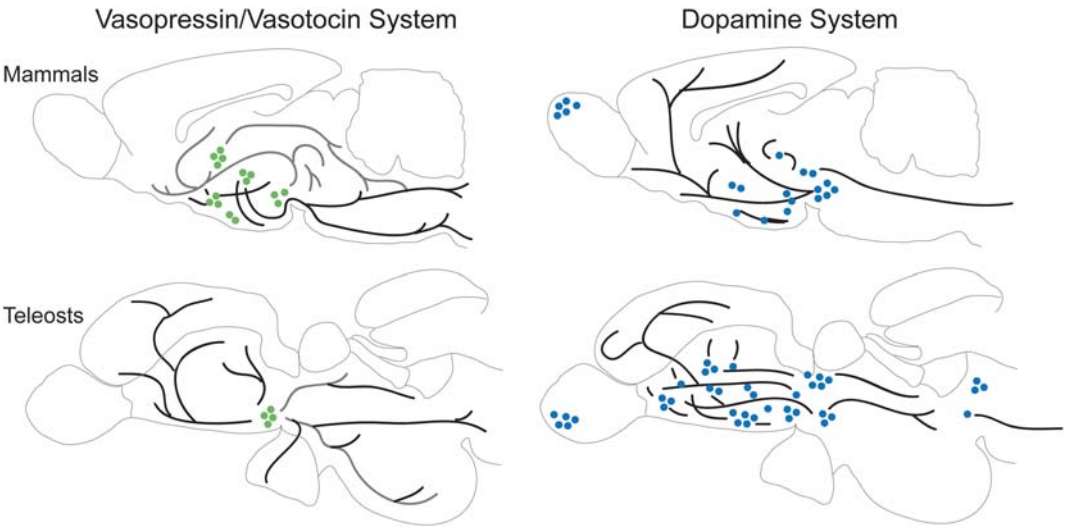

Figure 2. Vasotocin and dopamine system profiles in mammals and teleosts. From the evolution of fish (bottom) to mammals (top), the vasotocin system (left) has expanded and the dopamine system (right) has contracted in the number of cell populations synthesizing these neurochemicals, whereas fiber distributions remain widespread. Circles indicate cell bodies (green, vasotocin; blue, dopamine) and black lines indicate fibers. Fiber projections known to be sexually dimorphic are shown in gray.

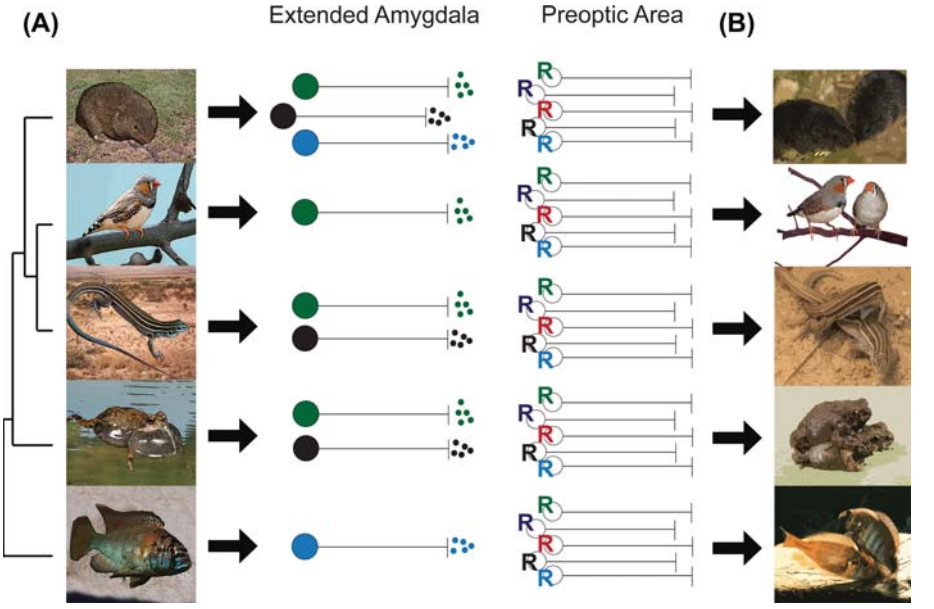

Figure 3. Neurochemical evolution across vertebrates. (**A**) The extended amygdala (including the medial amygdala and bed nucleus of the stria terminalis) is neurochemical diverse across vertebrates. In some vertebrate taxa, the extended amygdala produces dopamine (blue), vasopressin/vasotocin (green), or oxytocin/mesotocin/isotocin (black). (**B**) The preoptic area is neurochemically conserved across vertebrates, where receptors for dopamine, nonapeptides, and sex steroids are expressed in a highly conserved manner across vertebrates. This may support the integration of diverse signals into conserved behavioral outputs such as reproductive behavior.

whereas macroevolutionary changes across vertebrates are qualitative in nature. However, more quantitative work across vertebrates through comparable techniques and behavioral states are required to fully understand these apparent differences in the evolution of brain and behavior on different evolutionary time scales.

The Comparative Connectome

Understanding the neurochemical properties of specific brain regions across taxa will be a significant step in understanding how the brain evolves within ecological and behavioral constraints. However, it is ultimately how these various brain regions and cell types are connected throughout the brain that determines behavioral output. Remarkably little is known about connectivity in the brain, especially in nonmammalian vertebrate taxa, with the exception of the song circuit in songbirds and lordosis circuit in rodents (Farries, 2004; Pfaff et al., 2008).

Although connectivity and circuit mapping is widely researched in invertebrates with simple and experimentally tractable circuits (Harris-Warrick & Marder, 1991; Katz & Harris-Warrick, 1999; Marder et al., 2005), connectivity in vertebrate brains is sorely lacking. Determining brain connectivity with neurochemical specificity across a wide range of vertebrate taxa would be enormously helpful in understanding the circuit properties driving behavioral decision-making. An excellent example is the dopamine and nonapeptide systems within vertebrates. As mammals evolved from their aquatic anamniote ancestors over 450 million years, there has been an expansion of nonapeptide-producing brain regions and a contraction of dopaminergic cell populations (Figure 2). However, the spatial distribution of receptors for these neurochemicals is highly conserved across vertebrates, with little or no changes between teleosts and mammals (O'Connell & Hofmann, 2012). A crucial missing link between understanding neural circuit evolution and behavior is a comparative connectome map of behaviorally relevant cell groups. Thus, a critical next step to understanding how these neurochemicals modulate conserved behavior across vertebrates or contribute to lineage-specific behavioral traits will be to monitor the neural activity of these cell groups in response to various behaviorally relevant stimuli and then to identify the brain regions that receive signals downstream from these behaviorally relevant cell groups. However, within-species variation in connectivity makes this comparative connectome task even more challenging, as fiber distributions are highly variable within a species. For example, vasotocin/vasopressin fiber distributions can vary depending on sex and season (De Vries & Panzica, 2006). This is an incredibly plastic system that is under selective pressures to elicit diverse behavioral responses and thus an important goal to move the field of comparative brain evolution forward is to profile connectivity in the brain with neural specificity in many different biologically relevant contexts. Then, a species "consensus" on

connectivity could be derived and compared within an evolutionary context across taxa.

Understanding how brain regions are connected with neurochemical specificity across taxa is the next big challenge to address in brain evolution. Connectome mapping is technically more difficult than neurochemical profiling and perhaps even more challenging is that specific projections may be highly plastic. However, such experiments would be extremely useful in determining how connectivity within neural networks changes with various biological contexts and will also help in establishing neuroanatomical homologies across taxa.

EVOLUTION OF NEUROETHOLOGICAL SYSTEMS

The observation that many animals share the same neurochemical substrates and the same general behavioral responses to challenges and opportunities in their social environment raises some fundamental evolutionary questions about the brain and behavior (O'Connell & Hofmann, 2011a). I will discuss here four major concepts (Figure 4) on the neural mechanisms through which brain function can evolve and highlight how variations of neurodevelopmental themes supports each of these ideas.

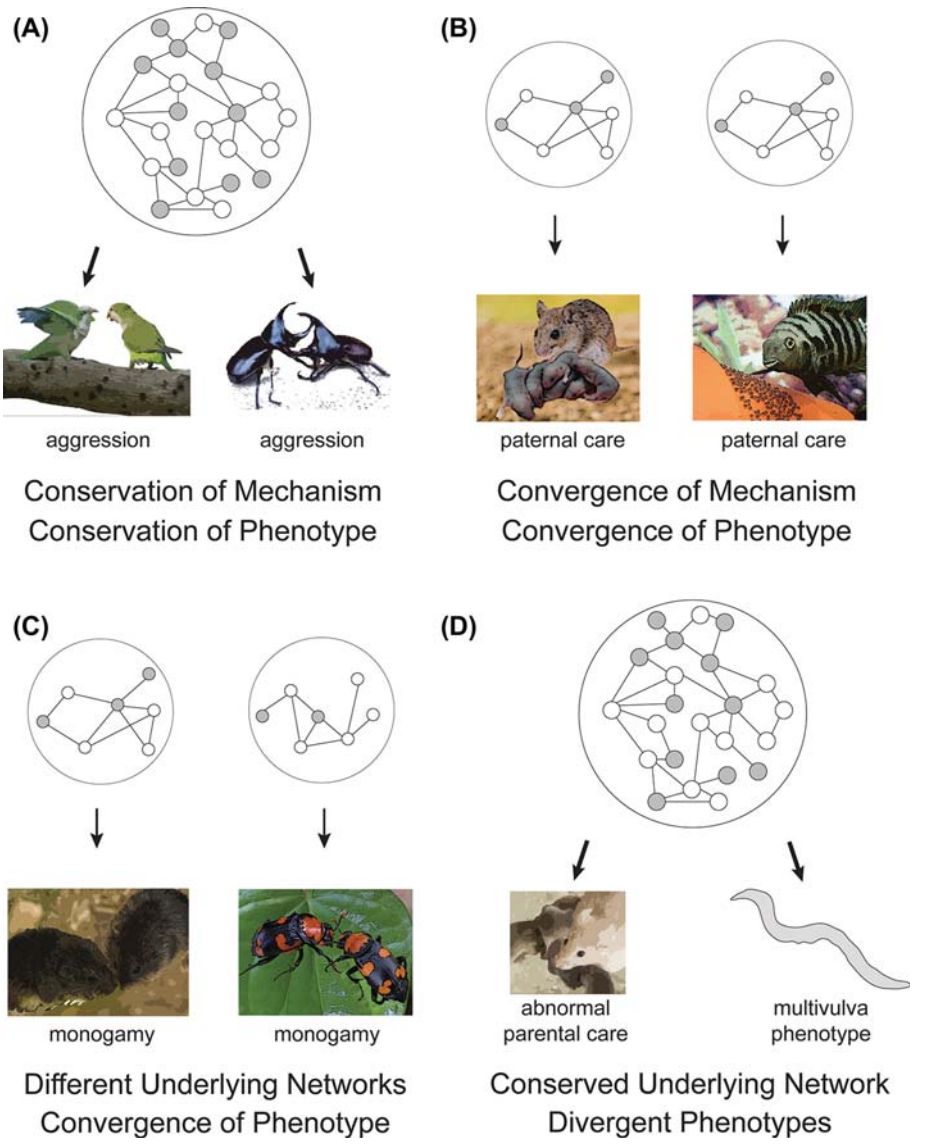

Figure 4. Evolution of neuroethological systems. (**A**) Deep homology refers to conserved phenotypes that are governed by conserved mechanisms across wide evolutionary distances. Ball and stick figure in each circle represents a gene network. (**B**) The convergence of behavioral phenotypes that have independently arisen in various taxa may rely on a convergence of underlying mechanisms. (**C**) A convergence of phenotype that has arisen independently in different animal taxa may have very different underlying mechanisms. (**D**) Phenologs refer to phenotypes that may appear very different, but share similar underlying protein interaction networks.

Deep homology is a concept born of evo-devo and refers to homologous molecular mechanisms or gene modules involved in homologous phenotypes that are conserved across wide evolutionary distances (Figure 4A). A classic example is eye development across metazoans, where pax genes (especially *pax6*) are frequently involved in the development of the eye (Shubin et al., 2009). The concept of deep homology has also recently been discussed in the context of brain function (Scharff & Petri, 2011). In the case of deep homology, behaviors that are shared across animals, such as aggression, reproductive behavior, or vocal communication, rely on ancient gene modules that are highly conserved and promote similar behaviors. An excellent example is the nonapeptide gene family, as many animals, including cephalopods (Takuwa-Kuroda et al., 2003), beetles (Stafflinger et al., 2008), annelids (Oumi et al., 1994), and vertebrates (Goodson & Thompson, 2010), have homologous neurosecretory groups that produce vasopressin-like or oxytocin-like peptides. These peptides have a conserved role in mediating reproductive behavior even across wide evolutionary distances through homologous signaling mechanisms (Goodson, 2008; Minakata, 2010; van Kesteren et al., 1995; Wagenaar et al., 2010). Although this concept accounts for conserved gene modules facilitating conserved behaviors across animals, it does not account for the repeated and independent evolution of behavioral phenotypes.

Some phenotypes, such as electric communication in gymnotiform and mormyriform fish (Rose, 2004), have evolved independently, and yet have convergent patterns of brain evolution to support such a mode of communication (Nishikawa, 2002). Other complex traits have also evolved independently and repeatedly in many taxa, such as monogamy or paternal care, which are present in some species of mammals (Brotherton & Komers, 2003), birds (Reynolds & Székely, 1997), reptiles (Gardner et al., 2002), frogs (Brown et al., 2010; Weygoldt, 2009), fish (Kuwamura et al., 1993; Whiteman & Côté, 2007), and arthropods (Fetherston et al., 2010; Nalepa, 1991). Intriguingly, some studies suggest that the convergent evolution of analogous behavior is accompanied by a convergence in underlying molecular and neural mechanisms (Figure 4B). For example, paternal care has independently evolved in mammals, where nonapeptides (especially oxytocin) promote paternal care through actions in the lateral septum and preoptic area (de Jong et al., 2009; Gordon et al., 2010; Parker & Lee, 2001; Wang et al., 1994). Paternal care has also independently evolved in fish, where there is also convergence in mechanism, as isotocin (teleost ortholog of the mammalian oxytocin) promotes paternal care through actions in the preoptic area and lateral septum (O'Connell et al., 2012). However, more comparative work is needed that examines the underpinnings of convergent phenotypes and its neural substrates across wide evolutionary distances in multiple taxa.

Although there are some examples of the convergence of behavioral phenotypes driven by convergence in neural or molecular mechanisms (Nishikawa, 2002; O'Connell et al., 2012), this is not a universal pattern, as there can be convergence in analogous phenotypes with very different underlying mechanisms (Figure 4C). For example, both lemurs and humans can have blue eyes but the underlying genetic mechanisms are very different (Bradley et al., 2009). A brain and behavior example of this concept is lacking, but with more investigation into the underlying mechanism of convergent evolution of behavior, this remains a possibility.

Finally, as most genes are evolutionarily ancient and conserved in many animals, similar gene networks may drive very different behavioral phenotypes (Figure 4D). An excellent example of this is work based on the so-called "phenologs" (McGary et al., 2010). This work suggests that gene interaction networks are conserved as modules between evolutionary distant organisms, even though the phenotypes ultimately produced may not be obviously analogous. For example, the gene network underlying parental care in mice is orthologous to the gene network that leads to multivulva phenotypes in worms (phenologs.org). This powerful approach has since been used to discover anticancer drugs (Cha et al., 2012), but also holds great promise for understanding the gene interaction networks underlying behavior.

CONCLUSIONS

Comparative approaches have shown that variations on brain developmental processes, such as early brain patterning or the timing of neurogenesis, can give rise to divergent neural and behavioral phenotypes. Although we know a great deal about where different neurochemical cell groups are located in animals brains, we still understand little about the specific conditions these cells respond to or how they are connected within a larger neural circuit. Determining how the brain evolves to promote divergent or convergent behaviors will require more comparative work, especially in nonmammalian vertebrates and invertebrates. However, with the advent of new high throughput technologies, this goal is now closer to our grasp than ever before. As information on the molecular and neural substrates of behavior from a diversity of animals becomes available, we will finally be able to mechanistically determine the patterns of brain evolution that underlie behavioral diversity.

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