Frontiers in Neuroendocrinology xxx (2010) xxx–xxx

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

journal homepage: www.elsevier.com/locate/yfrne

Review

Genes, hormones, and circuits: An integrative approach to study the evolution of social behavior

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ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Genomics
Social behavior network
Mesolimbic reward system
Comparative neuroanatomy
Evolution
Decision-making
Approach
Avoidance
Challenge response
Phenologs
Developmental system drift

ABSTRACT

Tremendous progress has been made in our understanding of the ultimate and proximate mechanisms underlying social behavior, yet an integrative evolutionary analysis of its underpinnings has been difficult. In this review, we propose that modern genomic approaches can facilitate such studies by integrating four approaches to brain and behavior studies: (1) animals face many challenges and opportunities that are ecologically and socially equivalent across species; (2) they respond with species-specific, yet quantifiable and comparable approach and avoidance behaviors; (3) these behaviors in turn are regulated by gene modules and neurochemical codes; and (4) these behaviors are implemented by brain circuits such as the mesolimbic reward system and the social behavior network. For each approach, we discuss genomic and other studies that have shed light on various aspects of social behavior and its underpinnings and suggest promising avenues for future research into the evolution of neuroethological systems.

1. Introduction

All animals continuously integrate their internal physiological state with environmental events and subsequently choose one action over another to increase their chances of survival and reproduction. These decisions are about obtaining and defending resources (such as food, shelter or mates) or evading danger (such as predator avoidance), and they often take place in a social context, such as dominance hierarchies, mate choice, and/or offspring care. Even though the survival value and evolution of behavioral decisions have been examined in great detail by behavioral ecologists [154], we are just now beginning to understand the neural and molecular mechanisms underlying these decision-making processes. As biologists have moved beyond the ultimately fruitless debates about the relative contributions of nature and nurture, we have come to understand that behavior – like all phenotypes – is the result of interactions between genetic, environmental, and developmental/epigenetic processes [8,50,120,248,293,316]. At the same time, comparative studies have illuminated the behavioral, neural, and molecular underpinnings of behavior, suggesting that – similar to developmental [38,284] and genetic systems [178] – at least some of the mechanisms regulating behavior across multiple levels of biological organization are conserved in a wide range of species [135,202,214,231,241,308].

How do animals decide which behavioral action to take when faced with a complex array of sensory stimuli and internal state conditions, and how did such a decision-making system evolve? In this review, we incorporate recent insights from a range of biological disciplines into a framework that promotes an integrative understanding of the evolution, survival value, causation, and development of behavioral decisions, as first proposed almost half a century ago by Tinbergen [278], the Nobel-prize winning co-founder of the scientific study of behavior [31].

We outline four pillars to support this framework (Fig. 1) and discuss them in the light of functional genomics. First, given the astonishing diversity of behavioral displays we find in nature, we need to define behavioral contexts of relevance to the life history and ecology of any given species such that comparisons across taxa are as unbiased as possible (see [109,214], for detailed discussions of this difficult subject). All animals, at one time or another, face challenges (e.g., territorial intrusions; competition for shelter; predation) as well as opportunities (e.g., finding a mate; a chance to climb in the social hierarchy; obtaining food) that affect their chances of survival and reproduction in similar ways. We suggest that comparative studies into the mechanisms of social behavior should expose individuals of different species to equivalent social stimuli. Second, by carefully determining the relative amounts of approach and avoidance (or withdrawal; see Schneirla [244] for a classical appraisal of this concept) in any challenge/opportunity

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0091-3022/$ - see front matter © 2010 Published by Elsevier Inc.
doi:10.1016/j.yfrne.2010.12.004

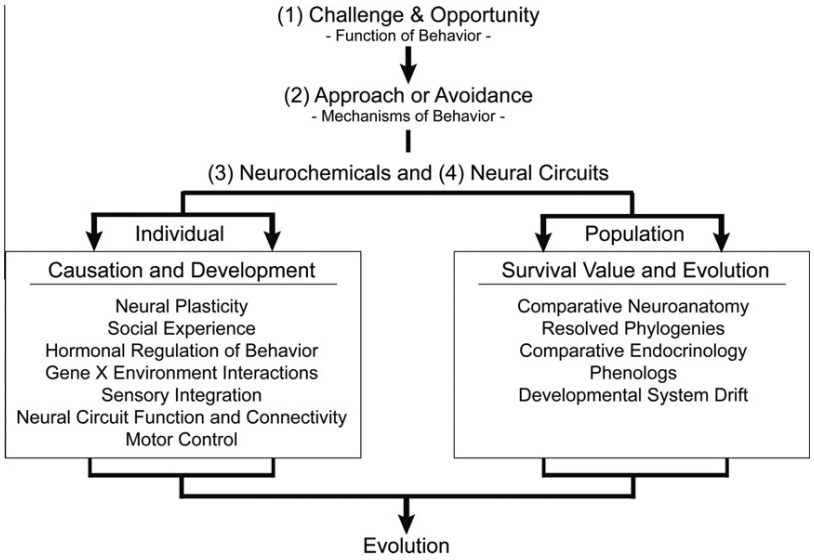

Fig. 1. An integrative framework for the analysis of social behavior and its evolution. Themes for studying both the proximate and ultimate mechanisms of social decision-making are presented on the level of the individual (left panel) and the population (right panel).

context we can obtain quantitative behavioral and physiological measures as an entry point into the neural, endocrine, and molecular mechanisms of the behavioral response in question. Third, the remarkably conserved actions of hormones, specifically sex steroid and neuropeptide hormones, in the regulation of behavior have long been a focus of research [1,15,49,83,134,165,288]. Similarly, the role of catecholamines, dopamine in particular, in encoding the salience and rewarding properties of a (social) stimulus appears to be conserved across a wide range of animals [22,111,314]. In addition, it has become evident that the coordinated activity of sets of genes (modules) can be conserved across species [169,259] or within species life history stages [9]. Fourth, because the orchestration of these neuroendocrine and molecular processes follows complex spatial and temporal patterns throughout the brain [48,130,195,313], we require a detailed understanding of the neural circuits involved in this regulation, such as the social behavior network [48,94,195] and the mesolimbic reward system [58,297]. Of course, within a comparative framework a neural network approach can only be accomplished if the homology relationships for the relevant brain regions have been resolved across a wide range of taxa [198,200,270].

2. Universal properties of living systems

All living systems share the same macromolecules (nucleic acids, amino acids) for the storage, transfer, and utilization of information, which is considered strong evidence for a common origin of life on earth. Even more important to modern biology, it suggests that throughout evolutionary history a shared set of building blocks – "tool box" [40,219] – has been deployed and expanded upon as novel traits and lineages arose. Based on the whole genome sequences that have become available for diverse species, we now know that a remarkably large number of protein-coding genes are shared (have orthologs) across all animals (and, to a lesser extent, all organisms). Similarly, conserved non-coding regions dispersed throughout the genome appear to play important regulatory and developmental roles across a wide range of taxonomic groups [220,257].

The realization that protein-coding genes are so highly conserved across species raises a question that is fundamental to our understanding of genetic information: how can highly conserved genetic codes generate the astounding array of body types and behavioral expression that mark the diversity of life? Advances in understanding the human genome have come from comparing variation in the sequences and in the expression patterns of genomes across species [39], a process that amounts to an experimental manipulation of genetic components, with nature providing the independent variables, and anatomy, physiology, and behavior being the dependent variables that allow us to understand the function of genetic sequences. Comparative genomics has given us the tools to dissect the human or any other genome with regards to transcription initiation sites, splice sites, number of protein-coding genes, as well as genes that do not follow canonical rules. Importantly, comparative genomics has been of tremendous utility for delineating promoter and other regulatory sequences, and the discovery of RNA genes and microRNAs [3,43,215]. Thus, genomics is most useful as a comparative science, and is instrumental for understanding the variation of brain and behavior across species and how this variation evolved.

Comparative research into the evolution of developmental processes (evo-devo) has taught us that regulatory pathways and developmental programs underlying morphological differentiation (e.g., those controlled by homeotic genes) are highly conserved across a wide range of taxa [38]. Small variations (e.g., via gene regulation in space and time, gene duplication/subfunctionalization) in these pathways can result in morphological novelties that may give rise to new lineages in the course of evolution. One example is the repeated convergent evolution of eyes as image-forming devices likely evolved independently in numerous lineages [80]. However, the transcription factor PAX6 appears to be crucial in the developmental programs of eyes in a range of distant lineages [35], suggesting that this gene has been recruited into an eye developmental program on multiple independent occasions. As PAX6 is pleiotropic (i.e., plays a key role in several other developmental programs), it remained intact during long periods of "eyelessness". Thus, as has previously been suggested, such "deep homologies" [121,230,255,272,299] might also underlie social behavior that – given the appropriate functional context and selection pressure – has evolved independently in multiple lineages [281]. Here, we provide an explicit framework to study the evolution of social behavior, spanning an arch from functionally equivalent social contexts via quantitative behavioral measures

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and molecular mechanisms of neural circuit function, all the way to the conserved roles of neurochemical systems.

3. Challenge and opportunity

An important consideration in studying how behavioral decisions are made and evolve is how to compare such complex behavior patterns across diverse species. While it has long been recognized that a full understanding of biological processes requires the study of diverse model systems [157], behavioral displays are remarkably diverse across species. This often confounds the comparisons of neural and molecular mechanisms underlying a given behavior across species [109,214]. Therefore, we need a framework in which to study behavior that is placed in an evolutionary context and that can be applied across many taxa.

We propose a classification scheme based on two of Tinbergen's [278] "four questions" – survival value and evolution – by categorizing animal behavior according to the life history and/or ecological context in which it takes place. Specifically, social interactions related to reproduction, offspring care, or foraging take place in the context of *opportunity*, whereas the aggressive defense of a territory (or other valuable resource) or offspring can be considered behavior patterns that occur in response to a *challenge* (Fig. 2). Such a grouping of diverse behavior patterns allows us to reduce the taxonomic diversity to basic functional contexts and already hints at the intriguing possibility that the neural and molecular networks underlying challenge and opportunity behaviors evolved from genomic, endocrine and neural processes that may at least in part be conserved.

Behavioral responses to challenges have been documented in all the diverse taxa studied and include the defense of resources (e.g., shelter, food, mates) and predator avoidance [116,153,182,218,274,305]. In many species, resource defense typically involves aggressive displays. For example, male fruitflies, *Drosophila melanogaster*, will display aggressive behavior in defense of females or territories [68,117], and variation in this behavior across populations can be explained in part by genetic differences [118] and can be subject to artificial selection [63,112,119]. Edwards and colleagues [71] profiled whole body transcriptomes of high and low aggression strains of *Drosophila* males and females and found a profound transcriptional response involving ~10% of the genome between the two lines. Genes whose activity differed significantly are involved in circadian rhythm, learning, courtship, neurotransmitter secretion/transport, and response to stress. Interestingly, many of the genes in these categories were down-regulated in the high aggression line compared to the low aggression line. This study also identified several novel genes implicated in aggression, highlighting how functional genomics can complement classical forward genetic screens in traditional genetic model systems.

The genomic response to a challenge within a species can also be plastic and vary with season. Male song sparrows, *Melospiza melodia*, for example, display territorial defense in the form of vocalizations. The type of song reflects the level of aggression and can be used as a predictor for whether the social interaction will result in an attack or flee [251]. A recent transcriptome analysis not only revealed that a subset of genes is differentially regulated between individuals encountering an intruder compared to non-social controls, but that these gene sets respond differently to social stimuli according to season [189]. This study indicated that the animals have a genomic response to a social challenge, and that the genomic response can vary with environmental input.

Gene modules that regulate response to social challenges can be influenced by both environment and evolutionary history. An elegant microarray study by Alaux and colleagues [2] in honeybees (*Apis melifera*) showed that the same genes that are constitutively up-regulated in an aggressive strain, the Africanized bees, compared to the more docile European bees are the same genes that are up-regulated when European bees are presented with alarm pheromone, a challenge that triggers aggressive responses in the defense of the colony. Interestingly, the activity of these genes was also increased in older bees compared to younger bees, in line with the observation that aggressive behavior increases as these animals age and assume defense-related tasks.

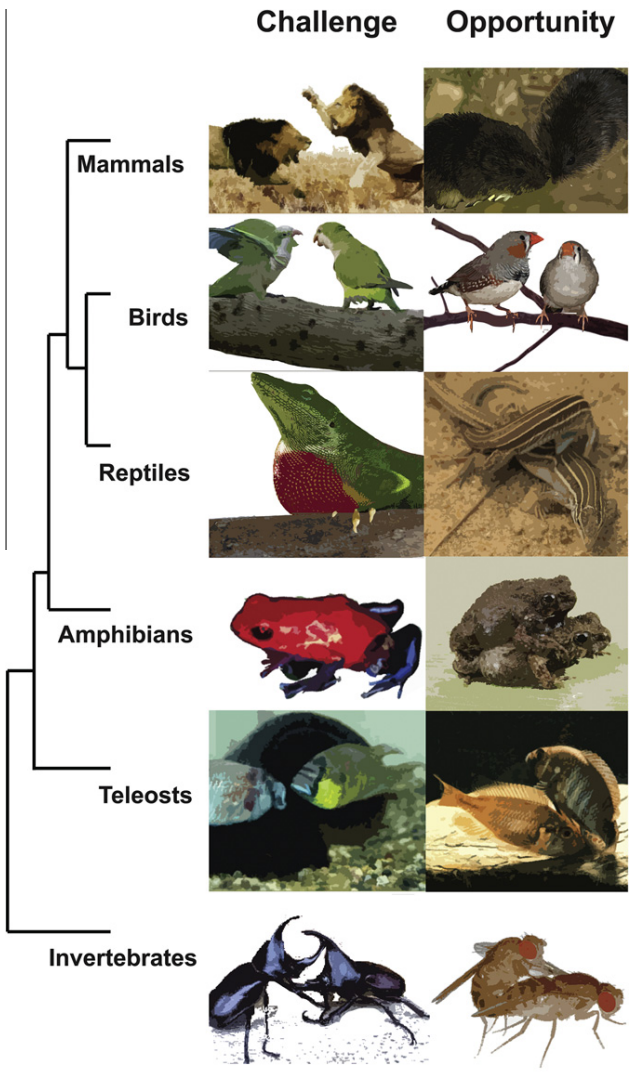

Fig. 2. Challenge and opportunity: a functional framework. Behavioral responses to challenge and opportunities in the social environment are equivalent across animals, although the specific behavioral response may be divergent across lineages due to life history, ecology, and/or evolutionary history.

Another genomic model system of aggression in the context of male–male competition is the cichlid fish, *Astatotilapia burtoni* [102,306]. Dominant males are highly aggressive and defend territories where they court and spawn with females, whereas subordinate males are reproductively suppressed and school with females. Importantly, these behavioral phenotypes are plastic and subordinate males will challenge dominant males for access to resources. Microarray analysis revealed that dominant males express higher levels of some neuroendocrine-associated genes, like vasotocin and prolactin, as well as structural proteins, like actin and tubulin, compared to subordinate males [224]. These studies have given important insights into the genomic regulation of social dominance behavior in a community context.

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In nature, challenge and opportunity rarely present themselves in isolation, which is an important factor in designing comparative experiments in this context. Recent studies in *A. burtoni* highlight the complex relationship between these functional contexts. For example, subordinate males with an opportunity to ascend in social status (and thus to obtain a territory for mate attraction) display aggressive behavior towards potential territorial challengers within minutes of being provided with a vacant shelter, followed closely by an increase in sex steroid hormones. There is a rapid genomic response to social ascent as expression of the immediate early gene *egr-1* in preoptic GnRH neurons is induced, as well as sex steroid receptors and steroidogenic acute regulatory (StAR) protein, which regulates androgen production, in the testes [32,128,174,175].

Behavioral responses to opportunities are often studied in the context of female mate choice and male courtship, although behavioral patterns associated with foraging and habitat selection have been studied in detail as well [265,268]. It is well established that sensory cues influence mate choice [37,235], but only recently has a combination of genomic and candidate gene approaches, coupled with hormonal and behavioral measures, begun to illuminate the molecular substrates of mate choice in the female brain. In female swordtails, *Xiphophorus nigrensis*, the presence of an attractive male stimulus elicits a remarkably fast (within 30 min) genomic response in 306 (8.9%) of the 3422 genes examined in a study by Cummings et al. [52]. Importantly, these authors found that 77 of these genes were associated with mate choice conditions (i.e., whether the female was allowed to choose between an attractive and non-attractive male, or whether she was exposed to two non-attractive males), and that the majority of these genes were down-regulated compared to the other social conditions. Also, the gene expression patterns in females exposed to mate choice conditions were almost exactly inverse to those exposed to other females: Genes that were down-regulated in females in the mate choice treatment were up-regulated in the female social control and vice versa.

The finding that the vast majority of genes associated with mate choice were down-regulated compared to the other social conditions is consistent with the classic notion that the execution of behavior is tightly controlled by central inhibitory mechanisms [232]. Cummings et al. [52] thus suggested that down-regulation of a suite of genes (i.e., suppression of activity at the molecular level) might result in the release of this (physiological) central inhibition of neural circuits that govern female mate choice. It would be fruitful to investigate the genomic responses in the context of female mate choice in other species to better understand the underlying genomic mechanisms and how they relate to the physiology of brain circuits. Anurans provide a tractable model system for this fundamental question in biology, and recent studies in the túngara frog, *Physalaemus pustulosus*, by Hoke and co-workers in the context of phonotaxis have examined immediate early gene induction in response to a mate choice stimulus as a proxy for neural activation [122–124]. These studies have begun to delineate the brain networks involved in assessing – and responding to – male call patterns and established an important foundation for understanding where in the brain mating decisions are made [125].

The act of courtship and mating also elicits a genomic response in female *Drosophila*. Following a courtship ritual that relies on multiple sensory cues from both sexes [103], genomic profiling was done for the whole animal [164]. Females that were courted but did not mate showed differential gene expression compared to females that were not courted, and females that were courted and mated had an additional gene set that was differentially regulated compared to females that had been courted but did not mate. This work suggests that the integration of sensory cues from the courtship experience influences a female's transcriptome in addition to the actual mating event. It remains to be seen which transcriptional changes were elicited in the brains of courted and mated females, as whole-organism profiling likely masks brain-specific gene regulation.

Insights into the neural basis of opportunistic foraging behavior have come from genomic studies in insects. Honeybees (*Apis mellifera*) have a distinct behavioral transition from hive-bound duties during the first couple weeks of life to pollen foragers. This distinct behavioral transition is associated with striking changes in the brain transcriptome on the order of thousands of genes [296], predominantly in transcription factors [106] and genes associated with metabolic processes [4]. Some of the genes involved in these processes show a conserved mechanism across insects. For example, the gene *foraging* (or *for*) is higher in forager bees than in hive bees [20], and is also increased in fruitflies expressing the rover (actively foraging) phenotype compared to the sitter phenotype (*D. melanogaster*; [260]). A recent study by Toth and colleagues [282] that used transcriptome analysis to compare brains of paper wasps (*Polistes metricus*) and honey bees suggests that gene expression associated with foraging behavior is highly conserved in social insects, while the activity of genes associated with reproductive behavior is more variable, possibly due to the major differences in the mating system of these two species.

The challenge and opportunity framework allows the development of behavioral paradigms that are applicable across many species. We have presented evidence that genomic responses to opportunities, such as foraging in insects, are similar across species, supporting the notion of conserved gene sets regulating functionally equivalent behavioral responses. More generally, our framework predicts that there is significant overlap between gene sets regulating foraging and those regulating mating behavior within and/or across species. However, variation in genomic responses, such as those found in the context of reproduction in insects, are also informative as they provide insight into how unique behavior patterns may have evolved in a lineage-specific manner, e.g., in response to unique selection regimes. Importantly, variation in genomic responses to functionally equivalent social stimuli can also reveal species differences in the relative contribution of different sensory modalities in association with a conspecific versus a food source.

Within this framework of challenge and opportunity, we can now begin to ask to which extent the molecular substrates underlying these behavioral responses might be conserved across diverse species [230]. However, few such analyses have been attempted thus far across relatively closely related species [169,259]. This is, of course, at least in part due to the still small number of genomic analyses of behavior, partially due to the limited genomic tools available for some species. However, a more fundamental limitation lies in the multitude of divergent behavioral measures researchers have developed to assess behavioral responses in diverse species [214]. We therefore need to consider whether there is a common "currency" for behavioral measures that can facilitate comparative analyses.

4. Approach and avoidance

In order to ask questions about the causation or development of behavior, there must first be fundamental behavioral measures that are principally valid across most species. Behavioral displays exhibited in the context of challenge and opportunity can usually be classified as either *approach* towards, an *avoidance* of (*withdrawal* from), or a passive response to a relevant stimulus. From the viewpoint of proximate mechanisms, this concept provides us with a heuristic framework for comparative studies aimed at development or causation of behavior across even diverse species [217,244,276]. Using the approach/avoidance scheme

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(including passive responses) in relation to environmental or social stimuli (summarized by [244]; see also [181,188]), we can operationally define shared behavioral categories that are independent of the specific sensory modalities or idiosyncratic motor patterns, which may characterize species-typical behaviors in each taxon (Fig. 3).

The decision to either approach or avoid a stimulus naturally has implications for the survival and reproduction of an individual. In noxious situations it may be most advantageous to withdraw, while an approach response is most appropriate to a mate or food resource. It is important to note that the appropriate response of an individual is dependent on prior experience, condition of the individual, and brain gene expression, and specializations in these mechanisms may have appeared through natural selection of traits that favor approach or avoidance in different situations [244]. Furthermore, this framework allows a quantification of behavior in relation to physiological and molecular measures, such as hormone levels or gene expression, to determine how these variables may covary across species.

There is a rich literature in behavioral ecology examining approach and avoidance responses, often in the context of foraging [reviewed by 267] and predator avoidance (reviewed by [65,104]). Propensity to approach or avoid a particular stimulus has a genetic basis that suggests there is within and between species variation in these adaptive responses [27,163,292]. These behaviors are comparable across taxa and have been documented in invertebrates and vertebrates in response to attractive or noxious stimuli [74,139, 243,267,279].

Functional studies investigating the genetics underlying approach/avoidance behaviors have mostly focused on odor-guided behavior, and studies exploiting other sensory modalities are needed. In many species, olfactory information provides salient information about species identity, sex, social status, and/or reproductive condition [28,107,140,143,309]. Anholt [6] and colleagues identified several genes involved in the odor-avoidance response in *Drosophila* using mutant lines that failed to respond to a noxious odor. Loci disrupted in these mutants include ion channels and genes implicated in odor recognition or postsynaptic organization. Mutant mice that have deletions of neuropeptide or steroid hormone receptor genes also have disrupted olfactory recognition [reviewed in 143]. These knockout strains can recognize predator (cat) odors but fail to recognize parasitized conspecifics [143,144].

Social networks can also influence an individual's response of approach or withdrawal to a stimulus. Work in guppies (*Poecilia reticulata*) has shown that behavior of individuals within the shoal can influence both foraging behavior and avoidance of noxious stimuli. In guppies, individuals will prefer the routes established by shoal founders either during foraging or while escaping predators, which suggests that social information facilitates decisions about movement in the local environment [29,161]. Social approach behavior, such as female mate choice, can also be influenced by group dynamics, as mate choice copying has been documented in every vertebrate lineage [86,148,160,221]. However, this transmission of approach or avoidance decisions through social groups can sometimes be maladaptive and prevent the adoption of optimal behaviors. For example, Laland and Williams [162] trained founder guppies to prefer a longer (more costly) route to a food source over a shorter route (less costly). Other guppies adapted this behavior and this maladaptive preference persisted even after the founder guppies were removed. Guppy avoidance behavior has a genetic component as animals from high or low predation populations will differentially respond to predator-induced alarm pheromones [129]. To date, no genomic analyses have been carried out in the context of social networks, though it would be interesting to determine the molecular correlates of information transmission in social groups.

In summary, while the challenge/opportunity framework provides equivalent social contexts in which to conduct experiments, the approach/avoidance framework makes possible quantification of behavior in ways that transcends species-specific conditions and sensorimotor processes, and thus facilitates the comparison of behavioral mechanisms across diverse taxa. For instance, approach/avoidance measures have a rich history in opportunity behaviors such as foraging [267] and mate choice [235], in strong support of the notion that "molecular universals" hypothesis can in fact be adequately tested. It is, however, important to note that the (proximate) approach/avoidance framework is most useful only when applied within carefully chosen (ultimate) challenge/opportunity contexts of adaptive relevance.

The behavioral responses of approach and avoidance must have neural origins that are specific to both defined brain regions and neurochemicals used to process the relevant information. Many mechanistic studies have highlighted the fundamental role that hormones and catecholamines play in regulating these behaviors. Studying the shared behavioral mechanisms underlying social challenges and opportunities at the behavioral level will allow us to fairly compare social decisions across vertebrates.

5. Hormones and monoamines

Studying behavior in the context of neurochemicals allows us to uncover its physiological and developmental basis [15,206,301].

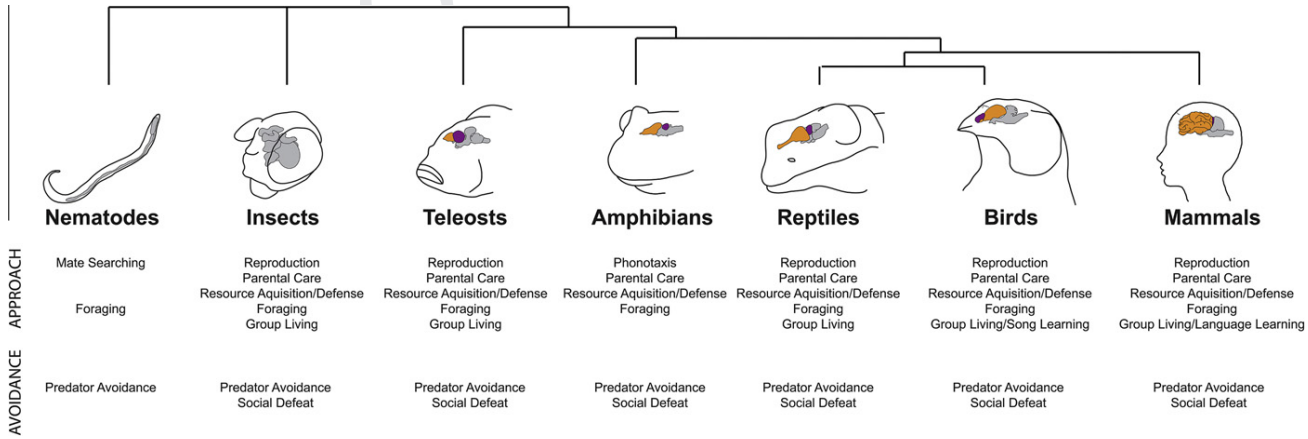

Fig. 3. Approach and avoidance: a mechanistic framework. Quantitative measures of behavioral responses to challenges and opportunities that are tractable in all species provide an important foundation for analyzing the molecular and neural basis of social behavior and its evolution. Brains are shaded differently by forebrain and midbrain.

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Given this, there may be universal codes underlying the evolution of behavioral mechanisms similar to the homeotic pathways that have become fundamental to our understanding of the evolution of developmental mechanisms. The crucial role of dopaminergic (and other aminergic) cells in encoding the salience (or rewarding properties) of a (social) stimulus appears conserved in all animals studied thus far [11,58,111,158,226,286,308]. For example, studies on the salience-encoding properties of the dopaminergic system in worms, insects, and vertebrates provide a framework for understanding drug addiction in humans [19,78,193,196,242]. More generally, the modulatory role of various neuroendocrine and neurotransmitter systems (neuropeptides, steroid hormones, biogenic amines) in social behavior is conserved across species, even though the specific manifestations of the behavior can vary greatly across species and/or conditions [1,21,283,308]. These patterns have also been investigated in human social cognition and attachment [79]. Above, we briefly addressed the involvement of catecholamines and hormones in approach/avoidance behavior from the perspective of behavioral ecology, and we will now discuss in greater detail the role of these neurochemicals in modulating behavior.

5.1. Hormonal modulation of approach and avoidance

The hormonal basis of behavior has been studied for decades by behavioral neuroendocrinologists, who have made great advances in understanding how the complex interactions of the brain and physiology result in meaningful behavioral responses. A classic example of this is the "challenge hypothesis", which predicts how androgen levels and dynamics relate to social behavior across diverse social systems and environments [302]. This powerful framework, originally developed for androgen responses in birds [302], has been expanded to other hormones (glucocorticoids, progesterone, juvenile hormone, etc.) and other animal taxa including mammals [57,205], reptiles [137,149], amphibians [33], teleost fish [60,115,128,203], and more recently to invertebrates [151,249,277]. However, some species appear to lack androgen responses to social challenges [185,250,290], possibly due to differences in ecology or mating system (see also the meta-analysis by [115]). Although endocrine responses to challenges, such as male–male interactions, have been studied in detail, hormonal changes in response to social opportunities have received less attention. A small number of studies in a range of taxa have clearly established that similar processes can occur in opportunity contexts when males are exposed to females (birds: [184,186,201]; mammals: [5]; fish: [263]). More comparative investigations into the challenge hypothesis in species with diverse life histories and mating systems will yield a better understanding of the evolution of hormonal responses to social challenges and opportunities.

Both sex steroids and neuropeptide hormones have been implicated in modulating all facets of social behavior including aggression [81,92,261,283], sexual behavior [10,131], parental care [61,166,190], and sociality [41,67,95]. Sex steroid hormones can affect neural circuits and behavior via long-lasting genomic mechanisms that involve changes in gene expression [204,287] as well as through rapid effects mediated by signal transduction cascades [171,177,223]. Neuropeptides, in contrast, exert their actions exclusively through signal transduction cascades [114,209]. Herbert [113] proposed the notion of a neurochemical code to describe the spatial and temporal dynamics of neuropeptide regulation in the brain. In this framework, one or more neuropeptides or steroid hormones act both independently and in concert to regulate complex behavioral outputs. These actions may be directed at a single target or involve multiple regions within a circuit, creating a "chemical coding system" that organizes adaptive behavioral responses to environmental (including social) challenges and opportunities. Herbert [113] already suggested that other neurochemicals, such as biogenic amines and steroid hormones, should be included in this model, as all these compounds can act on approach and avoidance behaviors [12,82,130,176,172,183,223].

In vertebrates, the decision to approach or avoid a stimulus can be modulated by neuropeptides, and these experiments are usually in the context of social stimuli rather than foraging (reviewed in [98]). For example, in male goldfish (*Carassius auratus*), social approach is modulated by arginine vasotocin (AVT), the non-mammalian homolog of arginine vasopressin (AVP), in that this nonapeptide inhibits social approach to another male, whereas an AVT receptor antagonist increases social approach in low-responding social fish [276]. Furthermore, injections of another nonapeptide, isotocin (the teleost homolog of mammalian oxytocin), also increases social approach in low-responding fish, showing that AVT and isotocin have opposite effects on male–male sociality in goldfish. Interestingly, a number of studies in other teleosts demonstrated that AVT treatment can stimulate courtship displays towards females [14,240,252], possibly suggesting opposing effects of this neuropeptide depending on the sex of the stimulus animal. These findings underscore the importance of studying neuropeptide modulation of approach/avoidance behavior in both challenge and opportunity contexts for a given species.

Although the modulation of neuropeptide regulation of approach avoidance may vary with social context, there is also variation in neuropeptide response between species (reviewed in [98]). Detailed insights into the molecular and genetic mechanisms of neuropeptide regulation of social approach and avoidance have mostly come from comparative studies of *Microtus* voles, the monogamous prairie vole, *Microtus ochrogaster*, and the polygamous montane vole, *Microtus montanus* (reviewed in [312]). Infusions of an oxytocin receptor antagonist into a female prairie vole before mating will block pair bond formation [132] while oxytocin infusions will enhance bond formation even in the absence of mating [300]. In males, injection of an AVP receptor antagonist decreased partner preference and AVP infusions facilitate partner preference, even in the absence of mating [303]. It is the genetically regulated spatial variation in AVP receptor and oxytocin receptor expression throughout the brain that facilitates the formation of pair bonds in prairie but not montane voles. This literature has been extensively reviewed elsewhere [24,133,167,210,312], although it should be noted that genome-scale studies are lacking thus far.

Lipid hormones can also influence approach behavior, although this relationship has been studied much less compared with the role of nonapeptides. One of the better known players is prostaglandin F2α (PGF2α), which in teleost fishes acts as an endogenous releaser of reproductive behavior in females and as an exogenous releaser in males. Specifically, PGF2α, which is released from ovarian tissues during final egg maturation, elicits the full repertoire of female reproductive behaviors even in non-gravid females treated with this hormone [44,254,262,289]. Additionally, gravid females release PGF into the surrounding water, where it acts as a pheromone to elicit courtship behavior in males [262]. Because most teleost fishes are broadcast spawners that require close coordination between males and females during spawning to ensure fertilization of the eggs, these actions of PGF2α are important for the synchronization of required approach behaviors of males and females during reproduction.

5.2. Regulation of approach and avoidance behavior by monoamines

The mechanistic analysis of approach and avoidance behaviors across a diverse set of species has clearly shown that, in addition to neuroendocrine modulators, the biogenic monoamines dopamine (DA) and serotonin (5-hydroxytryptamine, 5-HT) play a fundamental role. Specifically, 5-HT modulates escape (avoidance)

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behavior in many animals (mammals: [280]; teleosts: [101,295]; crayfish: [72,91,310]; sea slug: [138]). In vertebrates, 5HT is better known for its role in impulsivity and aggression [47,70,126,216].

Ever increasing evidence from diverse organisms ranging from worms to insects to vertebrates suggests that the evaluation of stimulus salience is regulated by catecholamines, particularly DA [7,22,158,197,264]. DA is an evolutionarily ancient biogenic amine that is found in most eukaryotes, where it is synthesized (along with norepinephrine and epinephrine, or octopamine in invertebrates) from tyrosine [36,159,304]. In many animals, DA plays an essential role as a neuromodulator in many behavioral processes, such as selection of motor programs, pair bonding, aggression, sexual behavior, and learning and memory [56,131,147,152,180,236,313].

Evidence for the role of monoamines in decision-making comes from extensive work on locomotion in the leech *Hirudo medicinalis* and the nematode *Caenorhabditis elegans*. Behavioral switching between two different locomotor patterns constitutes an important behavioral approach/avoidance choice that is critical for survival of these animals, and monoamines play an important role in this locomotor choice ([156,212,266, reviewed in [180]). DA not only activates crawling behavior in leeches, but also inhibits swimming behavior [51], which may be important for switching from searching to feeding behavior after finding a food source, whereas serotonin facilitates swimming behavior [87]. Similarly, DA also plays a role in nematode locomotion, as dopamine facilitates a behavioral switch from crawling to swimming [180]. 5-HT has also been implicated in promoting mate-searching behavior in male *C. elegans* [168], supporting a conserved role for monoamines in approach and avoidance behavior across large evolutionary distances.

It is becoming increasingly clear from work in insects that the role of DA in motivation is conserved beyond vertebrates. In *Drosophila*, for instance, DA action in the mushroom bodies (an association center of the insect brain) influences the decision to fly based on how the salience of visual cues is evaluated [314]. Pharmacological manipulation of DA receptors in both crickets and *Drosophila* also supports a role for this amine in encoding positive or negative valence when exposed to particular stimuli [152,286,291].

The complex social organization of honeybees has fascinated naturalists for centuries, and it is thus exciting that the molecular regulation of colony behavior is now becoming unraveled, as we already discussed the insights obtained from genomic analyses of honeybee behavior (see Section 3). In addition, several recent studies have provided evidence that catecholamines regulate behavioral motivation in this species as well. Beggs and co-workers have shown that pheromones released by the queen bee modulate behavioral circuits in workers by lowering DA levels, which in turn may serve to facilitate colony chores [17,18].

In vertebrates, DA plays a fundamental role in encoding the rewarding properties of a stimulus, or its valence [22,245–247]. In rodents, two model systems have jumpstarted our understanding of dopaminergic regulation of social behavior. First, work by Hull and colleagues in male rats, *Rattus norvegicus*, has elucidated the reinforcing properties of sexual experience, as DA is released into the preoptic area after sex (reviewed in [66,130]). Second, DA also reinforces pair bond formation in the monogamous prairie vole [53]. Given these important insights, it is thus not surprising that research into the role of DA in natural behaviors is now expanding to other vertebrates. In male songbirds, for example, DA plays an important role not only in song learning, but also in regulating context-appropriate song production in both challenge and opportunity contexts (reviewed in [158]). In reptiles, a few studies have implicated DA in reinforcing social behaviors: In male whiptail lizards, *Cnemidophorus inorantus*, sexual vigor is associated with the expression of tyrosine hydroxylase (TH; the enzyme that catalyzes the rate limiting step in catecholamine synthesis; often used as a marker of DA neurons) in the preoptic area [307]. In male leopard geckos, *Eublepharis macularius*, an opportunity to approach a female elicits a DA surge in the nucleus accumbens [62], suggesting that dopamine also plays a role in motivation or anticipation in reptiles. Unfortunately, at this point there is little evidence from amphibians or teleosts regarding the role of dopaminergic modulation of social behavior, but we predict that this will quickly become an avenue of interesting research that will lead to greater insights into the evolution of dopaminergic regulation of behavior in early vertebrates.

5.3. Importance of resolved molecular homologies

The study of the neurochemical and hormonal influences on behavior warrants a discussion of variation in the processing of neurochemical and molecular signals across vertebrates. Due to gene (or genome) duplication or gene loss and genetic divergence, a comparison of the gene products involved in these cascades of signal processing should be based on four criteria: (i) binding affinity of the receptor for the ligand; (ii) sequence similarity of the gene product; (iii) its tissue-specific expression patterns in the brain; and (iv) the nature of the signaling pathway. Not surprisingly, we find variation in all these variables, between vertebrates and invertebrates and, to a lesser extent, across vertebrate lineages as well, which offers an exciting opportunity to examine how this variation is related to life history, social system, and ecology of diverse species and their evolution. Although comparative studies looking specifically at the molecular evolution of neuroendocrine mechanisms regulating social behavior are lacking, a stimulating genome-scale study by McGary et al. [178] identified numerous protein-interaction networks that are highly conserved (orthologous) across eukaryotes (humans, mice, plants, worms, and yeast), even though the phenotypes they help generate may be diverged. The authors conclude that functional analyses of these orthologous protein networks (which they termed "phenologs") in one model system can thus provide important insights into the molecular underpinnings of seemingly unrelated phenotypic traits in other species [178]. We suggest that similar analyses should be conducted in the context of the neurochemical and molecular processes regulating social behavior. This would not only increase our understanding of the underlying neural and gene networks, but also allow us to determine whether for a given behavioral response these processes might indeed be conserved across organisms. For example ancient gene (or protein) networks may operate in diverse species in a multitude of behavioral contexts.

The neurochemical code, as proposed by Herbert [113], can only be understood within the context of complex spatial and temporal activation patterns in networks of dedicated brain nuclei. We therefore need to discuss the neural circuits that govern, for instance, reward processing and social behavior [58,195] within the integrative framework we are proposing in this review.

6. Neural circuits governing reward processing and social behavior

In most animals, coordinated neural circuits facilitate information processing into adaptive behavioral decisions. By studying behavior patterns within the context of neural circuits (rather than a single neuron or brain region), we can begin to understand the neural processing and integration of external environmental cues and internal physiological cues to produce the appropriate behavioral output. The study of relatively simple motor patterns and their underlying neural circuitry, like the Mauthner-cell mediated escape response in teleost fishes [75] or central pattern generators [142,173], provides an opportunity to understand how neural circuits act in concert to generate simple behaviors, and how much

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the circuit can vary from animal to animal while still maintaining function [102]. Similarly, orientating responses, such as phonotaxis in crickets and anurans [90,100,146], chemosensing in bacteria [208], and active sensing in bats and electric fish [191,222] have given us molecular or neural insights into how animals process information in the environment using highly specialized sensory mechanisms.

As far as the regulation of social decision-making in vertebrates is concerned, two neural circuits seem to be fundamental (Fig. 4): the mesolimbic reward system, with a central role for the connection between the dopaminergic ventral tegmental area (VTA) and the nucleus accumbens [58,297]; and the social behavior network [195], a collection of midbrain, hypothalamic and basal forebrain nuclei sensitive to sex steroid hormones and involved in sexual [13,110,123], aggressive [59,89,192], and parental behaviors [85,234]. Insights from birds and mammals have shown that regions involved in both the mesolimbic reward system and social behavior network are important in regulating naturally rewarding behaviors, such as sex [88,130,207], winning a fight [89], parental care [42], pair bonding in monogamous rodent species [313] and bird song and sociality [94,97,111,229]. Here we briefly discuss the progress made in understanding these circuits in vertebrates, although the studies published thus far typically focus on manipulating only one or two brain regions within a circuit. As deep sequencing technologies become less costly, it is our expectation that it will become feasible to profile the transcriptomes of several brain regions within a single individual to better understand how shifts in network gene expression influence behavior.

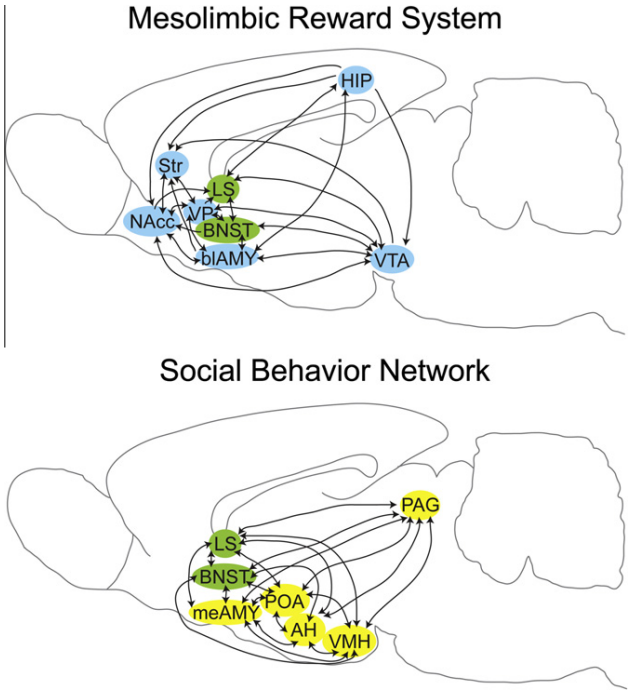

Fig. 4. A neural circuit framework. schematic representations of a mammalian brain are shown with brain regions of the mesolimbic reward system (blue; top panel) and social behavior network (yellow; bottom panel). Regions shared by both circuits are labeled in green. Adapted from O'Connell and Hofmann, submitted. Arrows indicated directionality of functional connections between brain regions. Abbreviations: AH: anterior hypothalamus; blAMY: basolateral amygdala; BNST: bed nucleus of the stria terminalis; HIP: hippocampus; LS: lateral septum; meAMY: medial amygdala; NAcc: nucleus accumbens; PAG/CG: periaquaductal gray/central gray; POA: preoptic area; STR: Striatum; VMH: ventromedial hypothalamus; VP: ventral pallidum; VTA: ventral tegmental area. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

6.1. The mesolimbic reward system

Animals must assess the relative value and consequence of an external stimulus in order to generate an adaptive response. 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 [58,297]. This circuit is characterized by massive dopaminergic projections from the VTA to the nucleus accumbens. Most depictions of the reward system also include the lateral septum, ventral pallidum, striatum, basolateral amygdala, the bed nucleus of the stria terminalis, and the hippocampus. Due to its biomedical relevance in the context of addiction and depression, it is not surprising that the mesolimbic DA system is best studied in mammals [150,170,275]. These well-studied addiction disorders are deleterious manipulations of a network that encodes the potential value and positive reinforcement effects of behavior [54,55,198].

As the functional contexts in which animals behave (i.e., male–male aggression, mate choice, foraging, etc.) are functionally equivalent across diverse species, it is reasonable to hypothesize that the reinforcing role of the mesolimbic dopamine system is conserved across vertebrates. Although no functional genomics studies have examined the reward system in non-traditional model systems with complex social behaviors, many studies have implicated the VTA in evaluating the salience of a stimulus, as well as reinforcing the production of rewarding naturalistic behaviors. Perhaps the best known example for involvement of the mesolimbic reward system in reinforcing naturalistic behaviors comes from the *Microtus* voles and pair bonding (reviewed in [311,313]). The strength of this system lies in the comparative work between two mating systems, and should encourage comparative studies for other social systems in order to increase our understanding not only of the molecular mechanisms underlying complex behaviors but also how these complex behaviors have evolved. As more genomic resources become available, we will be able to better understand not only the transcriptome changes associated with pair bonding, but also parental care and aggression [179].

The role of the mesolimbic reward system is particularly apparent in song production in many species of songbirds [64]; for a recent review see 158]. VTA neurons are more active during courtship singing than during undirected (non-courtship) singing [108,127]. Immunoreactivity for TH in the VTA is also context-dependent, as higher immunoreactivity is associated with courtship calls and not with undirected calls [111]. Further, ablation of dopaminergic neurons in the VTA results in a deficit in female-directed song, but not undirected song [108]. Given the evidence that the reward system plays a role in male song production in specific social contexts, it is surprising that no work has been done thus far in female birds exposed to attractive calls compared to undirected calls, but we predict that this will be a fruitful avenue of research.

Insights into the contribution of the VTA to reproductive decision-making in females has come from studies on anuran mate choice, in which females display phonotaxis (approach) behavior to attractive calls [235]. Lesions of dopaminergic neurons in the putative VTA homolog of the anuran brain disrupt female phonotaxis behavior such that its expression is correlated with the number of TH-neurons remaining in this region [73]. Studies that quantified induction of the immediate early gene *egr-1* as a marker for neuronal activation have also strengthened our knowledge of VTA-like neurons mediating mate choice in anurans. Specifically, female túngara frogs exposed to male conspecific calls exhibited strong induction of *egr-1* in the VTA [123], suggesting that a cellular response in this region contributes to female decision-making in anurans.

Research in female rodents has further expanded our understanding of the cellular and genomic processes involved in

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mediating the rewarding neural response to sexual behavior in multiple forebrain regions. Female sexual experience produces changes in neuronal activity within the nucleus accumbens and dorsal striatum [16,26,136], similar to drug use [34,211]. Using transcriptome analysis, Bradley and colleagues [25] found that prior sexual experience in female hamsters altered distinct gene sets within the nucleus accumbens and dorsal striatum including ion channels, transcription factors, neurotransmitter receptors, and genes involved in signal transduction. Sexual experience was administered by placing a male in the female's home cage once a week for six weeks. Experienced females that had sex on the final test day had a dramatic genomic response, with increased expression of many genes in these basal ganglia regions compared to sexually naive animals that had sex on the final test day. In contrast, sexually experienced females that did not have sex on the final test day showed a dramatic decrease in gene expression compared to sexually naïve females that also did not have sex on the final test day. This study not only demonstrated that in the reward system certain gene sets are regulated by sexual experience, but that anticipation of a sexual encounter in sexually experienced females that were (against expectation) not exposed to a male on the final test day led to a depression of gene expression in the nucleus accumbens and dorsal striatum, similar to the anticipation of a food or drug reward in trained animals [194]. These results underscore the notion that genomic responses underlying natural behaviors are inherently rewarding at the molecular level.

An individual's ability to adapt to chronic social stress is also mediated by the mesolimbic reward system [76]. There is surprising individual variation in this response even within inbred c57bl/6 mice, as some individuals will be highly susceptible to social defeat by displaying long-lasting social avoidance behavior while others will be resilient [23]. Transcriptional profiling revealed that key adaptive changes in the VTA underlie an individual's propensity for reliance or susceptibility to social defeat. Krishnan and colleagues [155] showed that there is an adaptive transcriptional response in resilient mice that results in an up-regulation of potassium channels in the VTA, thus altering the excitability of VTA neurons and an associated release of brain-derived neurotrophic factor (BDNF) into the nucleus accumbens. These groundbreaking studies have taught us that there can be dynamic changes in genome activity even in the absence of a behavioral response (e.g., resilience to social defeat). In fact, it is the mice that display social avoidance after social defeat that do not mount a genomic response to chronic stress. In a similar study, mice with chronic social stress (exposure to highly aggressive dominant male) down-regulated several genes in the hippocampus, including many transcription factors and ion channels as well as some gene products involved in metabolism and the cell cycle [77]. This body of work also highlights the importance of profiling the transcriptome in several brain regions in order to better understand how interconnected brain regions contribute to approach/avoidance behaviors. We predict that, as genomic technologies become more available, there will be more transcriptome studies looking at the contribution of the mesolimbic reward system to natural social behavior.

6.2. The social behavior network

Newman [195] presented a useful framework encompassing six brain regions implicated in the regulation of social behavior in mammals. The nodes of this "social behavior network" – lateral septum, extended medial amygdala (i.e., medial amygdala and bed nucleus of the stria terminalis), preoptic area, anterior hypothalamus, ventromedial hypothalamus, and periaqueductal gray/central gray – are all reciprocally connected [45,46,227] and express sex steroid receptors [187,256]. Although originally proposed for mammals, Crews [48] and Goodson [94] soon applied this framework to other vertebrate lineages. In reptiles, data from leopard geckos suggest that behavioral variation due to egg temperature incubation is correlated with the functional connectivity within this network [238,239], whereas studies in the plainfin midshipman fish, *Porichthys notatus*, which displays characteristic acoustic patterns based on social context and phenotype, have shown that at least some of these nodes are present in fish and modulate the vocal-acoustic circuitry [96]. Finally, this network has also been extended to birds where it plays a role in mediating sociality across species (reviewed by [94]). Taken together, there are multiple lines of evidence that this network was already in place in early vertebrates.

Surprisingly, there are no genomic studies within naturally (not hormonally manipulated) behaving animals investigating the genomic response of brain regions within the social behavior network to social behavior stimuli, although as sequencing technologies become cheaper and more readily available to non-traditional model systems, we predict that this will become an area of intense research.

Already, researchers have begun to analyze the potentially important effects of epigenetic modifications on brain function and behavior [145,315]. For example, a recent study by Gregg et al. [104] used next-gen sequencing to examine the epigenome in one hypothalamic node of the social behavior network, the POA, as well as several brain regions regulating motivation, such as the VTA and the nucleus accumbens. The authors found that in the adult POA there are significantly more genes expressed from the paternal, compared with the maternal, genome, although the behavioral consequences of this parent-of-origin bias in expression still need to be examined in detail. However, we already know from studies by Meaney and colleagues [141,294] that experience-dependent epigenetic reprogramming of single genes, such as the glucocorticoid receptor in the hippocampus, can result in significant differences in adult stress reactivity and maternal behavior of rodents. These studies highlight the growing appreciation of epigenetic effects that can lead to variation in social behavior [49,50,69,293]. Given the advances in sequencing technology, this area of research will soon greatly benefit from comparative analyses.

6.3. Importance of resolved brain homologies

Understanding the evolution of the neural substrates that underlie social behaviors across vertebrates ultimately depends on establishing reliable homology relationships for the brain regions in question [200,272]. Determining homologies across all major vertebrate lineages has been especially challenging, as brain architecture is remarkably diverse [271]. However, comparative neuroanatomists have made great strides towards increasing our understanding of brain evolution, homology, and neurochemistry [30,84,198,199,258]. Homologies have been inferred for many of the fore- and midbrain regions discussed in this review based on a number of criteria, including topography, hodology, development, neurochemical profiles, and functional lesion and stimulation studies. A recent survey by the authors [200] determined that most of the homologs to the mammalian brain regions that are part of the mesolimbic reward system and/or the social behavior network can be identified with some confidence across the major vertebrate classes, including mammals, birds, reptiles, amphibians, and teleosts. Yet despite this progress, the information available covers only a handful of species in each lineage and no systematic surveys have been conducted to include closely related species with diverse social systems. Many of the interesting questions addressing the neural evolution of social behavior are best addressed in clades that have diverged mating systems or sociality, such as *Microtus* voles, estrilid finches, and cichlid fishes

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[99,210,214,273]. These comparative systems have increased our understanding of how small changes in gene expression or brain development can lead to such striking variation in social behavior.

7. The evolution of neuroethological systems

We have reviewed here four conceptual areas that form the foundation for an integrative analysis of the neural and developmental mechanisms and evolution of adaptive social behavior, as envisioned almost half a century ago by Tinbergen [278]. Due to the remarkable conceptual advances brought about by behavioral ecologists, neuroethologists, behavioral neuroendocrinologists, comparative neuroanatomists, and developmental biologists, and because of the astonishing technological progress in such diverse areas as neurochemistry, molecular biology, and genomics, we are finally in a position where we can fulfill Tinbergen's vision.

We have presented here evidence that all animals have similar behavior responses to challenges and opportunities in their environment. There is a striking genomic response to these situations and similar molecules (monoamines and neuroendocrine chemicals) play a role in evaluating the environment and modulating the behavioral output. These observations raise some fundamental questions about the evolution of behavior: Were any conserved molecular processes underlying these behavioral responses assembled from a "genetic toolbox", such that orthologous building blocks are repeatedly recruited independently in various lineages, as appears to have been the case with PAX6 in eye development? Or are these processes the product of an evolutionary ancient system to respond to challenges and opportunities an individual encounters by utilizing a conserved mechanism? It may well be that the answer will depend on the phylogenetic level of analysis, such as whether one analyzes species within a specific monophyletic clade or across all vertebrates. Recent insights into the evolutionary origins and biochemical mechanisms of bioluminescence are illuminating in this context [298]. Luminescent behavior appears to have evolved independently at least 40 times, yet the process often involves similar enzymes and substrates in light-producing reactions, possibly because, as species began to conquer deeper waters, a reduction in light-induced oxidative stress shifted the selection pressure from the antioxidative to the chemiluminescent properties of the substrate molecule [298]. There might thus indeed be evolutionary mechanisms that result in the convergent recruitment of ancient and conserved molecular pathways, which, for instance, underlie the approach of mates or avoidance of predators.

Research in yeast suggests that responses to challenges and opportunities could indeed governed by ancient molecular mechanisms. Stern and colleagues [269] presented yeast with a severe food resource challenge, which they had never encountered in their evolutionary history, to which they adapted over approximately ten generations. This exceptionally fast adaptation was accompanied by a global transcriptional reprogramming of over 1000 genes. Further, only a few of the responding genes were similar when the experiment was reproduced, suggesting that this was largely a non-specific genomic response to novel challenge, as the overlapping genes had no significant functional similarity (according to the gene ontology framework). The authors concluded that the transcriptional response to a novel challenge is largely plastic, which is crucial for responding to broad and unexpected environmental challenges for which the genome cannot possibly have been pre-adapted in the course of evolution. In the context of our discussion here, however, this study also suggests, since similar molecular cascades are utilized in the social behavior of many animals, that these responses were in fact "written" into our genomes early on in our evolutionary history.

Systems biology has brought two hypotheses forward with which we can explain the evolution of social behavior: developmental system drift and phenologs (Fig. 5). The notion of developmental systems drift, which emphasizes the plasticity of developing systems in response to selection, states that even when developmental pathways diverge through time, there may be no accompanying change in the resulting phenotype [285]. In the context of social behavior this can mean that behavioral responses or brain regions that regulate behavior can be homologous even though their morphological substrates or developmental origins are not homologous [272]. A well-understood example is that of sex determination, as sex can be determined by chromosome dosage, sex-determining genes, or environmental factors such as temperature [93,213,225,237,253]. These very different underlying mechanisms give rise to males and females with sex-typical

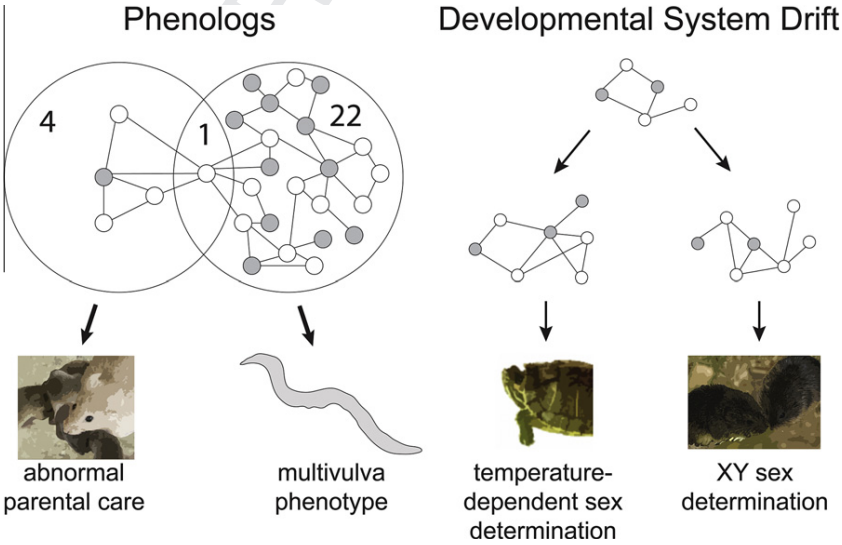

Fig. 5. Alternative hypotheses for the evolution of neuroethological mechanisms. The phenolog hypothesis predicts that some gene/protein-interaction networks underlying social behavior and other complex phenotypes can be conserved across animals, even if the phenotypes are completely different. The developmental system drift hypothesis states that the molecular mechanisms underlying homologous phenotypes can diverge substantially during the course of evolution. Nodes and edges represent gene networks involved in a phenotype.

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behaviors. In contrast, the phenolog hypothesis (discussed in Section 2) suggests that there can also be conserved gene networks associated with orthologous phenotypes [178]. A behavioral example for a phenolog is the gene network underlying abnormal parental care in mice, where an "orthologous" gene network leads to the multivulva phenotype in worms (phenologs.org). These two seemingly opposing ideas are not mutually exclusive, and can both be acting to shape different behavioral phenotypes across populations or species, where one functionally equivalent behavioral phenotype across vertebrates may have very different underlying mechanisms where as two different behavioral phenotypes in different vertebrates may indeed have the same underlying mechanism.

8. Conclusion

Genomics is inherently a comparative science, as any genome is impossible to interpret without comparisons to other genomes in an effort to find protein coding regions and genetic changes that may covary with life history strategies. In the same way, the search for the molecular basis and evolution of social behavior is also a comparative task, and much work is needed to better understand putative molecular and genomic universals underlying social decisions in animals. This is particularly true for non-mammalian vertebrates as well as invertebrates, as information on how the brain regulates behavior in these groups is still relatively sparse. As information on how the neural and genomic substrates of behavior across a diverse array of animals becomes available, we will be able to determine if there are indeed molecular universals underlying the diverse behaviors that we see on our planet.

9. Uncited references

Q3 [105,228,233].

Acknowledgments

We thank Peter Dijkstra, Matthew Fuxjager, Karen Maruska, Deena Walker, and Keith Whitaker for critically reading earlier versions of the manuscript, members of the Hofmann Laboratory and the Sociogenomics Initiative for discussion of some of the issues presented here, and three anonymous reviewers for insightful suggestions on further improving this manuscript. LAO is supported by NSF DDIG 1011253; HAH is supported by NSF Grants IOS 0843712 and IOS 0751311, the Alfred P. Sloan Foundation, and a Dwight W. and Blanche Faye Reeder Centennial Fellowship in Systematic and Evolutionary Biology.

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Please cite this article in press as: L.A. O'Connell, H.A. Hofmann, Genes, hormones, and circuits: An integrative approach to study the evolution of social behavior, Front. Neuroendocrinol. (2010), doi:10.1016/j.yfrne.2010.12.004

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