Evolutionary themes in the neurobiology of social cognition
Chelsea A Weitekamp¹ and Hans A Hofmann¹,²

Remarkable examples of social cognition have been described across a diverse range of species, yet surprisingly little is known about the neurobiological underpinnings of these behaviors. Recent studies suggest that the molecular pathways and neural networks that mediate social behavior have been relatively conserved across vertebrate evolution, suggesting that shared mechanisms may drive adaptive behavioral responses to social stimuli. Here, we review recent advances in the neurobiology of flexible and context-dependent social behaviors across vertebrate taxa, focusing on female mate choice, pair-bonding, and aggressive behavior. Furthermore, we highlight the outstanding opportunities for uncovering the mechanisms mediating cooperative behavior, an exemplar of social cognition. We suggest a framework for investigating context-dependent neural organization and the evoked neural response to social stimuli.

Addresses
¹Department of Integrative Biology, The University of Texas at Austin, USA
²Institute for Cellular & Molecular Biology, Institute for Neuroscience, The University of Texas at Austin, USA

Corresponding author: Hofmann, Hans A (hans@utexas.edu)

Current Opinion in Neurobiology 2014, 28:22–27
This review comes from a themed issue on Communication and language
Edited by Michael Brainard and Tecumseh Fitch
http://dx.doi.org/10.1016/j.conb.2014.06.005
0959-4388/© 2014 Published by Elsevier Ltd. All rights reserved.

Introduction
Members of social groups integrate in real-time the behavior of their social partners with memory of past interactions and predictions of future behavior in order to respond in a context-appropriate manner. It is thus not surprising that social behavior (such as aggressive, sexual, and parental behavior) is influenced by a variety of factors, including previous experience and the current social environment [1]. The expression of such behavioral flexibility has important fitness consequences for an individual [2]. In fact, evidence for sophisticated social cognitive abilities has been accumulating across diverse taxa and behavioral contexts. Complex social cognitive abilities are thus no longer considered to be limited to human and non-human primates. Rather, we are beginning to appreciate that most social animals have evolved cognitive mechanisms for assessing, evaluating, and responding flexibly to a wide variety of often subtle yet vital social cues [3–5]. For example, in many species females prefer males that are in the presence of other females, suggesting that such mate choice copying relies on the assessment of a male’s quality by other females [6]. An audience can strongly affect an individual’s response to social information more generally (e.g., [7]). For example, subordinate males of the cichlid fish Astatotilapia burtoni increase aggressive displays when the dominant community members are not paying attention [8]. Even more remarkably, these fish can use known relationships to deduce unknown ones to infer the social rank of other individuals transitively (e.g., using A > B and B > C to infer A > C; [9]). While great strides have been made in identifying a diversity of behaviors involving social cognition, little remains known about the neuromolecular basis of these behaviors. Given the recent advances in high-throughput approaches and our increased understanding of neural circuit evolution, there are now unprecedented opportunities to identify the neural and molecular mechanisms mediating social decision-making and cognition [10].

Spontaneous activity and recurrent connections between brain areas give rise to coordinated global network states, which affect neural processing as stimuli are incorporated into existing neural representations [11]. These patterns represent a baseline neural state of activity, which can be shifted at the level of single neurons as well as larger neural units by social experience and learning, as well as by genotype and life history factors [12]. Changes to this baseline can be encoded by modifications to the epigenome, hormone levels, functional connectivity between brain regions, as well as to gene expression networks. Plasticity in the perception of and response to a social stimulus is largely dependent on the structure of this baseline state. The stimulus-evoked neural response, as measured in terms of immediate neural activity, gene expression, and receptor–ligand binding, can then differ even in response to identical social stimuli. In Figure 1, we offer a framework integrating these concepts.

Here, we review recent research on three forms of social interactions that best highlight the remarkable advances that have been made in the neurobiology of social cognition, particularly in non-traditional, non-primate model
systems (the neurobiology of primate social cognition has recently been reviewed elsewhere [13,14]). Mate preference behavior, pair-bonding, and aggressive behavior are each composed of a variety of social cognitive core elements, such as individual and/or social recognition, partner preference and/or avoidance, and advanced learning and memory. Importantly, each behavior has the potential to be highly plastic and can be shaped by social context and experience. In addition to the advances made in studying these behaviors, we also outline, in Box 1, the outstanding opportunities for gaining functional insight into the mechanisms underlying cooperative behavior. We consider strategic cooperative behavior, and alternatively cheating or deception, to epitomize the elements of social cognition. Cooperation between members of a social group and even between heterospecific individuals has evolved repeatedly in numerous lineages of vertebrates and invertebrates [15]. Even though the factors that favor the evolution of cooperative behavior and its fitness benefits are well understood, the underlying neuromolecular mechanisms are largely unknown.

Conserved neural pathways

Although specific behavioral outputs vary widely among species, the biological functions and metabolic needs that drive these behaviors are deeply shared [10]. Also, the principles of brain development and organization are highly conserved across vertebrates [16,17]. Moreover, all systems subserving social behavior are keenly sensitive and responsive to social inputs, which are perceived and transduced by one or more sensory pathways. These neural signals, in turn, are processed and integrated in specific regions of the brain through various neuromodulatory systems such as steroid hormones, neuropeptides, and monoamines [10,18,19], which ultimately lead to adaptive behavior. Insights from mammals suggest two neural circuits of crucial importance in this context: the Social Behavior Network (SBN) [20,21] and the mesolimbic Reward System [22], which together form a larger Social Decision-Making (SDM) Network [23*,24*]. The nodes of this circuitry interact to integrate environmental and physiological cues and encode stimulus salience and valence to generate adaptive behavioral responses.

The Social Behavior Network and the Reward System were first described in mammals. Thus, in order to apply this framework to non-mammalian model systems we need to resolve homology for the relevant brain regions across a wide range of taxa (for the SBN, see [21]). O’Connell and Hofmann [23**] recently inferred homology relationships across taxa for the entire SDM Network. Although some of these homologies remain tentative [25], this work provided for the first time a comprehensive comparative synthesis of this circuitry, suggesting that it was already present in early vertebrates [23**]. In fact, the SDM Network is remarkably conserved across vertebrates not only in terms of neuroanatomy but also with regards to candidate gene expression patterns. In an additional study, O’Connell and Hofmann [24**] analyzed expression profiles for 10 neurochemical
colors across the 12 SDM Network nodes in 88 vertebrate species and found that gene expression patterns are highly conserved in this network 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. 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 differ greatly and have evolved independently.

Mate preference

Female mate preference is critical not only for maximizing fitness, but can also shape the evolution of male characters and can serve as a mechanism for species divergence [26,27]. In most mating systems, females must perceive, integrate, and evaluate signals from multiple males before choosing whether or not to mate with a given male. Furthermore, learning and plasticity can play important roles in mate choice [27]. Recent studies have shown teleost fishes, in particular, to be a powerful system in which to identify the neural mechanisms underlying female choice [28]. Wong et al. [29] examined expression of egr-1 and neuroserpin, genes previously implicated in mate preference behavior [30], across SDM Network nodes in female Xiphophorus nigrensis, the Northern swordtail. Using a dichotomous choice paradigm, they identified relationships between the degree of preference for the larger of two males and gene expression in regions associated with reward, sensory processing, and sexual behavior, providing further evidence that female mate preference involves complex, coordinated neural activity. A related study that included additional social conditions in the dichotomous paradigm examined the relationship between whole brain gene expression and preference behavior in X. nigrensis. The mate choice environment influenced an assemblage of genes associated with preference (e.g., neuroserpin, neurologin-3) whereas variation in affiliative behaviors was associated with genes that mediate social bonding (e.g. isococin and vasotocin) [31]. Interestingly, while neuroserpin and neurologin-3 expression was positively associated with female preference behavior in X. nigrensis, expression levels of the same genes tended to be negatively associated with preference in a species in which males exhibit coercive mating tactics, Gambusia affinis, the Western mosquito-fish [32].

Familiarity with males affects female choice in a number of species [27]. Okuyama et al. [33**] examined this phenomenon in medaka fish and found that visual familiarity with males enhances female preference. They identified mutant strains in which females did not exhibit preference behavior and found that preference was inhibited by abnormal development of terminal-nerve (TN)-gonadotropin releasing hormone 3 (GnRH3) neurons, which function to suppress female receptivity. Using additional mutant lines, ablation, and single neuron electrophysiology, the authors demonstrated that GnRH3 peptide released from TN neurons is necessary for the switch from suppressed receptivity to preference behavior. They also showed that GnRH3 peptides facilitate the pacemaker frequencies of TN-GnRH neurons, which may be involved in mediating preference for familiar males. This study represents one of the most compelling advances toward a complete understanding of the neural mechanisms underlying various forms of social cognition. There is ample opportunity in other model systems of mate preference for studies of similar depth and precision (reviewed in birds: [34]).
Pair-bonding
The neurobiology of pair-bonding has been studied most extensively in the monogamous prairie vole, Microtus ochrogaster [35]. The dynamics of the pair-bond can be surprisingly plastic, and are affected, for example, by the early-life social environment and can also differ between populations and mating strategies [36]. Pair-bond formation involves a variety of neurotransmitter pathways, most notably oxytocin (OT), vasopressin (AVP), and dopamine (DA). In a recent study, Wang et al. [37**] demonstrated epigenetic regulation of partner preference formation in female M. ochrogaster. Treatment with histone deacetylase inhibitors facilitated partner preference formation in the absence of mating by up-regulating OT and AVP receptors (OTR, V1aR) in the nucleus accumbens. Additionally, females exhibiting natural mating-induced preference had higher acetylation at the promoters of the OT and V1a receptors in the nucleus accumbens, likely leading to the observed increase in mRNA and protein levels of the receptors.

Pair-bonding has evolved independently numerous times in both vertebrates and invertebrates [4]. As such, there is a great opportunity to examine the extent to which the neurobiological mechanisms regulating pair-bond formation and maintenance are conserved across species. Pair-bond formation in the monogamous zebra finch, Taeniopygia guttata, was inhibited by intracerebroventricular administration of an OTR antagonist in females, with males following a similar trend [38]. Interestingly, a previous study found that systemic injections of OTR antagonist also reduced courtship behavior [39], suggesting the presence of sub-systems underlying different functions. Dopamine (DA) was also recently implicated in pair-bonding in zebra finches. Banerjee et al. [40*] report higher levels of DA and its metabolite in a portion of the brain encompassing the nucleus accumbens in newly pair-bonded zebra finches. Similarly, using c-Fos immunohistochemistry, they show that the proportion of active dopaminergic neurons is higher in the ventral tegmental area of pair-bonded birds. These results in zebra finches are similar to the mechanisms identified in prairie voles and are important first steps toward identifying conserved neural circuits.

Aggressive behavior
Aggressive behavior is often modulated by a variety of factors, including physical state, social status, previous fighting experience, resource quality, and the type of audience present, among others [5]. The neural pathways through which each of these factors influence the expression of aggressive behavior is an active area of research. An impressive array of signaling molecules have been implicated in aggression [41]. For example, a recent study by Coura et al. (2013) examined how the cholinergic, dopaminergic, and norepinephrine systems interact in regulating aggression and flexible social cognition [42]. Specifically, depletion of norepinephrine in the prefrontal cortex (PFC) of mice reduced behavioral flexibility and increased aggression in a social interaction task, an effect that was absent in mice lacking a specific subunit (B2) of the nicotinic acetylcholine receptor [42]. In the PFC, basal levels of monoamines and acetylcholine were also higher in the mutant strain [42].

Measures of circulating levels of hormones are not always consistent predictors of levels of aggression. Using free-living male and female dark-eyed juncos, Junco hyemalis, Rosvall et al. [43] examined variation in levels of circulating testosterone and gene expression of androgen receptor, estrogen receptor alpha, and aromatase in response to a simulated territorial intrusion. They found that gene expression levels in behavior-relevant brain regions relate to individual measures of aggressive behavior in both males and females, whereas testosterone levels related to aggression only in males. These results provide support for the hypothesis that sensitivity to sex steroids is an important mechanism by which selection may act to influence aggression, and likely plays a similar role in other forms of social cognition. Further support for the specific role of aromatase in the regulation of aggressive behavior comes from a recent study in the African cichlid fish, Astatotilapia burtoni. Socially subordinate males had higher levels of aromatase expression than dominant males in the preoptic area, a neuroendocrine relay station in the vertebrate brain [44]. Interestingly, pharmacologically blocking aromatase in dominant males decreased aggressive behavior and circulating estradiol, but increased circulating testosterone levels [44].

Future directions
As more high-throughput technologies and sophisticated modeling approaches become available, we expect the distinction between model and non-model systems to dissolve. As such, species can begin to be selected for neurobiological studies based on their unique social cognitive abilities and studied in interacting individuals within both free-living and captive populations. Bobry et al. [45**] provides a compelling example, applying novel technologies to social cognition by demonstrating the neural correlates of social facial touch in interacting rats, using extracellular recordings in the barrel cortex. Applying similar techniques to investigate flexibility in social behavior can greatly advance our understanding of the mechanisms regulating social cognition.

We outlined a framework for studying the neurobiology of social cognition, in Figure 1, with hopes that future research will continue to dissociate the contributions of each of these mechanistic levels to the factors mediating social cognition. Within this framework, a thorough understanding of the neurobiology of social cognition will require an integrative approach that tests (1) how animals behave in response to subtle social cues; (2) how
assessment of and response to social stimuli affect the activity of the underlying neural networks; (3) how the neuromolecular states of these networks regulate motor and hormonal outputs; and (4) how candidate neurochemical pathways mediate genomic, neural, and behavioral responses.

Conflict of interest statement
Nothing declared.

Acknowledgements
We thank Bridget Nugent and Bret Pasch for helpful comments on earlier versions of this manuscript. This work was supported by NSF Graduate Research Fellowship to CAW and NSF IOS-0843712 and IOS-1354942 to HAH.

References and recommended reading
Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest


In this important paper, the authors surveyed a broad literature across vertebrates and inferred homology relationships for the social decision-making network, comprised of twelve forebrain and midbrain regions implicated in regulating social behavior. This work provides a foundation for understanding the evolution of neural mechanisms underlying reward processing and behavioral regulation.


The authors analyzed expression profiles for ten social behavior-relevant genes across brain regions in the social decision-making network for five vertebrate lineages and report remarkable conservation across vertebrate evolution. They also provide evidence that neuroendocrine ligands are evolutionarily more labile than their receptors.


Female preference for visually familiar males is mediated by GnRH3 peptides synthesized in terminal-nerve GnRH3 neurons. This innovative study applied current technologies to address the mechanisms regulating a type of social cognition that can be placed within a relevant evolutionary framework.


37. Wang H, Duclot F, Liu Y, Wang Z, Kabbaj M: Histone deacetylase inhibitors facilitate partner preference formation in female prairie voles. Nat Neurosci 2013, 16:919-924. Treatment with histone deacetylase inhibitors facilitates partner preference formation in female prairie voles through increased expression of oxytocin receptor and vasopressin V1a receptor in the nucleus accumbens. This study is one of the first to investigate the role of epigenetic modifications in social cognition.


40. Banerjee SB, Dias BG, Creeds D, Adkins Regan E: Newly paired zebra finches have higher dopamine levels and immediate early gene Fos expression in dopaminergic neurons. Eur J Neurosci 2013 http://dx.doi.org/10.1111/ejn.12378. This study showed both higher levels of dopamine in the ventral medial striatum and a higher percentage of Fos labeled dopaminergic neurons in the ventral tegmental area of newly paired zebra finches. This result is important as it reflects the patterns of pair-bond formation in rodents and suggests conserved neural mechanisms.


42. Coura RS, Cressant A, Xia J, de Chaumont F, Olivo-Marín JC, Pelloux Y, Dalley JW, Granon S: Nonaggressive and adapted social cognition is controlled by the interplay between noradrenergic and nicotinic receptor mechanisms in the prefrontal cortex. FASEB J 2013, 27:4343-4354.


45. Bobrov E, Wolfe J, Rao RP, Brecht M: The representation of social facial touch in rat barrel cortex. Curr Biol 2014, 24:109-115. Using extracellular recordings in the posteromedial barrel subfield of primary somatosensory cortex in rats, the authors showed that social facial touch elicits distinct firing rates which differ between sexes and with sexual status. This study is unique in its application of a neurobiological model system to address social interactions.


