1.17 Brain Systems Underlying Social Behavior

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Abstract

Recent progress in animal behavior research, based on the insight that proximate mechanisms both shape and constrain behavioral responses to natural and sexual selection, has reinforced the importance of knowing the neuromolecular basis of social behavior for understanding its evolution. Here, we review the current state of knowledge of the neural substrates of vertebrate social behavior, with an emphasis on the neuroendocrine and neurochemical pathways involved. Using an integrative perspective, we then discuss the evolution of these mechanisms and highlight several challenges that have hampered progress in this area. Finally, we provide a road map for an integrative evolutionary neuroethology.

1.17.1 Why Study the Neural Basis of Social Behavior?

Animals search for food and mates, defend themselves from predators, and often care for offspring. Many species also live in groups and/or move often considerable distances in a collective manner. These behavior patterns are deemed "social" when they involve interactions among members of the same species. Even solitary animals need to engage in social behavior from time to time, eg, when looking for mates or defending resources. These interactions among conspecifics evolve via natural and sexual selection and have fitness effects on both the focal individual and other individuals in a social group. Interesting evolutionary dynamics emerge from selection induced by the social environment, compared to trait plasticity selected by the physical environment (Székely et al., 2010). While selection acts on behavioral traits and their interactions, the mechanisms underlying these traits must change in response. Thus, to understand social behavior it is helpful to move beyond the "phenotypic gambit," the assumption that underlying mechanisms will not influence evolutionary trajectories (Rittschof and Robinson, 2014; O'Connell and Hofmann, 2011a). Recent progress in the integrative study of animal behavior has bolstered our appreciation that understanding the mechanisms—hormonal, neural, molecular, etc.—underlying social behavior is essential for a deep understanding of social behavior since these mechanisms both shape and constrain behavioral responses to the environment (Hofmann et al., 2014; Rubenstein and Hofmann, 2015).

1.17.2 Decision-Making in Social Contexts

When interacting with conspecifics, individuals make decisions that influence their own future behavior, the behavior of other individuals around them, and their ultimate fitness. Such decisions often integrate, in real time, the behavior of their social partners with the stored experiences from past interactions (learning and memory) and predictions of future behavior. This ability can be referred to as social cognition, defined as awareness of and knowledge about conspecifics, and measured by examining an individual's perception of and insight into its own and others' social interactions and relationships (Seyfarth and Cheney, 2015). Social cognition may be mediated by a set of skills that ultimately enable individuals to have successful social interactions (eg, forming predictions of others' behavior, maintaining bonds, succeeding in competition) with selection acting on these skills (Seyfarth and Cheney, 2015). More recently, the notion that animals display "social competence" has gained traction as a useful framework that greatly facilitates the study of decision-making in the context of social behavior. In this context, social competence has been defined as the ability of individuals to optimize their behavior in response to social

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information (Taborsky and Oliveira, 2012). Central to this concept is that variation in behavioral flexibility is adaptive (Taborsky and Oliveira, 2012). The study of both social cognition and social competence depends critically on understanding how the brain processes social information to generate an adaptive behavioral response and how these neural mechanisms have evolved. However, the neural and molecular substrates subserving these processes are only poorly understood (Weitekamp and Hofmann, 2014).

1.17.3 How Do We Study Brain Systems Underlying Social Behavior?

There are two immediate challenges to studying the brain systems underlying social behavior. First, social behavior often appears to be incredibly complex and usually occurs within an intricate web of social interactions. Second, there are many, many layers of regulation between the brain and the expression of social behavior (including its development). Consequently, dissecting any behavioral process into its component parts is an important step in identifying the direct mechanisms underlying a behavioral trait (Robinson et al., 2005). It is then important to investigate each layer of neural processing in the regulation of a given behavior, from synaptic transmission to neuromodulation.

We previously presented a conceptual framework for studying social cognition within a comparative and evolutionary framework (Weitekamp and Hofmann, 2014). A variety of factors influence the state of the brain at any given time point, including the social environment and previous social experiences, genotype, developmental and life history, ecology, and condition. This "baseline" neural state can be measured across several levels in the brain—the epigenetic state, the hormonal state, the functional connectivity between regions, and the existing gene regulatory networks. The response of the brain to a social stimulus, or the evoked neural response, is, in many ways, dependent on this baseline state. The immediate response to a social stimulus can be measured by immediate neural activity, changes in gene expression, and receptor–ligand binding. We argue that it is important to consider both the baseline neural state and the evoked neural response, as individuals can have divergent neural and behavioral responses to similar social stimuli in a context-dependent manner (Hessler and Doupe, 1999; Haller et al., 2004; Denver et al., 2012).

1.17.4 Neural Substrates of Social Behavior

Social signals are spatially and temporally integrated throughout the brain via numerous regulatory pathways, including, but not limited to neural activity, transcription, translation, epigenetic modifications, and neuromodulation. Social information processing is generally controlled by coordinated neural circuits. There are two neural circuits that seem to be fundamental to social decision-making in vertebrates: the social behavior network (SBN) and the mesolimbic reward system (O'Connell and Hofmann, 2011a). These two circuits form a larger social decision-making (SDM) network involved in evaluating stimulus salience and valence, likely via different subsystems (Lin and Nicolelis, 2008), and in regulating appropriate behavioral responses in social contexts (**Fig. 1**; O'Connell and Hofmann, 2011b).

The neural substrates regulating social behavior in mammals have been described as the SBN, based on decades of work investigating the role of sex steroid–sensitive regions of the brain (Goodson, 2005; Newman, 1999). By definition, the core nodes of the SBN are involved in the regulation of multiple forms of social behavior (such as aggressive, sexual, and parental behavior), are reciprocally connected, and contain sex steroid hormone receptors (Newman, 1999). The core nodes are the medial extended amygdala [medial amygdala (meAMY) and medial bed nucleus of the stria terminalis (BNST)], preoptic area (POA), lateral septum (LS), ventromedial hypothalamus (VMH), anterior hypothalamus (AH), and midbrain periaqueductal gray (PAG) and adjacent tegmentum.

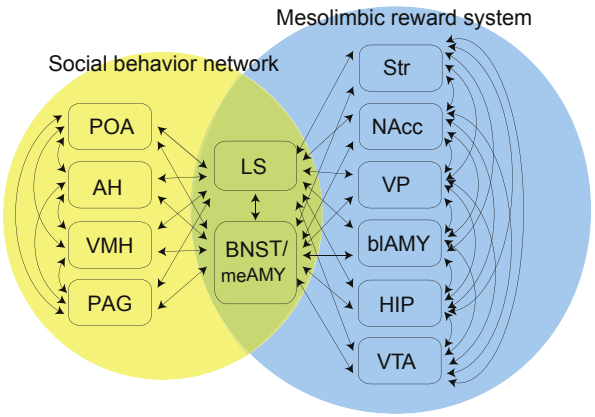

Figure 1 A vertebrate social decision-making network. Modified after O'Connell, L.A., Hofmann, H.A., 2012. Science, 336 (6085), 1154–1157.

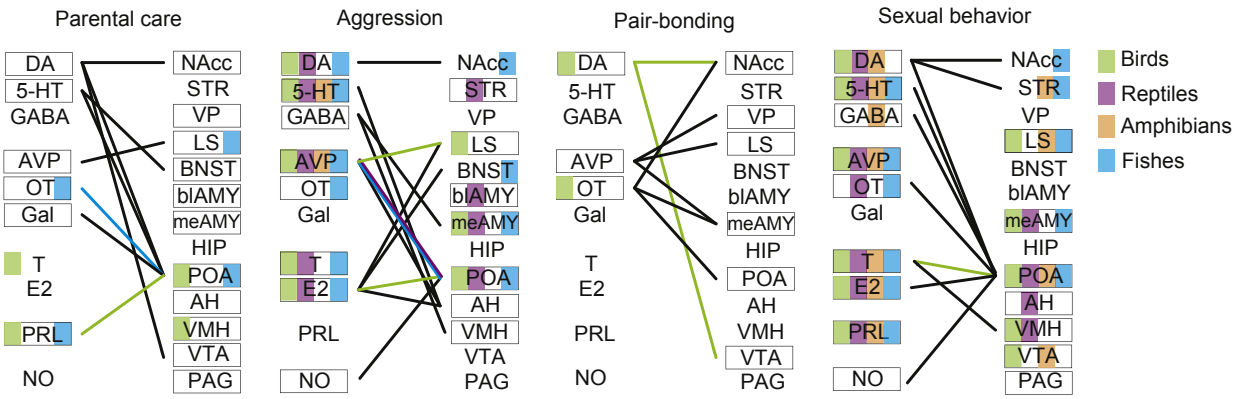

Figure 2 Neural mechanisms for parental care, aggression, pair-bonding, and sexual behavior. For each, we present a simplified network of the links between neurochemicals and brain regions that have been demonstrated to be critical to mediating the behavior in mammals (*black lines*). We highlight the connections for which there is support in nonmammalian species with *colored lines*, indicating that similar mechanisms have been identified in nonmammalian species [*green* = birds (Banerjee et al., 2013; Goodson et al., 2009; Buntin, 1996; Schlinger and Callard, 1990; Goodson, 1998); *purple* = reptiles (Hattori and Wilczynski, 2009); *orange* = amphibians (note: none identified); *blue* = fish (Kagawa, 2013; Yaeger et al., 2014; O'Connell et al., 2012)]. Furthermore, for each taxonomic group, we indicate whether there is support for a role of a particular neurochemical or brain region in a given behavior (*box* = mammals; *green* = birds; *purple* = reptiles; *orange* = amphibians; *blue* = fish).

Animals evaluate stimulus salience to generate appropriate behavioral responses. Many studies indicate that the mesolimbic reward system (including but not limited to the midbrain dopaminergic system) is the neural network where the salience of such stimuli is evaluated and behavioral decisions are reached (Berridge, 2007; Wickens et al., 2007; Wise, 2005). Together, the SBN and the reward system form a larger SDM network (O'Connell and Hofmann, 2011b, 2012). The nodes of this circuitry interact to integrate environmental and physiological cues and encode stimulus salience to generate adaptive behavioral responses. In addition to the SBN network nodes, this extended network also includes the hippocampus (HIP), basolateral amygdala (blAMY), ventral tegmental area (VTA), striatum (STR), nucleus accumbens (NAcc), and ventral pallidum (VP). While this network is a very useful heuristic tool, particularly for studying the neural basis of social behaviors for which little is known, it is important to recognize that other brain regions, such as the habenula (Chou et al., 2016) and much of the hindbrain (Bass et al., 2008), are also critically involved in mediating social behavior.

Different nodes of these general networks are involved to varying extent in regulating distinct behavior patterns. The neural circuits and molecular pathways for a variety of social behaviors are being elucidated. While much has been learned by focusing on mammals, particularly rodents, there is a growing literature on nonmammalian vertebrates suggesting that many of the same molecular pathways and brain regions govern similar behaviors in diverse species (O'Connell and Hofmann, 2011b). In **Fig. 2**, we highlight four well-studied social behaviors: parental care (Dulac et al., 2014; Numan, 2007; Wang et al., 1994), aggression (Nelson and Trainor, 2007; Delville et al., 1996; van Erp and Miczek, 2000; Veenema et al., 2010; Ferris et al., 1997; Lonstein and Gammie, 2002), pair-bonding (Young and Wang, 2004), and sexual behavior (Hull and Dominguez, 2007; Hull et al., 2004; Ball and Balthazart, 2004; Pfaus, 1999). The presented circuits are a simplification to demonstrate the "pleiotropy" of brain regions in the SDM network. Some of these connections likely differ between sexes, species, and experimental contexts. For example, there are many causes of aggressive behavior, from maternal aggression to intermale territorial aggression, and there are likely important differences in how these types of aggression are regulated in the brain.

1.17.5 The Issue of Homology

Importantly, the functional relevance of the various nodes of the SDM network was first described in mammals (Newman, 1999; Ikemoto, 2010). Thus, to apply this framework to nonmammalian model systems, the homology relationships for the relevant brain regions across a wide range of taxa need to be resolved (see O'Connell and Hofmann, 2011b; Goodson, 2005). But how do we decide that two brain regions are homologous across taxa? How similar do two regions in different species need to be in order to be given the same name?

Homologous traits are defined in terms of common ancestry. There are no exact criteria to be met in determining homology among brain regions, but rather consensus is often reached based on hodological, neurochemical, and developmental studies (O'Connell and Hofmann, 2011b). As such, progress made toward defining a common nomenclature will often need to be revisited and revised as more data accumulate (Goodson and Kingsbury, 2013). The very concept of homology itself has proven contentious, further demonstrating the challenges to defining homology across taxa (Striedter and Northcutt, 1991). Complex phenotypes, be it entire nervous systems or a certain forebrain nucleus, consist of multiple component parts (eg, gene families for ion channels in the former case or different cell types in the latter) that can evolve along independent evolutionary trajectories

(Liebeskind et al., 2015). As such, there is often not a one-to-one correspondence between regions in different species, but rather brain structures may be comprised of subcomponents from a common ancestor as well as novel components. These homologies are referred to as incomplete or partial (Wake, 1999). Furthermore, homologous brain regions may or may not have conserved function, and functionally similar regions may not be homologous (Striedter, 2002). Yet, inferring homology relationships is an important process that is essential to studying brain evolution, and the fear of misclassifying relationships should not stymie progress.

Identifying the homolog of the mammalian VTA and substantia nigra (SN) complex exemplifies some of these challenges (O'Connell et al., 2011, 2013). The VTA is central in the dopaminergic reward system, and the functional connection between the VTA and the nucleus accumbens is well studied for its role in mediating social behavior (Young et al., 2011). The SN is also part of the dopaminergic reward system and affects motor control (Fearnley and Lees, 1991). Neurochemical and hodological evidence suggest that the posterior tuberculum in anamniotes is composed of intermingled neurons homologous to the VTA and SN (Rink and Wullimann, 2001). The segregation into two distinct brain areas of these neurons may have happened after the anamniote–amniote transition (O'Connell et al., 2011).

Homology relationships were recently inferred across taxa for the entire SDM network (O'Connell and Hofmann, 2011b; Goodson, 2005), though some of these homologies remain tentative (Goodson and Kingsbury, 2013). This work provided for the first time a comprehensive comparative synthesis of this circuitry, suggesting that it was already present in early vertebrates (O'Connell and Hofmann, 2011b). In fact, the SDM network is remarkably conserved across vertebrates not only in terms of neuroanatomy but also with regard to candidate gene expression patterns. Analyzing expression profiles for 10 neurochemical genes across the 12 SDM network nodes in 88 vertebrate species revealed gene expression patterns that are highly conserved over 450 million years of evolution, suggesting that the diversity of social behavior in vertebrates can be explained, at least in part, by variations on a theme of conserved neural and gene expression networks (O'Connell and Hofmann, 2012). Thus, social stimuli may trigger shared common molecular pathways and neural networks that drive adaptive behavioral responses, even if the species-specific motor programs they orchestrate have evolved independently.

1.17.6 Neurochemical and Neuroendocrine Substrates of Social Behavior

There are many molecular and neurochemical pathways that influence social behavior, including hormones, neuromodulators, and neurotransmitters (Adkins-Regan, 2005). Hormones were classically thought of as long-distance messengers secreted from endocrine glands, which functioned in contrast to the rapid between-neuron communication of classical neurotransmitters. The distinction between these chemicals is no longer clear; the actions of signaling molecules are diverse across animals (Adkins-Regan, 2005). Here, we highlight some of the best-studied signaling pathways of importance in the regulation of social behavior: the nonapeptides, the sex steroids, and the monoamines dopamine and serotonin.

1.17.6.1 Nonapeptides

The nonapeptides oxytocin (OT) and arginine vasopressin (AVP) have broad and fundamental effects on social behavior across vertebrates (Goodson and Thompson, 2010) and beyond (van Kesteren et al., 1996). They are the result of an ancient gene duplication early in the evolution of vertebrates and differ by only two of nine amino acids (Keverne and Curley, 2004). In bony fishes, the homolog of OT is isotocin (IT), and the homolog of AVP is arginine vasotocin (AVT). In lungfish, amphibians, reptiles, and birds, the homolog of OT is mesotocin (MT). These peptides have specific effects on social behavior through both direct effects on the central nervous system and indirect effects in the peripheral system (Goodson and Thompson, 2010). OT is synthesized in the magnocellular neurosecretory cells of the hypothalamus which links to the posterior pituitary and leads to secretion in the periphery. OT is also synthesized in the parvocellular neurons of the paraventricular nuclei. Projections from the parvocellular cells link to the limbic system, to regions such as the AMY, STR, and NAc. Similar to OT, AVP is synthesized in magnocellular cells of the hypothalamus which leads to release in the circulation. AVP is also synthesized within parvocellular neurons of the paraventricular nuclei, the BNST, the medial AMY, and suprachiasmatic nucleus. Synthesis in these regions is highly androgen dependent (Skuse and Gallagher, 2009; Lim and Young, 2006).

The nonapeptides influence a great diversity of social behaviors, ranging from communication to parental care (for reviews see Goodson and Thompson, 2010; Donaldson and Young, 2008; Goodson, 2008, 2013; Insel, 2010; Kelly and Ophir, 2015). OT broadly affects maternal behavior (Pedersen et al., 1982), social recognition–dependent behaviors (Ferguson et al., 2001), and social motivation (Dölen et al., 2013), whereas AVP has general effects on aggression (Bester-Meredith et al., 1999), stress reactivity (Rivier and Vale, 1983), and learning and memory. The sex- and species-specific effects on behavior, as well as plasticity, are much greater in the nonapeptides than those of any other neurochemical systems. The rate at which nonapeptide receptor distributions evolve makes these pathways evolutionarily very plastic (Goodson, 2008).

1.17.6.2 Steroid Hormones

The nonapeptides interact with sex steroid hormones in mediating behavioral responses; steroid hormones can modulate the synthesis of these neuropeptides and their receptors. Steroid hormones and their receptors are crucial in mediating SBN function,

as they relay acute social information as well as reproductive status (Newman, 1999). The major classes of steroids, all of which have been implicated in the regulation of social behavior, are the mineralocorticoids, glucocorticoids, androgens, estrogens, and progestins (Balthazart, 1989; Miller, 1988). Estrogens act over both long and short timescales. Long-term, enduring effects of estrogens are often exerted via nuclear receptor activation of estrogen receptor alpha (ERα) or ERβ, which lead to transcriptional regulation of target genes. Rapid effects of estrogens, within minutes or seconds, occur via activation of membrane-bound receptors. The synthesis of steroid hormones within the brain and the ability of steroids to alter neural circuit dynamics have led to the suggestion that steroid molecules can function as genuine neuromodulators (Balthazart and Ball, 2006; Cornil et al., 2012; Remage-Healey, 2014; Remage-Healey et al., 2008).

1.17.6.3 Monoamines

Dopamine is a neurotransmitter involved in encoding incentive salience and underlies motivation (Berridge, 2007). It has been implicated in pair-bonding (Aragona et al., 2006), aggression (Miczek et al., 2002), undirected singing (Riters, 2012), and social reward (Bell and Sisk, 2013), among other social behaviors. DA is also well studied in the context of both appetitive and consummatory sexual behavior (Balthazart, 1997). Five DA receptor subtypes have been identified (Sibley and Monsma, 1992), though D1 and D2 receptor subtypes have been most thoroughly studied for their effects on social behavior (Yamamoto et al., 2015). These receptors often have opposing effects on behavior; for example, D1 stimulates, while D2 inhibits male sexual motivation (Kleitz-Nelson et al., 2010).

Like DA, serotonin (5-HT) is a highly evolutionarily conserved neurochemical with an essential role in diverse physiological processes. There are at least 14 5-HT receptor subtypes distributed throughout the brain (Olivier, 2005). 5-HT has been most studied for its role in aggressive behavior, where it is often found to be inversely associated with aggression, particularly the 5-HT_{1A} and 5-HT_{1B} subtypes (Nelson and Trainor, 2007). 5-HT also has documented effects on social dominance, though the directionality may be species-specific (Edwards and Kravitz, 1997). In general, the effects of 5-HT on social behavior appear complex, likely owing to the diversity of receptor subtypes and to the complex interactions with other signaling pathways (Nelson and Trainor, 2007; Dölen et al., 2013).

1.17.6.4 Other Classes of Molecules

There are several other classes of molecules implicated in social behavior, including the opioids (Panksepp et al., 1980; Resendez et al., 2012), cannabinoids (Haller et al., 2004; Trezza et al., 2012), other biogenic amines such as adrenaline and noradrenaline (Rodriguez Moncalvo et al., 2013), steroids and hypothalamic neuropeptides (Parhar et al., 2016), eg, vasoactive intestinal peptide (Kingsbury, 2015), as well as nitric oxide (Nelson et al., 1997), and GABA (Nelson and Trainor, 2007), among others. Given that social behavior involves many complex layers of neural processing, there are likely many more important molecules yet to be discovered.

1.17.7 Evolution of the Neuromolecular Mechanisms Underlying Social Behavior

To what extent are the mechanisms underlying similar behavioral phenotypes conserved across taxa (O'Connell and Hofmann, 2011a; Hofmann et al., 2014; Toth and Robinson, 2007)? We recognize five major possible pathways to the evolution of neuromolecular systems that mediate behavior (**Fig. 3**). (1) The same neural and molecular mechanisms may have been recruited repeatedly as novel behavioral traits arose independently in diverse lineages, analogous to the notion of a shared "genetic toolkit," also referred to as "deep homology" (Toth and Robinson, 2007; Shubin et al., 2009). (2) The observation that homologous characters between closely related species are often divergent suggests that "developmental system drift" is also at play and may enhance evolutionary plasticity (True and Haag, 2001). (3) An additional process that may be involved in neuromolecular evolution is the "phenolog" concept, where conserved gene networks may underlie different (behavioral) phenotypes (McGary

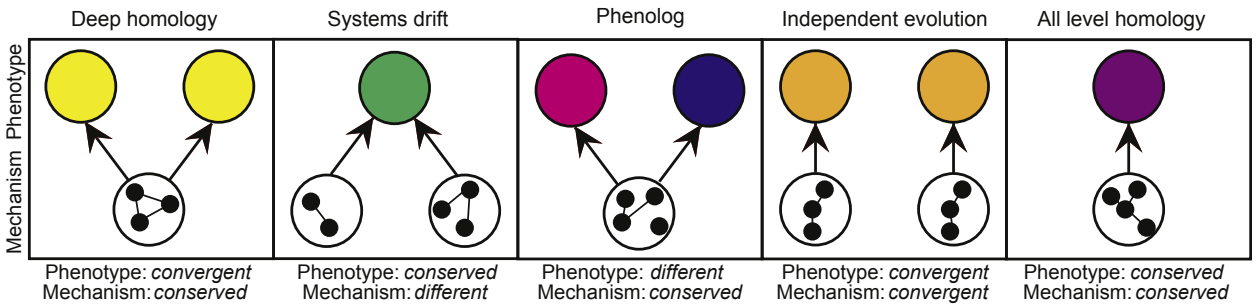

Figure 3 Hypothesized pathways for the evolution of the neuromolecular mechanisms underlying social behavior.

et al., 2010). There are also two "null" hypotheses for the routes to the evolution of shared behavioral phenotypes. (4) Independent evolution can occur whereby both the phenotype and mechanism are convergent. (5) Finally, there can be homology across all levels, whereby both phenotype and mechanism are conserved. These pathways are not mutually exclusive, and it seems safe to assume that all play a role in the evolution of behavior (Hofmann et al., 2014).

The concept that has received the most attention in the context of social behavior is the "genetic toolkit" (O'Connell and Hofmann, 2011a; Toth and Robinson, 2007), also referred to as "deep homology," which has been adapted from the field of evolutionary development, or "evo-devo" (Shubin et al., 2009). The general hypothesis is that a conserved set of genes that regulate core physiological processes have been repeatedly used in the convergent evolution of social traits. This framework has been most thoroughly studied in the eusocial insect lineages. Most studies take a comparative approach to investigate whether there are shared differentially regulated genes in similar, independently evolved castes across species. Support for this hypothesis has been mixed, with studies often reporting little overlap in lists of differentially expressed genes (Mikheyev and Linksvayer, 2015; Manfredini et al., 2014). Instead of specific genes being repeatedly recruited in the evolution of convergent traits, there may be general pathways, such that gene networks are conserved but individual genes are not shared (Rehan and Toth, 2015; Berens et al., 2015). It also appears that novel, taxonomically restricted genes have been important to the evolution of social behavior (Feldmeyer et al., 2014; Sumner, 2014), and these novel genes may be added to more conserved, core networks (Mikheyev and Linksvayer, 2015).

It has been argued previously that it is difficult to quantitatively test evolutionary hypotheses that arise from "-omics" data without an explicit framework from social evolution theory (Hofmann et al., 2014; Akçay et al., 2015). Many important questions remain to be addressed. For instance, how do the unique characteristics of social traits affect the evolution of neural and genomic mechanisms differently than other traits? What is the relationship between conserved neural circuits and conserved (or convergent?) gene regulatory networks? Is there a common currency for behavioral displays that will facilitate comparative analyses across a broad range of taxa that differ in their brain organization, social system, and/or behavioral repertoire? Tremendous progress has been made in developing genomics and bioinformatics tools for a diverse array of species and questions, but explicit hypothesis testing has proven challenging without formal evolutionary models (see also Rubenstein and Hofmann, 2015).

1.17.8 Future Outlook

Advancing our understanding of the brain systems underlying social behavior and how they have evolved relies on a highly comparative and integrative approach. The comparative approach, phylogenetically informed and based on insights from behavioral ecology, can reveal general principles of brain function underlying social traits that may not be apparent in single species (Hofmann et al., 2014; Taborsky et al., 2015). Comparative analyses examine patterns of associations between traits with the aim of inferring patterns of adaptation, while accounting for phylogenetic independence and confounding variables (Krebs, 1990; Harvey and Pagel, 1991). Such analyses can clarify our understanding of how the molecular substrates of social behavior evolve by reconstructing the evolutionary history of these traits across broad phylogenetic time (Striedter et al., 2014).

Clearly, the complex spatial and temporal integration of social signals in the brain limits the utility of studies focused on only one pathway, one brain region, or one species for inferring the evolution of mechanisms. Thus, for evolutionary neuroethology and systems neuroscience to be successful, a number of formidable challenges have to be overcome. Specifically, the concept of time is critical, whether investigations focus on rapid neuronal communication within or between functionally connected nuclei or on coherent neural activity across even distant brain regions. Further, the investigator has to account for the possibly confounding effects of development, life history, and phylogeny when inferring mechanistic insights across species to phylogeny. Further, the lack of spatial resolution that characterizes many studies poses an additional challenge, eg, because neurochemicals may exert different effects at the level of individual neurons or entire neural circuits. In agreement with Striedter et al. (2014), detailed nervous system "maps" for any given species of interest that integrate cellular, molecular, and circuit data across spatial and temporal scales will provide a rich and valuable resource to the study of social behavior. Also, as pointed out by Hofmann et al. (2014) and Taborsky et al. (2015), emerging technologies that allow the targeted (in space and/or time) manipulation of genomes (eg, CRISPR/Cas9; viral gene delivery) will need to be forcefully implemented in a wide variety of species, especially for those where rich ecological and evolutionary datasets already exist (Taborsky et al., 2015). Such an advance will facilitate the application of real-time circuit analyses [eg, through optogenetics (Fenno et al., 2011) or chemogenetics (Sternson and Roth, 2014)], even under natural (or at least naturalistic) conditions. As data on variation in the genome and epigenome, gene expression, hormones, and proteins for specific social behavior patterns are fast accumulating, there is also an urgent need for the development of bioinformatics tools that will allow for modeling the complexity of and interactions between these various levels of regulation of behavior in the brain (Ritchie et al., 2015). The integration of data into a systems level approach will indubitably yield valuable insights and lead to a further appreciation of the complexity and richness of the brain systems underlying social behavior (Székely et al., 2010).

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