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Evolutionary diversity as a catalyst for biological discovery

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Abstract

The tremendous diversity of animal behaviors has inspired generations of scientists from an array of biological disciplines. To complement investigations of ecological and evolutionary factors contributing to behavioral evolution, modern computational, genetics, genomics, and neuroscience tools now provide a means to discover the proximate mechanisms upon which natural selection acts to generate behavioral diversity. Social behaviors are motivated behaviors that can differ tremendously between closely related species, suggesting phylogenetic plasticity in their underlying biological mechanisms. Additionally, convergent evolution has repeatedly given rise to similar forms of social behavior and mating systems in distantly related species. Social behavioral divergence and convergence provides an entry point for understanding the neurogenetic mechanisms contributing to behavioral diversity. We argue that the greatest strides in understanding social behavioral diversity will be achieved through integration of interdisciplinary comparative approaches with modern tools in diverse species systems. We review recent advances and future potential for discovering mechanisms underlying social behavioral variation, highlighting patterns of social behavioral evolution, oxytocin and vasopressin neuropeptide systems, genetic/transcriptional "toolkits," modern techniques, and alternative species systems, with particular emphasis on *Microtine* rodents and Lake Malawi cichlid fishes.

Keywords

social behavior; oxytocin and vasopressin; toolkits; voles; cichlids

Introduction

Animal behavior has been of great interest to integrative zoologists and ethologists for many decades, and its scientific investigation led to the 1973 Nobel Prize in Physiology or Medicine being jointly awarded to Karl von Frisch, Konrad Lorenz and Nikolaas Tinbergen. This research tradition has not only aimed to discover biological mechanisms contributing to behavioral diversity, but also to understand the degree of variation and generalizability of

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these mechanisms within and across species. Interest in animal behavior has continued to grow as biomedical researchers have aimed to understand the biological basis of human behavior and cognition through animal models. In pursuit of this aim, behavioral genetics and neuroscience research has grown increasingly focused on a narrow range of model species. Here we argue that, with regards to social behavior in particular, the limitations of such strategies are amplified; and that such strategies will, by default, be unable to access a diverse array of gene regulatory and neural circuit mechanisms contributing to natural social behavioral variation. Instead we argue that a synthesis of comparative perspectives with modern neuroscience, genetics, genomics, and computational tools in alternative species systems will be necessary to discover the fundamental biological mechanisms and organizing principles underlying social behavioral diversity.

Social behavior as an integrative phenotype

Selective pressure to adaptively transmit, receive, and respond to signals with conspecifics has led to the evolution of complex social behaviors in diverse species spanning microbes and humans (Crespi; West et al, 2007). Social behaviors have long been recognized as fundamentally integrative phenotypes that emerge as functions of evolutionary history; external factors such as abiotic environment, resource distribution, population density, and behaviors or cues from other individuals; and internal biological factors including genetic composition and expression, developmental stage, experience, epigenetic modification, sex, hormonal state, and neurogenetic architecture (Nescent Working Group on Integrative Models of Vertebrate Sociality: Evolution et al, 2014). Interactions among these factors have profound effects on social behavioral variation across multiple levels of biological organization—spanning individuals, populations, and species—and a high degree of variation in any one or a combination of these factors frequently exists at these levels. The labile, variable, and combinatorial nature of these factors establish the potential for diverse gene regulatory and neurogenetic mechanisms to drive patterns of natural social behavioral variation in individuals, populations, and species.

Patterns of social behavioral variation in nature

Convergent evolution of social behaviors

Convergent evolution of integrative traits pervades the evolutionary history of life on Earth, including many examples of independently evolved and rare social behaviors. Several mating and parental systems—e.g. socially monogamous mating systems and biparental care—have repeatedly and independently evolved in invertebrates and every major vertebrate lineage (Bull, 2000; Burley & Johnson, 2002; French et al, 2017; Johnson & Young, 2015; Reynolds et al, 2002; Roland & O’Connell, 2015; Suzuki, 2013; Whiteman & Cote, 2004). Vocal learning, or the acquisition of learned vocalizations through imitation, has independently evolved in several avian and mammalian lineages, including humans (Jarvis, 2007). Mating systems in which males congregate into leks and construct elaborate courtship “bowers” have evolved in bowerbirds (Ptilonorhynchidae) and cichlid (Cichlidae) fishes (Kusmierski et al, 1997; York et al, 2015). The capacity for empathy-like consoling behavior has evolved in corvids (Corvidae), rodents (Rodentia), elephants (Elephantidae), dogs (*Canis familiaris*), and primates (Burkett et al, 2016; Clay & de Waal, 2013; de Waal & Preston, 2017; Fraser et al, 2008). And eusocial systems have evolved in termites (Isoptera); ants, bees, and wasps (Hymenoptera); *Synalpheus* shrimp; and African mole rats (Bathyergidae) (Chak et al, 2017; Duffy & Macdonald, 2010; Nowak et al, 2010; Thorne, 1997; Toth & Rehan, 2017).

The repeated evolution of nature's rarest social behaviors in distant taxa—and in nervous systems of varying sizes, organizations, and complexities—suggests that in response to common selective forces, the underlying and diverse architectures of animal biology have frequently given rise to the same patterns of social behavior, either through distinct or shared mechanistic pathways. It has been proposed that evolutionary plasticity within common neurobehavioral substrates—including reward/reinforcement, feeding/foraging, sexual, aggression, and maternal behavior circuits; conserved neuromodulatory systems, including steroid hormone, oxytocin (OT), vasopressin (AVP), and dopamine systems; and conserved transcriptional "toolkits"—has repeatedly contributed to the evolution of convergent social behavioral phenotypes (Ament et al, 2010; Fischer & O'Connell, 2017; Johnson & Young, 2017; Newman, 1999; Numan & Young, 2016; Rittschof & Robinson, 2016; Toth et al, 2007). In vertebrates, these systems are thought to function and interact within a broader "social decision-making" neural network with a predominantly conserved core neuroanatomical architecture (O'Connell & Hofmann, 2011).

What is the *degree* of mechanistic overlap underlying independently evolved social behaviors? Evidence from butterflyfishes (Chaetodontidae), *Microtine* voles, *Peromyscus* mice, and primates suggest that evolutionary plasticity in conserved neuromodulatory systems—namely OT, AVP, and dopamine systems within ventral striatal reward and reinforcement circuits—has repeatedly contributed to the convergent evolution of socially monogamous mating systems across vertebrate lineages (Bendesky et al, 2017; Johnson & Young, 2015; 2017; Nowicki et al, 2017b). However, additional evidence from cichlid fishes and rodents suggests that the detailed gene regulatory and neural circuit mechanisms can differ between closely-related species (Fink et al, 2006; Johnson & Young, 2017; Renn et al, 2017; Turner et al, 2010). These findings are consistent with emerging evidence that common—but in some cases "loose"—genetic and/or transcriptional "toolkits" have repeatedly been selected upon in the evolution of vocal learning and eusociality (Berens et al, 2015; Pfenning et al, 2014; Rittschof & Robinson, 2016; Toth et al, 2010). To date, however, comparative neurogenetic investigations of social behavior are limited to a relatively small number of species systems, and therefore the degree of mechanistic overlap across species remains a major question.

Rapid evolutionary divergence of social behaviors

Social behaviors can rapidly diverge (and repeatedly evolve) in groups of closely-related species (York & Fernald, 2017). For example, divergent mating and parental care behaviors are exhibited between closely-related species of Hymenopteran insects (ants, bees, and wasps), butterflyfishes, cichlid fishes, poison frogs (Dendrobatidae), African mole rats, *Microtine* voles, *Peromyscus* mice, and primates (Emlen & Oring, 1977; Ferkin, 1990; French et al, 2017; Jasarevic et al, 2013; Kidd et al, 2012; Lukas & Clutton-Brock, 2013;

Nowicki et al, 2017a; Opie et al, 2013; Roland & O'Connell, 2015; Toth & Rehan, 2017). Diverse patterns of flocking behavior are frequently exhibited between closely-related species of birds, such as Estrildidae finches and Emberizidae songbirds; and divergent group burrowing behaviors are exhibited between closely-related species of South American Ctenomys tuco-tuco rodents (Anacker & Beery, 2013; Beery et al, 2008; Goodson et al, 2009; Goodson et al, 2012).

Social behavior can also vary within species at the population level. For example, populations of threespine stickelback fish (*Gasterosteus aculeatus*) and cavefish (*Astyanax mexicanus*) exhibit differences in schooling behavior; and prairie voles (*Microtus ochrogaster*) exhibit population differences in socially monogamous behavior (Greenwood et al, 2015; Greenwood et al, 2016; Kowalko et al, 2013; McGraw & Young, 2010).

These and many other examples suggest that the genes and neurobiological systems modulating social behaviors are evolutionarily labile, frequently varying within and between closely-related species. Strategic comparisons of social behavioral divergence at the species and population levels have discovered causal genetic and neurobiological mechanisms contributing to specific social behaviors (Bendesky et al, 2017; Goodson et al, 2009; Greenwood et al, 2016; Haesler et al, 2007; Haesler et al, 2004; Insel & Shapiro, 1992; Insel et al, 1994; Kowalko et al, 2013; Lim et al, 2004). For example, investigations in alternative species systems spanning teleost fishes and mammals have begun to reveal the roles of brain-region specific OT and AVP receptor (OTR and V1aR, respectively) populations in modulating species-specific social behaviors (DeAngelis et al, 2017; Donaldson & Young, 2008; Goodson & Bass, 2000; Keebaugh et al, 2015; O'Connell et al, 2012; Oldfield & Hofmann, 2011; Song et al, 2014). Comparative investigations followed by causal manipulations and have demonstrated the role of region-specific OTR and V1aR populations in modulating flocking behavior in Estrildidae finches and pair bonding behavior in *Microtine* voles (Goodson et al, 2009; Insel & Shapiro, 1992; Insel et al, 1994; Lim et al, 2004; Young et al, 2001). However, much remains to be discovered about the detailed neuronal populations and neural circuits mediating these effects.

Individual variation and plasticity in social behaviors

Social behavioral divergence between closely-related species is sometimes paralleled by a high degree of social behavioral variation within species (Johnson & Young, 2017). For example, although prairie voles (*Microtus ochrogaster*) are classified as socially monogamous, individual males and females exhibit a high degree of variation in sociospatial and mating behaviors (McGraw & Young, 2010). This variation has been linked to single nucleotide polymorphisms in the OXTR/AVPR1A (the genes encoding OTR and V1aR, respectively) gene region, indicating that naturally-occurring genetic variation within species contributes to individual social behavioral phenotypes (King et al, 2016; Okhovat et al, 2015). In humans, genetic variation in *OXTR* and *AVPR1A* has also been linked to variation in brain region-specific OTR/V1aR expression; brain function during social contexts; and pair bonding, social recognition, and psychiatric phenotypes such as autism (Johnson & Young, 2017; LoParo & Waldman, 2015; Reuter et al, 2017; Skuse et al, 2014; Walum et al, 2012; Walum et al, 2008). Taken together, these findings suggest that naturally-occurring polymorphisms in homologous genes can contribute to individual variation in brain gene expression patterns and social behavior in humans and alternative species systems. Furthermore, the diversity of OTR/V1aR brain expression profiles within and between species suggests that diverse transcriptional mechanisms selectively recruit OTR/V1aR expression to specific neuronal populations and circuits to modulate behavior; and that understanding these mechanisms will require investigation in diverse species.

Individuals can also exhibit social behavioral plasticity at several timescales. For example, male cichlid fish rapidly transition to dominant physiological and behavioral phenotypes in response to social opportunities; Siberian hamsters (*Phodopus sungorus*) exhibit seasonal variation in aggression; and honeybees (*Apis mellifera*) transition through different social roles in the colony throughout the lifespan (Ben-Shahar, 2005; Maruska & Fernald, 2010; Maruska et al, 2013; Rendon et al, 2017; Robinson, 2002; Wen et al, 2004). These and many other examples suggest that the biological systems modulating social behavior exhibit functional plasticity across developmental, seasonal, and rapid neuromodulatory timescales in a species-specific fashion. Investigations in alternative species systems have discovered novel mechanisms regulating several forms of social behavioral plasticity at different timescales (Ament et al, 2008; Ben-Shahar, 2005; Carpenter et al, 2014; Juntti et al, 2016; Maruska et al, 2013). For example, Juntti et al. recently combined CRISPR/Cas9 and hormonal manipulations to demonstrate the causal role of prostaglandin F2α in modulating the rapid expression of female mating behaviors in *Astatotilapia burtoni* cichlid fish (Juntti et al, 2016).

Comparative investigations have also generated evidence that conserved gene regulatory networks contribute to similar forms of social behavioral plasticity across species. For example, studies in cichlid fishes have identified core transcriptional “modules” associated with rapid transitions to social dominance in both sexes and across species; and recent studies suggest that aggression and territorial behaviors are associated with conserved genetic “toolkits” across honeybees, stickelback fish, and house mice (*Mus musculus*) (Alaux et al, 2009; Liu et al, 2016; Renn et al, 2016; Rittschof et al, 2014).

Limitations of traditional laboratory models

For many decades Krogh’s principle (the notion that the most appropriate model system should be carefully selected for a given research question) led to numerous breakthrough discoveries in biology (Krogh, 1929). The electrochemical mechanisms of action potentials were discovered in giant axons of squid (*Loligo pealii)*, and neuroplasticity mechanisms mediating learning and memory were elucidated through studying the accessible neurons of sea slugs (*Aplysia*) (Yartsev, 2017). In recent decades, however, behavioral genetics and neuroscience research has become predominantly focused on a narrow set of model species, most notably inbred laboratory strains of house mice. This general strategy aims to make biomedical discoveries by applying cutting-edge techniques to study conserved and translationally relevant biological functions in animal models. Concentrated effort in developing experimental resources for specific systems (e.g. transgenic mouse strains), combined with invasive approaches that cannot be employed in humans, allows such processes to be studied in unprecedented detail and has led to discoveries of novel mechanisms underlying human disease and other traits of interest.

Despite these strengths, strategies focusing on a small number of species are poorly suited for understanding unique functional specializations, complex integrative traits, and phenotypic diversity; and are therefore poorly positioned for understanding social behavioral diversity (Brenowitz & Zakon, 2015; Yartsev, 2017). In traditional and “knockout” laboratory strains, the vast majority of natural genetic variation present in wild populations has been eradicated through inbreeding, genetic drift, and artificial selection; eliminating naturally-occurring functional polymorphisms and reducing the genetic complexity underlying complex traits (Chalfin et al, 2014). Furthermore, inbreeding, adaptation to captivity, and artificial selection frequently impact reproductive, parental, aggressive, and other social behaviors; altering or eliminating wild-type behavioral phenotypes (Champagne et al, 2007; Connor, 1975; Margulis & Altmann, 1997; Wilson, 2000). Indeed, complete loss of natural social behaviors (and gain of “unnatural” social behaviors) has been demonstrated in common laboratory mouse strains (Chalfin et al, 2014). Therefore, traditional model systems have presumably lost many natural genetic polymorphisms and transcriptional mechanisms contributing to variation in brain gene expression patterns and social behavior at the individual, population, and species level.

Social behaviors are also specialized products of the unique evolutionary history, ecology, and biology of a given organism or lineage. For example, although sex steroids play a dominant role in regulating aggression in mice and rats, species with different life history strategies—some exhibiting stronger hormonal parallels to humans—regulate aggression through other hormonal mechanisms, including several species of hamsters and songbirds (Soma et al, 2008). Mechanistic diversity underlying conserved behaviors highlights an additional limitation of pursuing traditional laboratory systems as translational models for human social cognition and behavior. As another example, although investigations in laboratory mice have contributed to our understanding of parental behavior, laboratory mice exhibit differences in the onset, expression, and expiration of parental behaviors compared to wild house mice and other mammals; and in some instances exhibit complete loss of wild-type parental behaviors (Chalfin et al, 2014; Champagne et al, 2007; Olazabal et al, 2013a). Understanding how gene regulatory and neural circuit mechanisms shape natural variation in parental behavior will require investigation in alternative species systems exhibiting a range of parental behavioral phenotypes (Olazabal et al, 2013a; b). Other unique social behaviors reflect additional dimensions of human sociality and are completely absent in traditional laboratory species and their wild-type counterparts, such as pair bonding, vocal learning, and consoling behavior; the mechanistic basic of these behaviors can only be studied in alternative species systems.

Modern tools for investigating social behavior

Molecular genetics, neuroscience, genomic sequencing, and computational tools have rapidly advanced in recent decades, placing us in a unique position for studying the social brain. New and powerful technologies such as CRISPR/Cas9, single-cell RNA sequencing, computer vision, and optogenetics enable investigation of the biological mechanisms of social behavior in diverse species at unprecedented levels of precision. Decreasing costs of high-throughput and next-generation "omics" sequencing technologies and advances in bioinformatics have created opportunities for gene regulatory network analyses and large scale comparative genomic and transcriptomic investigations of social behavior across species (Baran et al, 2017). Taken together, these ongoing trends will continue to increase the cost-effectiveness and potential impact of prioritizing neurogenetic investigations in new and diverse species. In the following sections, we highlight discoveries in *Microtine* voles to illustrate the power of applying modern genetics and neuroscience tools to alternative species systems. We then highlight the social behavioral diversity of Lake Malawi cichlids as a promising system for future discoveries.

Microtine rodents and prairie voles

Background

Microtine rodents include more than 60 species of North American, European, and Asian voles exhibiting diverse mating strategies, parental care behaviors, and patterns of group living. For example, although socially monogamous mating systems are rare in mammals, these systems have repeatedly evolved in independent *Microtine* lineages. Comparative strategies focusing on *Microtine* social behaviors have provided mechanistic insights into convergent evolution, rapid divergence, and individual variation in complex social behaviors that are not expressed in laboratory mice; and have simultaneously provided translational insights relevant to human social cognition, behavior, and psychiatry

Comparative investigations in Microtine voles

Pair bond formation in monogamous species such as the prairie vole (*Microtus ochrogaster*; Figure 1A, B) can be studied in the laboratory using a partner preference test (Fig. 1E), in which subjects can freely choose to spend time near a familiar mating partner, near an unfamiliar opposite-sex conspecific, or in a neutral chamber (Young & Wang, 2004). Socially monogamous and promiscuous vole species exhibit robust behavioral differences in the partner preference test. Behavioral pharmacological studies in socially monogamous prairie voles have demonstrated that the neuropeptides OT and AVP facilitate mating-induced partner preference formation (Winslow et al., 1993, Cho et al., 1999). Socially monogamous and promiscuous *Microtine* species exhibit strikingly different expression patterns of OTRs and V1aRs in the brain (e.g. Fig. 1C, D); with socially monogamous prairie and pine voles exhibiting higher expression levels of OTR and V1aR in a ventral striatal (nucleus accumbens-ventral pallidum) reward and reinforcement circuit compared to promiscuous meadow and montane voles (Insel & Shapiro, 1992; Insel et al, 1994).

Comparative genetic investigations have revealed both individual and species level differences near the genes encoding OTR and V1aR, providing potential genetic mechanisms underlying species differences in the brain and social behavior (Hammock & Young, 2004; King et al, 2016; Young et al, 1996; Young et al, 1999). In one set of experiments, V1aR was selectively overexpressed in the same reward and reinforcement circuit in promiscuous meadow voles using viral vectors. This manipulation caused promiscuous meadow voles to exhibit prairie vole-like patterns of brain region-specific

V1aR expression as well as monogamous-like behavior, demonstrating that variation in expression of a single gene in a conserved neural circuit can significantly contribute to variation in complex social behaviors (Lim et al, 2004). Unlike mice and rats, high expression levels of OTR and/or V1aR in this circuit have been noted in socially monogamous species of *Peromyscus* mice and primates, supporting the possibility of a convergent functional specialization involving expression patterns of conserved genes in a conserved neural circuit (Freeman & Young, 2016; Johnson & Young, 2015; Young, 1999). Investigations in human brain tissue have used ligands that bind promiscuously to both OTR and V1aR, and have also revealed high expression levels in this circuit, suggesting discoveries in alternative species systems can contribute unique discoveries relevant to human brain gene expression (Loup et al, 1991).

Prairie voles

Comparative investigations in *Microtine* voles also provided the foundation for laboratory investigation of additional complex social behaviors in prairie voles that are not exhibited in laboratory mice (Donaldson & Young, 2008; Lim et al, 2004; McGraw & Young, 2010). Like humans, prairie voles exhibit selective social attachments between mating partners, biparental and alloparental care (Fig. 1A), depressive-like behavior following partner loss, and consoling behavior towards partners following unobserved stress (Fig. 1B). Application of both traditional and cutting-edge genetic and neuroscience techniques have provided insights into the neurogenetic mechanisms underlying these behaviors. For example, pharmacological manipulations have shown that brain region-specific populations of OTR, V1aR, dopamine receptors, and other neuromodulatory receptors play causal roles in regulating pair bonding behavior (Aragona et al, 2003; Burkett et al, 2011; Curtis & Wang, 2005; Gingrich et al, 2000; Keebaugh et al, 2015; Lim et al, 2007; Lim & Young, 2004; Liu & Wang, 2003; Young et al, 2001). These techniques have also been used to investigate the neural basis of social attachments in socially monogamous Mandarin voles, and suggest similar neurogenetic circuit mechanisms may contribute to independently evolved mating systems across *Microtine* species (He et al, 2017; Yu et al, 2013). In addition to pair bonding, receptor autoradiography, selective antagonists, viral vector gene transfer, and RNA knockdown have been used to discover novel neuromodulatory mechanisms contributing to other complex social behaviors including selective aggression, alloparental care, and consoling behavior (Barrett et al, 2013; Burkett et al, 2016; Burkett et al, 2011; Gobrogge et al, 2009; Johnson et al, 2016; Keebaugh et al, 2015; Lim & Young, 2004; Liu et al, 2001; Young et al, 2001). These techniques have also been used in combination with patch-clamp electrophysiological recording and microdialysis to dissect neural circuits underlying depressive-like behavior following partner loss, which is thought to play a role in the maintenance of pair bonds (Bosch et al, 2016). Additional studies have revealed neuroepigenetic mechanisms contributing to pair bonding (Wang et al, 2013). Recently, we combined *in vivo* electrophysiological recordings in multiple brain regions, computer vision, and optogenetic manipulation to show that a corticostriatal circuit—a neural pathway that has been repeatedly implicated in human addiction and compulsive behavior—modulates pair bonding in prairie voles (Amadei et al, 2017; Horga et al, 2015; Marquand et al, 2017; Volkow et al, 2012). Taken together, these findings reinforce the potential for discovering neurogenetic and circuit mechanisms in alternative species that may be relevant to human cognition and behavior, and that may not be present in traditional laboratory models. The ability to use CRISPR/Cas9 to generate transgenic vole lines that express Cre-recombinase in specific neuronal populations will significantly enhance the usefulness of voles for elucidating the neural circuitry of social behaviors.

Investigations in prairie voles have also revealed neurogenetic mechanisms contributing to individual variation in social behavior. Recent investigations have identified single nucleotide polymorphisms in the *OXTR* and *AVPR1A* gene region that predict individual variation in brain region-specific OTR and V1aR expression and social behavior (King et al, 2016; Okhovat et al, 2015). Individual variation in OTR expression influences how early life social experience affects social bonding in adulthood, providing a potential mechanism for gene by environment interactions (Barrett et al, 2015). Additional experiments have demonstrated that central and region-specific OTR populations shift patterns of neural activation across widely distributed brain networks during sociosexual interactions, offering clues as to how individual and species variation in brain gene expression can generate functional diversity in the brain during social contexts (Fig. 1F) (Johnson et al, 2016; Johnson et al, 2017; Johnson & Young, 2017).

In humans, genetic variation in OXTR and AVPR1A predict individual variation in region-specific receptor expression, brain function during social contexts (including shifts in patterned activation across widely distributed brain networks), social behavior, social cognition, and psychiatric phenotypes, suggesting investigations of natural individual variation in alternative species systems can discover biological mechanisms that are relevant to human health (Johnson & Young, 2017; LoParo & Waldman, 2015; Reuter et al, 2017; Skuse et al, 2014; Walum et al, 2012; Walum et al, 2008). Indeed, clinical trials assessing the therapeutic potential of OT administration for autism spectrum disorders are currently underway (https://clinicaltrials.gov/), demonstrating that investigations of social behavior in alternative species systems has already helped stimulate lines of translational research (Johnson & Young, 2017).

Conclusions

The application of a wide array of experimental techniques to investigate social behavior in prairies voles has led to the discovery of novel neurogenetic mechanisms contributing to individual and species variation in brain function and behavior. Similar, but not identical, mechanisms have been linked to social behavior in other vertebrates and humans, contributing to our understanding of mechanistic variation and generalizability across species. Combining comparative approaches with modern tools in alternative species systems can thus accelerate discoveries of biological mechanisms driving ethologically relevant behaviors, and simultaneously advance biomedical research goals.

Cichlids and Lake Malawi bower builders

Background

Teleost fishes possess putative homologues for all core neuromodulatory and neuroanatomical components of the social decision making network, a conserved neural network that regulates social behaviors across vertebrates, including humans. Among teleosts, zebrafish have emerged as a “model” laboratory system for studying genes, brains, and behavior; and behavioral genetics and neuroscience studies in zebrafish have contributed to our understanding of genetic mechanisms underlying human health and psychiatric phenotypes (Norton, 2013). Despite their unique strengths, laboratory strains of zebrafish share many limitations of other laboratory model organisms (see above under “Limitations of traditional laboratory models“), notably the loss of natural genetic variation and the absence of many complex social behaviors that are expressed by other teleost species, such as cichlid fishes.

Cichlidae is the most species-rich family of vertebrates on Earth (Kocher, 2004). Cichlid evolution in the East African Rift Valley (Lakes Tanganyika, Malawi, and Victoria) has attracted the attention of evolutionary biologists due to the explosive speciation in recent evolutionary history, with more than 2,000 cichlid species estimated to populate these lakes today. East African cichlids exhibit tremendous phenotypic diversity in habitat preference, diet, morphology, neural organization, and behavior—including many rare and complex social behaviors that are not expressed in zebrafish or other traditional laboratory species (Brawand et al, 2014). Cichlids thus represent a premier system for discovering novel neurogenetic mechanisms and organizing principles underlying social behavioral diversity.

Comparative investigations in cichlids

To date, the majority of comparative genetic investigations in cichlids have focused on speciation, trophic morphology, and vision/color patterning (Albertson et al, 2005; Brawand et al, 2014; Gante et al, 2016; Hauser et al, 2017; Hulsey, 2009; Lee et al, 2005; Loh et al, 2008; Owens & Rennison, 2017; Parsons et al, 2014; Roberts et al, 2017; Spady et al, 2005; Streelman et al, 2003). Additional studies have investigated the diverse genetic mechanisms regulating sex determination, and differences in brain organization associated with ecology (Bohne et al, 2013; Sylvester et al, 2013). These efforts have discovered genes contributing to phenotypic variation, demonstrating proof of principle for behavioral studies. Despite this exciting progress, to date there have been relatively few comparative genetic and neural investigations of social behavior in cichlids.

Cichlids exhibit extraordinary social behavioral diversity including many examples of repeated behavioral evolution, rapid behavioral divergence, and robust behavioral plasticity within individuals (Balshine-Earn & Earn, 1998; Emlen & Oring, 1977; Kidd et al, 2012; Klett & Meyer, 2002; Maruska & Fernald, 2010; 2013). Cichlid species exhibit many social behaviors that cannot be studied in traditional laboratory species—including complex social hierarchies; cooperative breeding; biparental and exclusively paternal care systems; maternal care and mouthbrooding; monogamous and lek-like mating systems; and male bower building (Emlen & Oring, 1977; Fernald, 2017; Kidd et al, 2012; Kidd et al, 2006). Recent studies have also demonstrated OT and AVP modulation of social behavior in cichlids, including species-specific parental and mating behaviors (Huffman et al, 2015; O’Connell et al, 2012; Oldfield & Hofmann, 2011). Therefore, cichlids also represent an unparalleled opportunity to discover novel transcriptional mechanisms through which OTR/V1aR expression can be recruited to conserved neuronal populations and circuits to modulate behavior. Links between natural polymorphisms in the OXTR/AVPR1A gene region, brain region-specific OTR/V1aR expression, and social behavior and cognition in humans suggest that such discoveries may provide valuable translational insights (Johnson & Young, 2017). In the following section we highlight male bower-building behavior in Lake Malawi as a promising behavioral system for discovering neurogenetic mechanisms modulating complex social behavior.

Bower building behavior in Lake Malawi

Lake Malawi (Fig. 2A) is home to approximately 1,000 cichlid species, making it the most species-rich freshwater lake on Earth. Collectively, Lake Malawi cichlids are estimated to possess a total genetic diversity just 2.5 times greater than that of the human species; therefore, species exhibiting striking social behavioral differences are typically separated by a relatively small number of genetic polymorphisms, comparable to that between human individuals (Loh et al, 2013). Lake Malawi cichlids thus represent an unparalleled opportunity to discover causative natural polymorphisms contributing to social behavioral variation.

Within Lake Malawi, dozens of sand-dwelling species exhibit “bower building” behaviors that parallel dimensions of bower building in Ptilonorhynchidae bowerbirds—an example of convergent evolution across long evolutionary scales (McKaye et al, 2001). During the breeding season, male bower-building cichlids congregate into leks—large communal breeding grounds—and devote enormous energy to building, maintaining, and defending species-typical structures, or bowers, in the sand that serve as temporary territories for courtship and spawning (Kidd et al, 2006; York et al, 2015). Species-typical bowers come in different shapes and sizes, and several forms have repeatedly evolved. For example, “pits,” or crater-like bowers that are dug into the sand, and “castles,” or volcano-like bowers that are built up from the sand, are independently expressed in dozens of Lake Malawi lineages (Fig. 2B) (Kidd et al, 2006; York et al, 2015).

Bowers are constructed through the same motor pattern: collecting or “scooping” a mouthful of sand and spitting it elsewhere. Species differences in bower form are thus mediated by differences in patterned spatial decision-making about where to scoop and spit sand over time. Field observations have revealed that courtship, spawning, and intermale aggression occur most frequently at the center of the bower, and that bower size, shape, and position interact within the social landscape of the lek to influence intermale aggression and female mate choice (Genner et al, 2008; Martin & Genner, 2009; McKaye et al, 1990; Young et al, 2009). Many closely related species express divergent bower forms (e.g. pit versus castle), and distantly related species express the same bower form (Fig. 2B). The evolution of bower building systems in Lake Malawi therefore represents rapid diversification as well as repeated evolution of unique and species-specific extended phenotypes and suites of sociospatial behaviors. Interestingly, some Lake Tanganyikan species also exhibit bower building behaviors, enabling comparisons across longer evolutionary timescales (Morita et al, 2014). As teleosts, bower building species possess putative homologues of all major components of the social-decision making network. Bower building behavior is thus a promising system for discovering how neurogenetic specializations within conserved neural circuits generate functional and behavioral variation across evolutionary, seasonal, and rapid timescales.

Interdisciplinary approaches to investigate bower building

Reproductively naive males of many bower-building species reliably construct species-typical bower forms in aquariums, facilitating investigation in laboratory environments. Many bower-building species are commercially available and can thus be easily introduced and maintained in the laboratory. Cichlid males can be socially housed with multiple reproductive females in aquarium tanks with sandy bottoms, enabling behavior in semi-naturalistic “home” environments to be investigated over extended periods of time (Fig. 2C). Advances in computer vision and depth sensing technologies also enable high-resolution and high-throughput behavioral phenotyping (as has recently been demonstrated to measure social behavior in mice) as well as structural analysis of bower form over time (Fig. 2C) (Hong et al, 2015).

High genetic similarity between Lake Malawi species enables powerful experimental strategies that are impossible or ineffective in other vertebrate systems. For example, divergent Malawi cichlids can be intercrossed in the laboratory, producing hybrid offspring that are genetic and phenotypic mosaics. First generation (F1) hybrids possess full copies of both parental genomes, enabling analyses of context-specific parental allele expression in the brain. Subsequent hybrid generations (F_2, F_3, F_4, etc.) are genetic mosaics of the parent species, and can be used for quantitative trait loci (QTL) mapping of genes contributing to species-specific behaviors. QTL mapping has been used to identify genetic loci associated with many traits of interest in Malawi cichlids (Holzman & Hulsey, 2017; Husemann et al, 2017; Nandamuri et al, 2017; O’Quin et al, 2012; Parnell et al, 2008; 2012; Parsons et al, 2015; Selz et al, 2014; Svensson et al, 2011); and has recently been used to discover genetic loci contributing to extended phenotypes (burrow structures) and social behaviors in *Peromyscus* mice (Bendesky et al, 2017; Metz et al, 2017; Weber et al, 2013).

Rapid advances and decreasing costs of next-generation sequencing enable comparative genomic and brain transcriptomic investigations across bower building species. These approaches have already been integrated to reveal neurogenetic specializations associated with social behaviors in alternative species systems, including Lake Tanganyikan cichlids (Renn et al, 2016; Renn et al, 2017; Sanogo et al, 2011; Toth et al, 2010). New techniques such as single-cell RNA sequencing in the brain have the potential to reveal neuronal populations and neuromodulatory systems regulating social behavior in unprecedented detail. Additionally, in contrast to mammalian systems, eggs are fertilized externally in cichlids, facilitating CRISPR/Cas9 approaches that are more technically difficult in laboratory rodents. CRISPR/Cas9 has already been successfully applied in East African cichlids to link specific genes to social behavior; and can similarly be applied to investigate the roles of specific (and potentially translationally relevant) genes, single nucleotide polymorphisms, and neuronal populations modulate bower building (Juntti et al, 2016).

Conclusions

The explosive diversification of cichlids in the East African Rift Valley is perhaps the greatest opportunity on Earth for discovering causative genetic variants that shape brain gene expression and behavior. The clear success of comparative strategies in cichlids highlights the potential for discovering neurogenetic mechanisms contributing to complex social behaviors that are absent in traditional laboratory organisms. Several unique biological features position Lake Malawi cichlids as a particularly promising system for such discoveries. Integrating comparative approaches with modern tools to investigate bower building behavior has the potential to reveal novel mechanisms and organizing principles underlying neurogenetic and social behavioral diversity, and may simultaneously advance our understanding of conserved genes, transcriptional mechanisms, and neural circuits that are relevant to human behavior, cognition, and psychiatric phenotypes.

Summary

Social behavioral diversity has long been of interest to biologists, and is of growing interest to biomedical researchers seeking to understand human social cognition, behavior, and psychiatry. Traditional behavioral genetics and neuroscience strategies are poorly suited for understanding social behavioral diversity; in contrast, outbred and alternative species systems have already helped elucidate neurogenetic mechanisms and organizing principles underlying social behavioral diversity, while simultaneously advancing biomedical research goals. The greatest advances in the years to come will be rooted in a synthesis of comparative strategies with modern genetics, genomics, neuroscience, and computational tools in new and diverse species systems.

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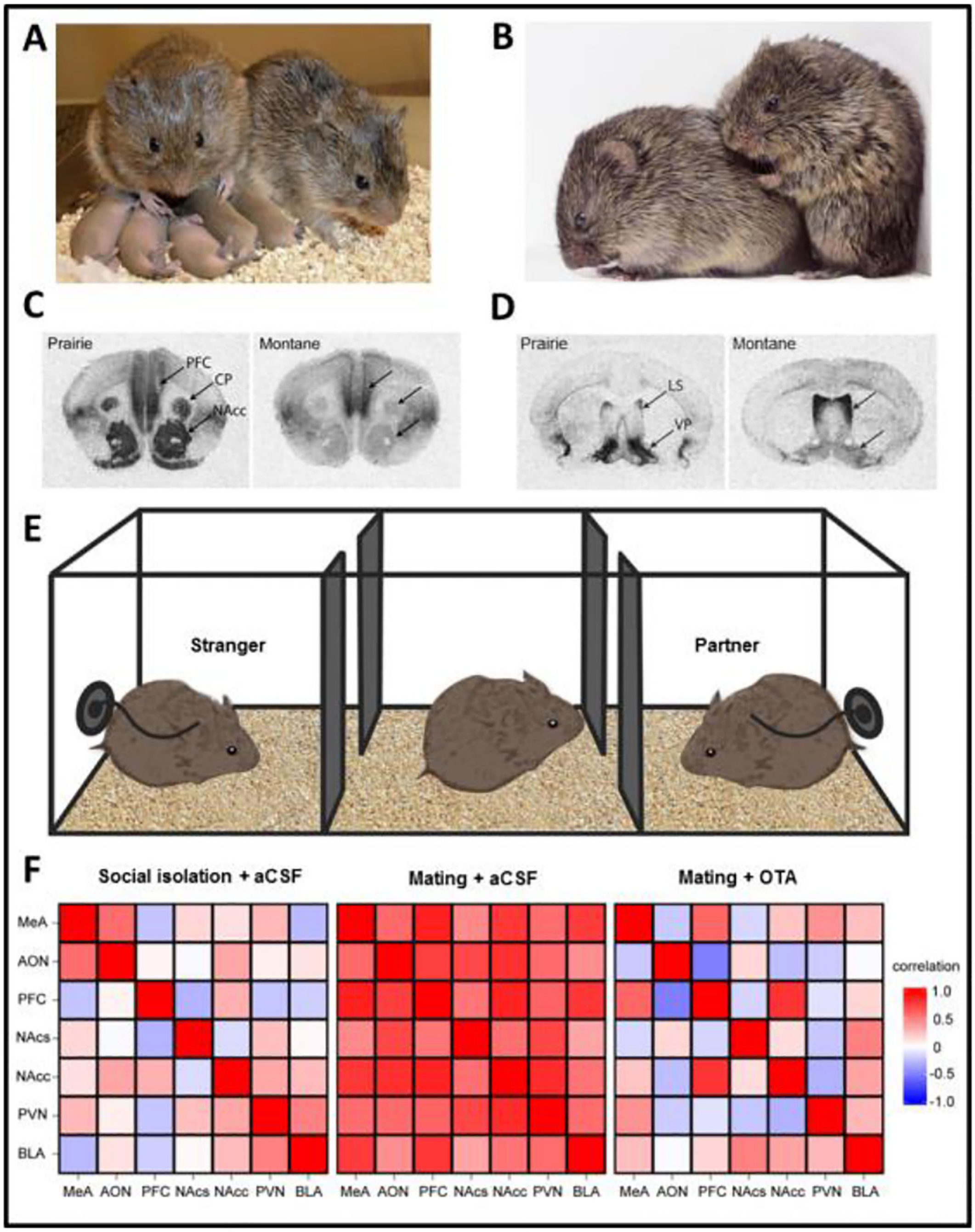

Figure 1. Neurogenetic investigations of complex social behaviors in prairie voles (*Microtus ochrogaster*).

Prairie voles exhibit complex social behavioral phenotypes that are not exhibited in traditional laboratory organisms, including pair bonding and biparental care (A), and consoling behavior (B). Comparative neurogenetic investigations across *Microtine* species have revealed robust divergence in brain expression patterns of OTR and V1aR between closely related species. Socially monogamous prairie voles exhibit higher OTR expression selectively in the nucleus accumbens (NAcc) compared to promiscuous montane voles (C), meadow voles, mice, and rats (not depicted); and higher V1aR expression selectively in the ventral pallidum (VP) compared to promiscuous montane voles (D), meadow voles, mice, and rats (not depicted). The laboratory partner preference test (E), in which a male or female subject can freely spend time with a familiar mating partner, with a novel opposite-sex conspecific, or in a neutral chamber, has been used to discover detailed neurogenetic mechanisms regulating pair bonding behavior. Recent investigations in prairie voles suggest the OT/AVP systems can generate functional diversity in the brain and behavior by modulating conserved and widely distributed neural networks during social contexts (F) (Johnson et al, 2016; Johnson et al, 2017). Heatmaps represent pairwise correlation coefficients of Fos expression (an activity-dependent immediate early gene widely used to study brain function) between seven interconnected, OTR-expressing brain regions in three treatment groups. Following central administration of artificial cerebral spinal fluid (aCSF), social isolation is associated with weakly correlated Fos expression across brain regions. In contrast, aCSF-treatment followed by sociosexual interaction and mating with a female is associated with strongly and positively correlated Fos expression across the network. This effect is disrupted by central administration of a selective OTR antagonist (OTA) prior to sociosexual interaction and mating, which causes a significant decrease in correlated Fos expression across the network. Abbreviations (see above): AON=anterior olfactory nucleus; BLA=basolateral amygdala; CP=caudate putamen; LS=lateral septum; MeA=medial amygdala; NAcc=nucleus accumbens core; NAcs=nucleus accumbens shell; PFC=prefrontal cortex; PVN=paraventricular nucleus of the hypothalamus; VP=ventral pallidum. Autoradiograms (C-D) were adapted from (Young & Wang, 2004) with permission. Partner preference schematic (E) was adapted from (Barrett & Young) with permission. Heatmaps (F) were adapted from (Johnson et al, 2016) with permission. Images in A-B are courtesy of Todd Ahern, Quinnipiac University, USA; and Zachary Johnson, Georgia Institute of Technology, USA.

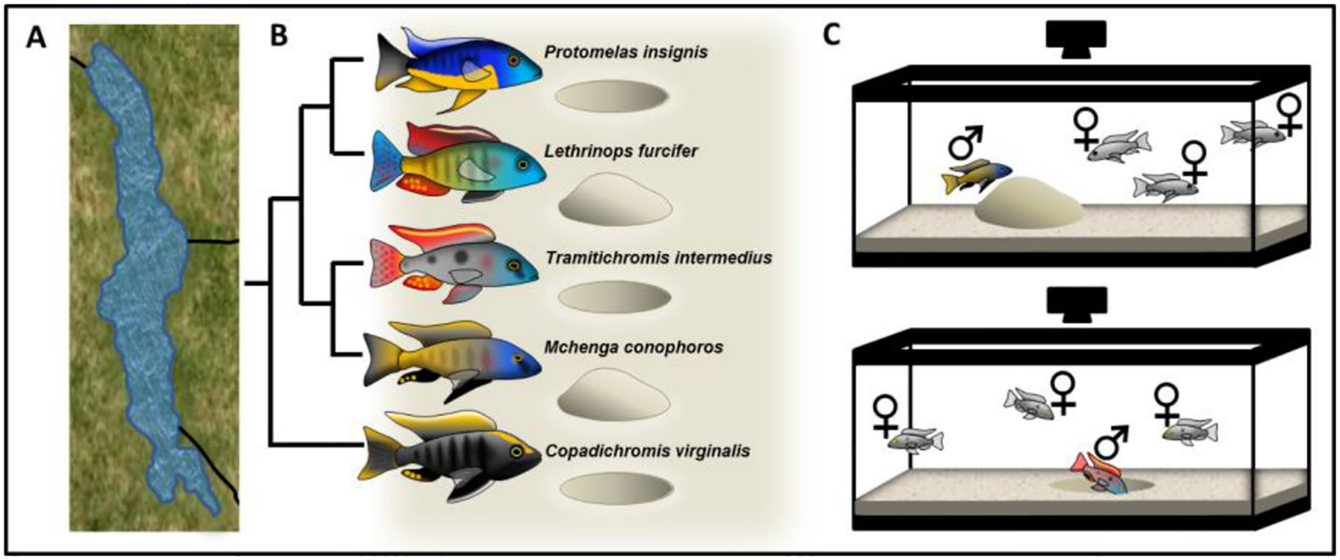

Figure 2. Bower building behavior in Lake Malawi cichlid (Cichlidae) fishes.

Lake Malawi (A) is the most species-rich freshwater lake on Earth, and is home to an estimated 1,000 species of cichlid fishes that have diverged within the past 5 million years, including dozens of species exhibiting bower building behavior during the breeding season. Different forms of bower-building behavior have repeatedly evolved, with many closely related species expressing divergent "pit" versus "castle" bower phenotypes. The phylogeny is based on York et al. 2015 (York et al, 2015) (B). Bower building behavior is reliably performed in aquarium tanks. Advances in computer vision, depth sensing, and neurogenetic approaches will facilitate rigorous investigation of bower building behavior in the laboratory (C).