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CHAPTER 3

Comparative neurobiology and genetics of mammalian social behavior

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3.1 Introduction

Despite advances in our understanding of the ecological and evolutionary factors that drive sociality, relatively little is known about the genetic and neurobiological mechanisms underlying group living. Decades of laboratory investigations into the neural substrates supporting parental behavior and social bond formation between mates have yielded important insights into how those specific social behaviors are reinforced and maintained (reviewed in McGraw & Young 2010; Young et al. 2011). This has laid the groundwork for recent studies of the mechanisms supporting social behavior between non-mate peers, particularly relationships found in group-living species. This chapter will present an overview of the current scientific understanding of genes, brains, and social behaviors with an emphasis on mammals, and with special attention paid to caviomorph rodents. Section 3.2 surveys the molecules implicated in a range of social behaviors, particularly the neuropeptides oxytocin (OT) and arginine vasopressin (AVP), and the neural circuits in which they act. We then turn to the neurobiology of parenting, monogamy, and sociality. Section 3.3 discusses the genetic underpinnings of these pathways. The study of sociality is a topic for which research on caviomorphs may be particularly helpful, as several species exhibit sociality in the absence of monogamy. This offers a valuable opportunity to study the mechanisms supporting social bonds between group-living peers. Thus, Section 3.4 details what is known about the aforementioned pathways in

Sociobiology of Caviomorph Rodents: An Integrative Approach, First Edition.
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caviomorph rodents, including new data on degus (*Octodon degus*). Finally, we discuss the types of data needed to improve inferences about the connections between behavior and neurobiology.

3.2 Molecular and circuit bases of social behavior

Social behaviors can be described in terms of specific individual actions, such as social approach or avoidance, as well as by patterns of behavior that arise when individual behaviors occur in different circumstances, for example, group-living, monogamy, or dominance. The underlying **neural circuitry** may involve shared signaling molecules functioning in distinct circuits and temporal patterns to support different patterns of behavior. A few neurotransmitters, neuromodulators and hormones stand out as important for many different aspects of social behavior. In this chapter we focus on two of the best-studied neuropeptides—oxytocin and vasopressin—and provide a brief review of dopamine and stress pathway signaling. While we focus on specific molecules, it is important to note the significance of the neural circuits in which they operate. Within each section we present the known roles of these molecules in supporting specific behaviors in different mammalian species.

3.2.1 Oxytocin and vasopressin

Across a wide range of invertebrate and vertebrate species, neuropeptides mediate sexual and social behaviors, ranging from egg-laying to affiliation. Neuropeptides in particular are well suited to affect behavior because they are expressed in discrete regions of the brain, they typically function as long-acting neuromodulators, and both their release and their effects are subject to substantial plasticity based on environmental cues. In particular, a family of related nonapeptides—including arginine vasopressin, vasotocin, isotocin, mesotocin, and oxytocin—affects gender-specific social behaviors in vertebrates (Insel & Young 2001).

In mammals, the 9-amino acid peptides oxytocin and arginine vasopressin are synthesized in the paraventricular and supraoptic nuclei (PVN and SON) of the hypothalamus and released from the posterior pituitary. Outside of the brain, OT plays an important role in reproductive muscle contractions, especially during lactation, uterine contraction, and ejaculation (Gimpl & Fahrenholz 2001). AVP (also known as ADH: antidiuretic hormone) is best known for its effects on water balance. AVP binds to receptors in the distal tubule of the kidney where it increases water reabsorption across the epithelium (Campbell & Reece 2005). While peripheral OT and AVP are not believed to cross the blood–brain barrier (but see Cushing & Carter 2000; Neumann et al. 2013), these peptides are also released centrally in the brain, mostly from parvocellular cells in the PVN (Ross & Young 2009). OT binds most effectively to the oxytocin receptor (OTR), and AVP binds to the V1a, V1b, and V2 receptors in the brain; of these, V1aR is of

primary importance for the behavioral effects of AVP. Cross-binding of OT and AVP to each other's receptors is also of biological relevance. Experiments with transgenic rats which have genomically integrated DNA sequences containing the blowfish isotocin gene (the teleost homolog of oxytocin) demonstrate that isotocin expression occurs within the oxytocin neurons of the hypothalamus. This suggests these ancient oxytocin/vasopressin homologs have regulatory features that direct their expression (Venkatesh et al. 1997).

Since the initial discoveries of behavioral influences of OT and AVP, these neuropeptides have been implicated in a wide range of socially relevant processes including individual recognition, anxiety, parental behavior, partner-preference formation, and non-reproductive affiliation.

3.2.2 Neuropeptides, parenting, and monogamy

Social bonds can be quite intense; for example, rat mothers (*Rattus norvegicus*) prefer their pups to cocaine (Mattson et al. 2001; Ferris et al. 2005), and prairie voles (*Microtus ochrogaster*), that have been separated from their mates provide a laboratory model of depression (Grippo et al. 2007). Models of strong, rewarding social bonds involved in maternal behavior and monogamy are the focus of this section. Their investigation has formed the foundation on which the study of other social behaviors has become possible.

Neuropeptides and parenting

Research on a variety of species has shown that OT is an important trigger for maternal behavior—from selective attachment formation to the initiation of behaviors that do not require individual recognition. In precocial mammals such as sheep (*Ovis aries*), oxytocin facilitates the rapid recognition and attachment required for a ewe to form a specific relationship with her lamb. OT rises during delivery and its associated vagino-cervical stimulation. The role of OT is so profound in this setting that administration of OT into the cerebrospinal fluid of estrogen-primed virgin ewes is sufficient to induce the display of a complete repertoire of maternal behaviors (Kendrick et al. 1987).

In rodents, peripartum changes in steroid hormone levels and ratios, together with increases in oxytocin, can promote the onset of maternal behavior quickly after birth (reviewed in Broad et al. 2006). Infusion of OTR antagonists into the brains of rats prevents maternal behaviors (Pedersen et al. 1994). Oxytocin may be important for paternal behaviors in some biparental rodents; juvenile and adult male prairie voles have a transient increase in oxytocin when exposed to pups (Kenkel et al. 2012). Not all species require OT to initiate maternal behavior, for example, virgin female mice (*Mus musculus*) can be spontaneously maternal despite lacking the hormonal changes of pregnancy. Even in this species, however, maternal behavior may be enhanced by prior pup exposure (e.g. Brown et al. 1996; Lucas et al. 1998; Hamaguchi-Hamada et al. 2004; Pedersen et al. 2006), and exogenous OT improves maternal behavior by reducing infanticide (reviewed in Numan & Insel 2003); similarly, virgin OT knockout mice display

subtle but significant deficits in the quality of care provided to foster pups, relative to wild type females (Pedersen et al. 2006).

Neuropeptides and monogamy

The discovery that oxytocin is important for maternal affiliation led to a second line of research focusing on the **pair-bond** formed between mated prairie voles. Prairie voles are one of less than 5% of mammalian species that exhibit **social monogamy**, or formation of a lasting partnership with their mate. Following mating or extended cohabitation, the majority of male and female prairie voles form preferences for their partner. Closely bonded breeding pairs cohabit in pairs, or in larger groups consisting of non-dispersed members of the extended family and potentially unrelated individuals (Carter & Getz 1993).

Experimental manipulations of OT have profound effects on behavior in social choice tests in this species: in females, blockade of the OTR decreases time spent next to a familiar animal, while infusion of OT into the brain hastens pair-bonding (Williams et al. 1992; Cho et al. 1999). In contrast, manipulations of OT in a non-monogamous vole species (*Microtus montanus*) have little effect on time spent with familiar opposite-sex individuals (Insel & Young 2001).

Monogamous prairie voles and pine voles (*Microtus pinetorum*) have a pattern of OT and AVP receptor expression in the forebrain that is distinctly different from that of non-monogamous montane voles and meadow voles (*Microtus pennsylvanicus*), with high densities of OTR in the **nucleus accumbens**, and high densities of V1a receptors (V1aR) in the ventral pallidum (Young 1999; Lim et al. 2004b). Similar contrasts in V1aR distributions are found between monogamous and promiscuous mice (*Peromyscus californicus* and *P. leucopus*) (Young 1999). These parallel differences in receptor expression between related monogamous and non-monogamous species suggest that this correlation may relate to distinct patterns of behavioral responses to recognition of familiar animals, although such findings do not hold up in all comparisons (Anacker & Beery 2013). While the genes for AVP and the V1a receptor are relatively conserved across diverse mammalian taxa, natural variations exist in the promoter region for the V1a receptor. These variations underlie at least some of the differences in expression patterns between species, and point towards a potential mechanism for the repeated evolution of monogamous social behavior (Donaldson & Young 2013).

Targeted infusions of OT or an OT antagonist to the nucleus accumbens are sufficient to induce or prevent pair-bond formation in females (Young et al. 2001), and infusions of AVP or a V1aR antagonist have corresponding effects when infused into the ventral pallidum of male prairie voles (Lim et al. 2004a; Lim et al. 2004c). Compelling evidence of the causal nature of the relationship between V1aR distribution and **affiliative behavior** comes from the manipulation of receptor expression. Following transfection of the *AVPR1a* gene for prairie vole V1a receptors (including the upstream regulatory region) into the ventral

forebrain of male meadow voles, these formerly polygamous voles were induced to show partner preference (Lim et al. 2004c).

3.2.3 Neuropeptides and sociality

Much of what is currently known about the role of neuropeptides in life in groups comes from research on several species of birds (Goodson et al. 2012a). Jim Goodson's lab drove this effort by comparing the neurochemistry of several bird species with different patterns of flocking and aggression (Goodson et al. 2006). They also conducted within-species comparisons of bird species that vary seasonally in their aggregation behaviors (Goodson et al. 2012b). Among other outcomes, these studies indicated the importance of nonapeptides (mesotocin and vasotocin in birds) in brain regions collectively described as the social behavior network or as part of the larger social decision-making network (Newman 1999; Goodson 2005; O'Connell & Hofmann 2012). These regions consist of extended limbic system structures involved in motivation, social discrimination, fear and anxiety regulation, and behavioral output.

Parallel work in mammals has grown considerably in the past few years, and reveals a role for these peptides in non-reproductive social behavior between peers (Anacker & Beery 2013). Below we detail studies in meadow voles and African mole-rats. In addition to these species, studies on striped mice, singing mice, and other species have begun to approach these questions, and together form the basis for our current understanding of the mechanisms of behaviors involved in group living (sociality). Table 3.1 presents a summary of studies on the neurobiology of sociality across a broad range of taxonomic groups.

Meadow voles

Meadow voles provide a valuable opportunity to study mechanisms supporting sociality, as both group-living and solitary behavior are exhibited within a single species. This plasticity is environmentally regulated by seasonal variation in day length. Female meadow voles are territorial and nest alone in long summer day lengths, but in short winter photoperiods these territories collapse, and voles live together in mixed-sex groups of 3–10 individuals (McShea & Madison 1984; Madison & McShea 1987). Males and females are tolerant of both nest-mates and strangers during winter months when the gonads are regressed or not yet developed. By spring, aggression towards strangers increases in both sexes, concurrent with gonadal development (McShea 1990). These variations are particularly pronounced in females, who maintain non-overlapping territories in summer (Webster & Brooks 1981). Unlike prairie voles, meadow voles do not form socially monogamous partnerships (Getz 1972; Boonstra et al. 1993), allowing for the study of non-reproductive social behavior outside the context of monogamy.

In the laboratory, female meadow voles are capable of forming specific and enduring preferences for a familiar individual (Parker & Lee 2003), and variations

Table 3.1 Select "non-classic" species used for comparative neurobiological studies of vertebrate social behavior.

Characteristics of interest for the study of sociality	Compared across	Models used	Neurobiological substrates studied	Evidence/references
Variation in group-living and social behavior	Seasons/treatments	Meadow voles *Microtus pennsylvanicus*	OTR	(Parker et al. 2001)
			OT and OTR	(Beery & Zucker 2010)
			CRF receptors	(Beery et al. 2014)
	Seasons	4 sparrow or finch species (Family Estrildidae)	Vasotocin, mesotocin, CRF, VIP, TH, aromatase	(Goodson et al. 2012)
	Species/treatments	Estrildid finches (Family Estrildidae)	VIP receptors	(Goodson et al. 2006)
			V1a, CRF receptors	(Goodson et al. 2009)
			MT (OT analog)	(Goodson & Kingsbury 2011)
			VT (AVP analog)	(Kelly et al. 2011)
	Species	**Tuco-tucos** (genus *Ctenomys*)	OTR, V1a	(Beery et al. 2008)
		Degus (*Octodon degus*)	OTR	This chapter
	Species	Mole-rats (Family Bathyergidae)	OTR	(Kalamatianos et al. 2010)
	Populations/housing	Striped mice *Rhabdomys pumilio*	OT, AVP	(Schradin et al. 2013)
	Species	Interspecific comparisons within primates and carnivores	Neocortex size ratios	(Dunbar 1992)
				(Dunbar 1998)
				(Sawaguchi & Kudo 1990)
				(Dunbar & Bever 1998)
Social hierarchy	Reproductive status/ treatments	Naked mole-rats *Heterocephalus glaber*	Neuronal morphology	(Holmes et al. 2007)
			Neurogenesis	(Peragine et al. 2014)
			AR	(Holmes et al. 2008)
			OT	(Mooney & Holmes 2013)
			OTR	(Mooney et al. 2014)
			CRF receptors	(Beery et al. 2015)

	Reproductive status	Damaraland mole-rats *Fukomys damarensis*	Neuronal morphology	(Anyan et al. 2011)
Mating system	Species	Multiple vole species Genus *Microtus*	OTR, AVP CRF receptors Brain region size ratios	(Young 1999) (Lim et al. 2006) (Kingsbury et al. 2012)
	Species	Peromyscus mice *P. Californicus, P. leucopus*	OTR, AVP receptors AVP, AVP receptors	(Insel et al. 1991) (Bester-Meredith et al. 1999)
	Treatments	Prairie voles *M. ochrogaster*	OT, OTR, AVP, V1aR, CRF Dopamine transmission Opioid systems Gene regulation	*Examples and reviews:* (McGraw & Young 2010) (Young et al. 2011) (Carter et al. 2008) (Carter et al. 2008) (Bales et al. 2007) (Aragona & Wang 2009) (Resendez & Aragona 2013) (Donaldson & Young 2013) (Barrett et al. 2013)
	Populations/ behavioral phenotype	Prairie voles *M. ochrogaster*	V1aR Avpr1a gene	(Ophir et al. 2008) (Solomon et al. 2009) (Mabry et al. 2011)
Space use and social structure	Species	Singing mice (*Scotinomys*) *S. teguina*, *S. xerampelinus*	OTR distribution	(Campbell et al. 2009)
	Species	Cichlid fish *Cichlidae family*	Brain region size ratios Gene regulation Vasotocin, isotocin	(Pollen et al. 2007) (Renn et al. 2008) (Oldfield & Hofmann 2011)

Note: Further work has been conducted in humans and non-human primates (not included here). Caviomorph rodents are listed in bold.

in day length in laboratory studies trigger changes in social preferences (Ferkin & Seamon 1987). In long day lengths (LDs, e.g. 14 hours of light), female meadow voles prefer the odors of males over those of females, consistent with summer breeding. In short day lengths (SDs, e.g. 10 hours of light), however, females prefer the odors of other females over their own odor or those of males (Ferkin & Zucker 1991). Same-sex female prosocial behavior in SDs extends to social interactions as well as olfactory preference. Female meadow voles housed in SDs form selective partner preferences for cohabiting females, while females housed in long day lengths exhibit greatly reduced social huddling (Beery et al. 2008b).

Same-sex partner preferences in SD-housed meadow voles are altered by oxytocin administration. Infusion of oxytocin into the ventricles of the brain enhances preferences for a partner over a stranger, indicating a role for oxytocin in the specificity of huddling behavior. Interestingly, blockade of oxytocin receptors does not reduce preferences below the unmanipulated baseline, suggesting that oxytocin is not necessary for this level of preference and that other mechanisms promote this social behavior (Beery & Zucker 2010).

Regions in which oxytocin may act to influence social behaviors have been identified by receptor autoradiography. OTR distribution and density vary with day length in meadow voles (Parker et al. 2001; Beery & Zucker 2010). Behavioral and neural plasticity within individuals suggests that a fixed genome is capable of generating markedly different gene expression patterns and downstream protein production in different settings.

Individual variation in OT receptor binding in meadow voles is associated with huddling behavior, most notably in the **lateral septum** and to a lesser extent the central amygdala (Beery & Zucker 2010). In the lateral septum, oxytocin receptor density is negatively correlated with huddling time. This is of particular interest as it parallels the interspecific difference between meadow and prairie voles; prairie voles have lower OTR in the lateral septum (Insel & Shapiro 1992) together with higher huddling behavior (e.g. Lim et al. 2004a). This is also congruent with receptor density differences between social and solitary tuco-tucos, presented in Section 3.2.1. While oxytocin is typically thought of as enhancing **prosocial behaviors**, accumulating evidence suggests that the social effects of oxytocin are circuitry- and context-specific, at times enhancing aggression and **agonistic behaviors** (Beery 2015, in press). Enhanced aggression may be related to the selectivity of oxytocin's prosocial effects. For example, partner preference formation in prairie voles involves affiliation towards a mate with concomitant increases in aggression and aversion towards unfamiliar individuals (Getz et al. 1981; Gobrogge & Wang 2011; Resendez & Aragona 2013). In humans, oxytocin facilitates social behavior towards in-group members at the expense of an out-group (De Dreu et al. 2011). Oxytocin may thus play a role in both prosocial and antisocial aspects of social behavior.

Perhaps the most intriguing finding to date is that the OT facilitation of social preferences in meadow voles appears not to be related to oxytocin receptors

in the nucleus accumbens (Ross et al. 2009; Beery & Zucker 2010). Given the importance of this circuitry in sexual pair-bonding, it suggests that non-sexual affiliation must be examined in its own right as it is not maintained through the same pathways. Future studies on meadow voles should follow up on regions outside the nucleus accumbens (such as the lateral septum) in which oxytocin exerts specific effects on social huddling. Meadow voles also present an opportunity to examine non-neuropeptide pathways contributing to seasonal variation in mammalian sociality.

African mole-rats

African mole-rats are Old World histricognaths, more closely related to the New World histricognaths, including caviomorphs, than to rats, mice, and other rodent species. The Bathyergidae (and now Heterocephalidae) family of mole-rats is striking because it contains the only known mammalian examples of eusociality—in which colonies exhibit a caste structure with only a few individuals reproducing. The most social of the mole-rat species is the naked mole-rat (*Heterocephalus glaber*). Naked mole-rats live in groups consisting of 70–80 individuals (and up to 300), most of which are reproductively suppressed non-breeders (Sherman et al. 1991). Both sexes provide alloparental care to the offspring of the breeding members of the colony (Jarvis 1981; Lacey & Sherman 1991). Studies of mole-rats have compared social species to Cape mole-rats (*Georychus capensis*), and compared naked mole-rats across breeding status (see Table 3.1, and below).

Naked mole-rats exhibit a high density of oxytocin-neurophysin positive fibers in the nucleus accumbens (Rosen et al. 2008; Kalamatianos et al. 2010). The density of these fibers is greater in naked mole-rats than in solitary Cape mole-rats, as is OT fiber density in the lateral septum (Kalamatianos et al. 2010). Eusocial naked mole-rats display higher oxytocin receptor density in the nucleus accumbens, as well as other regions including the indusium griseum, central and other nuclei of the amygdala, bed nucleus of the stria terminalis, and the hippocampal CA1 region (Kalamatianos et al. 2010). Naked mole-rats also exhibit variation in the oxytocin system with sex and breeding status; subordinate (non-breeding) males and females have greater numbers of OT immune-reactive cells in the paraventricular nucleus of the hypothalamus when compared to breeders or non-suppressed individuals housed with a mate (Mooney & Holmes 2013). Males exhibit higher OTR density in the medial amygdala (Mooney et al. 2015). Finally, peripheral injection of oxytocin appears to enhance huddling behavior in naked mole-rats in a manner prevented by antagonist administration (Mooney et al. 2014).

Naked mole-rats have a striking lack of vasopressin-immuno-reactive fibers in the lateral septum (Rosen et al. 2008), as might be expected if vasopressin activity in this region is associated with mediation of agonistic interactions. While vasopressin and the vasopressin type 1a receptor are thought to be most important for male social behavior (Carter 2007), a few studies suggest

that vasopressin neurotransmission might also play a role in female behavior (Caldwell & Albers 2004; Rosen et al. 2006; Rosen et al. 2007). Whether this is the case in naked mole-rats is currently unknown.

3.2.4 Dopamine

Several studies on social behavior have centered on the role of the catecholamine neurotransmitter dopamine. Dopamine projections from the ventral tegmental area to the nucleus accumbens and other forebrain regions form a pathway involved in reward-seeking behaviors, stimulus salience, and expectation mismatch evaluation. Dopamine actions in ventral forebrain regions such as the nucleus accumbens may be particularly important for understanding social behaviors that involve intense or rewarding aspects of partnerships, such as parental behavior and reproductive pair-bonds involved in monogamy.

In humans, striatal dopamine systems are activated by viewing images of a loved one, and there appears to be a reduction in activity of critically-oriented brain regions (Zeki 2007). Striatal dopamine pathways are also important for sexual bond formation in rodent models. In prairie voles, oxytocin action in the nucleus accumbens is most likely accompanied by the release of dopamine. Dopamine transmission is critical to the subsequent partner preference formation (Aragona & Wang 2009). Blockade of D2-type dopamine receptors prevents preference formation (Liu & Wang 2003; Aragona et al. 2003; Wang & Aragona 2004), while D1-type receptors are involved in bond maintenance and prevention of new bond formation (Aragona et al. 2006).

In meadow voles, dopamine does not appear to play this critical role in affiliation towards same-sex peers. Blockade of dopamine receptors with the drug haloperidol (a D2 receptor blocker with some non-specific effects) does not impair partner preference formation in female meadow voles (Beery & Zucker 2010). This finding highlights differences between reproductive pair-bonds and non-reproductive affiliation between peers, as well as the importance of studying diverse species.

3.2.5 Stress-related molecules

Stress may impair or enhance social behavior, and a growing literature suggests that glucocorticoids, together with the hormones that regulate them, co-vary with social behavior (reviewed in DeVries et al. 1997; Hostetler & Ryabinin, 2013; Beery & Kaufer, 2015). Glucocorticoids (GCs) such as cortisol and/or corticosterone (CORT) are released following a hormonal cascade that begins with a corticotropin-releasing hormone (CRF) from the hypothalamus. CRF travels through local circulation to the pituitary where it induces the release of the adrenocorticotropic hormone (ACTH), which in turn circulates in the periphery where it stimulates GC production from the adrenal cortex. Most studies have focused on the role of CORT concentration, or on CRF and related urocortins acting centrally on CRF receptors within the brain.

Manipulation studies have shown that corticosterone exposure affects social behavior in monogamous prairie voles, with opposite effects in males and females. In males, corticosterone injection or exposure to a brief swim-stress facilitates the formation of a partner preference for a female. This effect is prevented by adrenalectomy (DeVries et al. 1996). In females, the opposite is true, as CORT injection prevents partner preference formation, but adrenalectomy facilitates it. Interestingly, CORT facilitates *same-sex* partner preferences between paired prairie vole females (unpublished data presented in Carter 1998). Studies in free-living rodents are also beginning to add to our understanding of CORT and social behavior, and this is an area in which caviomorph rodents have contributed important insights (discussed in Section 3.2.2).

CRF receptor densities (subtypes CRF_1 and CRF_2) have also been related to social behavior, and vary extensively between vole species. Some of these differences may correspond to variations in the mating system. Monogamous prairie and pine voles have less CRF_1 receptor in the shell of the nucleus accumbens, with subtly less $CRFR_1$ in the olfactory bulb and superior colliculus than promiscuous meadow or montane voles (Lim et al. 2005). Both monogamous vole species have higher $CRFR_2$ in the septal pole of the nucleus accumbens than promiscuous species. Infusion of CRF into the nucleus accumbens facilitates partner preference formation in males (Lim et al. 2007). CRF receptors also vary seasonally with non-reproductive social behavior in meadow voles, with specific correlations between receptor binding and huddling behavior (Beery et al. 2014).

3.3 Genes and social behavior

The availability of genetic tools such as knockouts and the capability to induce overexpression have enhanced our understanding of the roles of signaling molecules in distinct brain circuits. Specific attention has also been paid to the role of gene and promoter structure in regulating social behavior. The roles of a few genes were discussed in the sections above. We now illustrate the role of genes in social behavior in greater depth with two examples: one of single nucleotide polymorphisms (SNPs) in the oxytocin receptor gene (OXTR) that have been related to human social behavior, and the other of variation in promoter structure of the V1a receptor gene (AVPR1a) that has been linked to mating strategy in monogamous voles.

The availability of **high-throughput sequencing** methodologies has led to a recent surge of non-hypothesis-driven assessments of gene expression across species varying in social behavior, and in gene expression overlap with patterns of neural activity (e.g. O'Connell et al. 2012). These techniques may be particularly valuable in identifying targets from the so-called "brain ignorome" that have been overlooked because they lack a research base (Pandey et al. 2014).

3.3.1 Oxytocin receptor polymorphisms

A single nucleotide polymorphism in the third intron of the OXTR gene (A/G at rs53576) provides one example linking oxytocin receptor genetics to behavior. This SNP has been identified as one of many genetic changes associated with autism (Wu et al. 2005; Lerer et al. 2007) and relates to signs of empathy in multiple studies. Individuals with two copies of the G allele (GG) are less likely to be diagnosed with autism and are also more likely to be rated as more empathic.

In one study, GG individuals scored higher on the "Reading the Mind in the Eyes" test—an empathy assessment in which participants are asked to match descriptions of emotional state to facial expressions in photographs cropped to a horizontal bar around the eyes. GG individuals also displayed lower stress reactivity, assessed by both heart rate responsivity in a startle anticipation task and in a self-report scale (Rodrigues et al. 2009).

In another study by some of the same researchers, differences in prosocial behavior of GG versus AG/AA individuals were assessed in 20-second silenced video clips of romantic partners listening to a partner recounting a difficult time. Genotype-blind observers identified GG individuals as more prosocial at rates far better than chance by their behavior towards a loved one. These assessments were accounted for by significant differences in the physical prosocial behaviors of GG individuals (Kogan et al. 2011). Another study found behavioral associations with parental style in humans for both this SNP and one other (rs1042778) (Michalska et al. 2014).

3.3.2 Vasopressin receptor 1A promoter variation

Multiple studies have demonstrated a functional role for V1aR in behavioral variation within and among vole species (Pitkow et al. 2001; Hammock & Young 2004; Ophir et al. 2008). Comparisons of four vole species suggested that expansion and variation in a microsatellite in the regulatory region upstream of the *Avpr1a* locus encoding the V1aR gene might play a role in brain-region specific expression, and thus behavior (Hammock et al. 2005). Specifically, the *Avpr1* locus in monogamous prairie and pine voles contains a microsatellite sequence consisting of simple sequence repeats interspersed with non-repetitive elements. In comparison, the polygamous montane and meadow voles have truncated versions of this microsatellite. This truncated microsatellite was proposed to relate to the polygamous nature of the montane vole (Young & Wang 2004). The full microsatellite in the *Avpr1a* locus was shown to regulate gene expression of the V1aR in a cell-specific manner using luciferase report assays in four different rat cell line cultures (Hammock & Young 2004). In laboratory tests, male prairie voles bred for the shorter microsatellite were less likely to form partner preferences and have different *Avpr1a* expression patterns compared to males with the longer version of the microsatellite (Hammock & Young 2005).

Although initially promising, this explanation may not be as powerful as originally suspected. The truncated microsatellites observed in the two polygamous species are likely due to the fact that these species are sister taxa, as

most other polygamous vole and mouse species have longer microsatellites in the *Avpr1a* locus (Fink et al. 2006). Studies in monogamous and promiscuous deer mice also showed no association between microsatellite length and mating system (Turner et al. 2010). Despite laboratory differences in behavior with *Avpr1a* variation, field tests of prairie voles with intraspecific variations in *Avpr1a* microsatellite length failed to find associations with social or genetic monogamy (Ophir et al. 2008; Mabry et al. 2011). Most recently, functional tests of variants of the 2.2kb sequence upstream of the *Avpr1a* gene have revealed that this region exerts only a modest influence on receptor distribution, and mimics only a subset of species-specific receptor patterns (Donaldson & Young 2013). Nonetheless, the sequence content of this region did play a role in the pattern of V1aR expression in the amygdala, thalamus, and hippocampus, with some resulting effects on stress-coping behavior in a forced swim task (Donaldson & Young 2013).

Whether relevant targeting sequences are to be found in proximal promoter regions or more distal regulatory regions, variations in gene regulatory elements have been proposed to act as "evolutionary tuning knobs" by providing a means to introduce variation in receptor distribution based on mutations that are frequent but rarely deleterious. By altering receptor density and distribution rather than binding properties, these modifications would alter the role of *Avpr1a* within neural circuits, rather than acting as an on–off switch for functional proteins (Young & Hammock 2007).

This example highlights the importance of keeping in mind that the genetic underpinnings of monogamy and sociality are not restricted to a single gene locus, and that regulation of individual loci is complex (Phelps et al. 2010). As a case in point, the repetitive sequences upstream of the *Avpr1a* locus in humans and primates are different from those observed in rodents, even though these sequences in humans have also been associated with social bonding (Fink et al. 2006; Walum et al. 2008). The same message applies to virtually all findings in which a single gene or protein seems to hold the key to behavior: reality is sure to be more complex. Nonetheless, studies of candidate genes and proteins in particular brain regions have informed our understanding of the pathways that underlie social behavior in a general context. Studies of caviomorph rodents may enhance our understanding further by providing comparative data and a range of additional behaviors to study.

3.4 Mechanisms of sociality in caviomorphs

Caviomorphs are an excellent taxonomic group in which to examine mechanisms supporting sociality because of the variation in social structure across the group. Closely related species differ in whether they are solitary or live in groups (see Chapter 2 in this book), and most group-living species in this clade do not exhibit monogamy, allowing the dissociation of peer social relationships

from reproductive attachments. Studies of species in which groups are composed primarily of related females afford a valuable opportunity to characterize the neurobiological substrates for formation and maintenance of non-reproductive social relationships between adult mammals. Among rodents, female kin groups represent a common form of sociality (Lacey & Sherman 2007). In addition, studies of the mechanisms supporting sociality in caviomorphs can be used to understand the generality of findings in other mammalian taxa (Hayes et al. 2011).

Multiple lines of inquiry have explored the substrates of sociality in caviomorph rodents. In Section 3.4.1, we detail a comparative examination of oxytocin and vasopressin receptor distributions. In Section 3.4.2, we discuss studies of GC secretion and the endocrine system, and in Section 3.4.3, we summarize additional approaches including next generation sequencing studies and hippocampal lesion studies. In addition, caviomorph rodents have been used for a variety of other research pursuits. For example, caviomorph rodents provide opportunities to study developmental plasticity in precocial but slowly developing species (e.g. Gruss et al. 2006). Degus have been used extensively to study circadian rhythms in a diurnal rodent (Lee 2004; Hagenauer & Lee 2008), and guinea pigs are a widely used laboratory model species. Many other studies have taken advantage of particular behavioral and biological traits of this taxonomic group, such as studies of alternate ribosomal subunit slicing in tuco-tucos (Melen et al. 1999). In this section we focus on studies relating to mechanisms supporting sociality in caviomorphs.

3.4.1 OT and AVP in caviomorphs

The first study of oxytocin and vasopressin receptor distributions potentially associated with group living in a mammalian species compared two species from the genus *Ctenomys* (commonly known as tuco-tucos). This monophyletic clade of approximately 60 species of subterranean rodents is endemic to sub-Amazonian South America. While most members of the genus are solitary, at least three species have been identified as social (Lacey et al. 2000; Chapter 7 in this book); recent phylogenetic analyses (Parada et al. 2011) suggest that these species each represent independent origins for group living within the genus. Detailed field studies of two of these species (*C. sociabilis* and *C. opimus*) have revealed that group structure is based on extended social relationships among female kin (Lacey & Wieczorek 2004; E.A. Lacey, unpublished data). At the same time, *C. sociabilis* exhibits pronounced intraspecific variation in social structure, with local populations including both lone and group-living adult females. The initial comparison within this genus focused on one social species (*Ctenomys sociabilis)* and one solitary species (*Ctenomys haigi*) (Beery et al. 2008a). This is currently being extended to a broad-scale comparison of approximately 10 caviomorph rodents. In this chapter we present data from the two-species comparison as well as novel data from *Octodon degus*. Studies of oxytocin and social behavior have also been conducted on domesticated guinea pigs, *Cavia porcellus* (Wallner et al. 2006), not discussed here.

Ctenomys sociabilis versus *C. haigi*

Patterns of OTR and V1aR binding differ dramatically between the solitary and social species of *Ctenomys* examined, as well as between *Ctenomys* and other rodents (Beery et al. 2008a). Such diversity in receptor distributions is consistent with previous data on variation in OTR receptor distributions in closely related rodent species (e.g. Insel et al. 1991; Insel & Shapiro 1992). Interestingly, *Ctenomys* binding patterns do not appear more similar to those of guinea pigs (another caviomorph rodent) than to New World rodents for which data are available (Tribollet et al. 1992; Beery et al. 2008a).

In contrast to the OTR and V1aR binding profiles thought to be associated with social bonds between mates, neither species of tuco-tuco had detectable OTR binding in the nucleus accumbens and *C. sociabilis* had much less V1aR binding in the ventral pallidum than did *C. haigi*. Thus, the social study species did not exhibit the pattern of receptor binding associated with opposite sex pair-bond formation and **biparental care** in voles. Preliminary laboratory trials indicate that female *C. sociabilis* do not display a preference for familiar over unfamiliar conspecifics (E.A. Lacey, unpublished data), suggesting that the nature of social bonds in this species also differs from reproductive pair bonds. If oxytocin and vasopressin are involved in the regulation of social behavior in colonial tuco-tucos, then the neuroendocrine pathways by which these peptides shape social interactions must differ from those associated with the formation of reproductive pair bonds in voles.

Oxytocin acting in other brain regions may nonetheless play an important role in facilitating sociality. Overall, OTR binding was greater for *C. haigi*. This is particularly interesting in light of recent discoveries of the antisocial effects of oxytocin signaling in various brain regions (Beery 2015). As we discussed earlier, for example, meadow voles with more OTR in the lateral septum huddle less (Beery & Zucker 2010). OTR density in this region has also been associated with maternal behavior (Curley et al. 2012), **alloparental care** (Olazábal & Young 2006; Olazábal 2014), social memory (Lukas et al. 2013), and fear conditioning (Guzmán et al. 2013). It is intriguing to consider the possibility that low OTR in the lateral septum is a permissive factor for prosocial behaviors such as cohabitation.

With regard to vasopressin receptors, no differences in V1aR binding in the lateral septum were found between *C. sociabilis* and *C. haigi*. Thus, although increased V1aR binding in this region has been implicated in social recognition and anxiety in male rodents (Bielsky et al. 2005) and in male aggression and territoriality (Everts et al. 1997; Bester-Meredith et al. 2005; Rosen et al. 2006), this tendency does not appear to be associated with differences in social structure between the study species. The present findings in tuco-tucos differ from data in birds indicating that members of more gregarious species have greater vasotocin binding in the lateral septum (Goodson et al. 2006). Of note, however, is that male behavioral differences between these tuco-tuco species are not as great as female differences. Although adult male *C. sociabilis* cohabit with females,

they respond aggressively to one another and do not share burrows with other males. In this regard, male–male interactions may be fairly similar between the study species, rendering lack of lateral septum V1aR unsurprising.

In the field, colonial tuco-tucos are not obligately social—female young sometimes disperse to new burrow systems, and sometimes remain in the natal burrow. This social flexibility implies that while females can cohabitate with one another, it is not essential that they live in groups—in fact, group living appears to reduce individual direct fitness (Lacey 2004). In the laboratory, female *C. sociabilis* rarely fight when paired with novel females (J. Woodruff, pers. comm.), but also do not behave differently toward familiar and unfamiliar females during partner preference tests (E.A. Lacey, unpublished data). This suggests that sociality in this species may not represent social bonding as much as social tolerance.

Degus

Like colonial tuco-tucos, degus (*Octodon degus*) live in social groups and are plural breeders with communal care of offspring (Colonnello et al. 2011; Ardiles et al. 2013). Degus are known to live in social groups in at least four populations within its geographical range (Fulk 1976; Jesseau 2004; Ebensperger et al. 2004, 2011; Hayes et al. 2009). In 2011, one of us (RS) monitored 23 females and 7 males in Parque Nacional Bosque Fray Jorge (PNBFJ) in northern Chile. Following methods described previously (Hayes et al. 2009; Ebensperger et al. 2011), a total of 355 radiotelemetry scan sessions were completed during night hours and used to assign radiotagged degus to resting locations. We recorded 82 occasions in which degus shared resting locations. Provided that resting location associations represent truly social groups, we identified 12 social groups ranging from 2–6 adults (1–5 females and 1–2 males). Group structure was diverse and included the following types: male–female pairs (n = 19), female–female pairs (22), 3 females (8), 1 male–2 females (8), 1 male–3 females (14), 1 male–4 females (4), 1 male–5 females (6), and 2 males–1 females (1) (L.A. Ebensperger, A. Ly Prieto & R. Sobrero, unpublished data).

Oxytocin receptor autoradiography was completed on male and female degus obtained from PNBFJ (Fig. 3.1, Table 3.2) according to the same methodology used for other species in our laboratory, alongside previously assayed samples. Comparison of OTR binding patterns in degus to the two tuco-tuco species that have been assayed revealed interesting similarities and differences. Like both species of tuco-tucos, indusium grisium binding was highly present, OTR density was high in both the medial preoptic area of the hypothalamus and the ventromedial hypothalamus, and binding in the nucleus accumbens was not detectable.

In common with social tuco-tucos (*C. sociabilis*), degus exhibit intense infralimbic pre-frontal cortex binding (Fig. 3.1, panel b) as well as pronounced receptor density in the endopiriform nucleus (Fig. 3.1, panel c), both of which are reduced or absent in solitary Patagonian tuco-tucos (*C. haigi)*. Basolateral amygdala binding was low, as in *C. sociabilis*, with the greatest amygdala binding

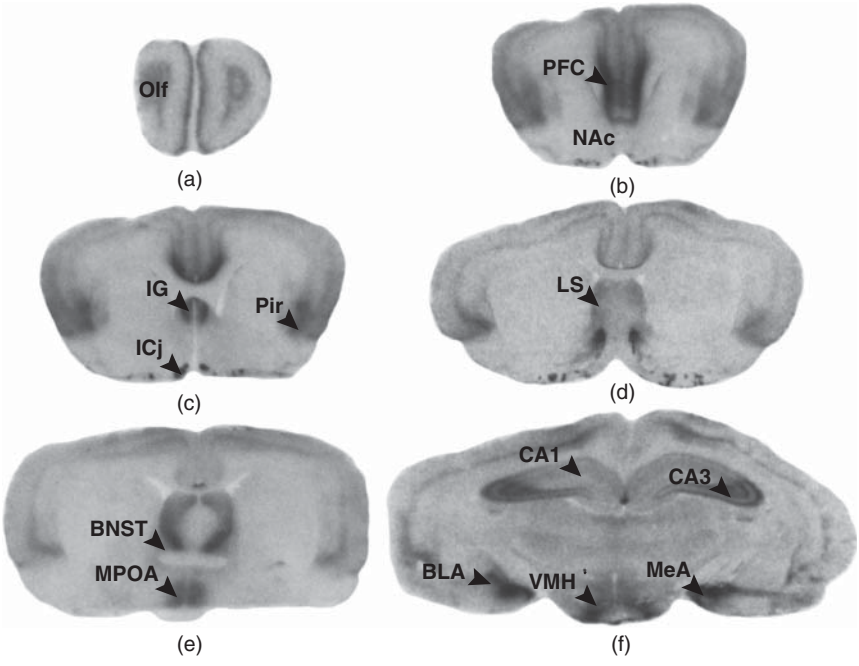

Figure 3.1 Overview of oxytocin receptor distribution in the degu forebrain. Olf = olfactory bulbs, PFC = infralimbic prefrontal cortex, NAc = nucleus accumbens, IG = indusium grisium, Pir = piriform cortex, ICj = islands of Calleja, LS = lateral septum, BNST = bed nucleus of the stria terminalis, MPOA = medial preoptic area of the hypothalamus, VMH = ventromedial nucleus of the hypothalamus, BLA = basolateral amygdala (shown later than scored region), MeA = medial amygdala, CA1 = cornu ammonis 1 of the hippocampus, CA3 = cornu ammonis 3 of the hippocampus. Not all subregions scored are illustrated.

in the posterior aspect (Fig. 3.1, Panel f). Lateral septum binding was present at a moderate level. Unlike both species of tuco-tucos, no central amygdala binding was evident in degus. Degus did display OTR binding in a ventral brain region called the islands of Calleja, which is unlike the two tuco-tucos, but similar to other rodent species, including rats, prairie voles, deer mice, Syrian hamsters (*Mesocricetus auratus*), and both naked and cape mole-rats (Beery et al. 2008a; Kalamatianos et al. 2010).

Broad scale conclusions about oxytocin receptor densities and sociality await a more complete survey of related rodent species with appropriate phylogenetic controls. Larger samples will also allow for more detailed breakdowns of aspects of sociality, for example, the presence or absence of selective partner preferences, alloparental care, degree of stranger tolerance, group size, and group composition. In the meantime, however, some hypotheses can be eliminated. For example it is not the case that all group-living species share high nucleus accumbens binding, as do most social mole-rat species (Kalamatianos et al. 2010), nor do they all have high central amygdala binding as proposed based on a

Table 3.2 Oxytocin receptor binding densities in the degu forebrain.

Brain region	Abbreviation	Binding (nCi/mg)
Cortex		
Prefrontal cortex (infralimbic)	PFC	10.7 ± 1.3
Piriform cortex	Pir	8.4 ± 0.6
Indusium Griseum	IG	10.8 ± 2.2
Accumbens		
Nucleus accumbens: posterior, shell	NAcc Shell	NA
Nucleus accumbens: posterior, core	Nacc Core	0.29 ± 0.06
Septum		
Lateral septum: Total	LS–T	5.2 ± 0.4
Lateral septum: Dorsal	LS–D	5.0 ± 0.5
Bed Nucleus of the Stria terminalis	BNST	6.6 ± 0.8
Hypothalamus		
Ventromedial nucleus	VMH	10.2 ± 1.6
Medial Preoptic Area	MPOA	9.6 ± 0.8
Hippocampus		
Field 1	CA1	2.1 ± 0.3
Field 2	CA2	2.5 ± 0.3
Field 3	CA3	8.3 ± 0.5
Dentate Gyrus	DG	0.78 ± 0.3
Amygdala		
Central	CeA	0.97 ± 0.3
Basolateral	BLA	4.1 ± 0.1
Posterior	PostA	31.0 ± 4.4

Notes: Values represent the mean +/- SEM of selective antagonist (I^{125}-OVTA) binding in four individuals (two females, two males) collected from Fray Jorge, Chile. The assay was performed as described in Beery et al. (2008a) with background subtraction assessed by coincubation of radioactive I^{125}-OVTA and non-radioactive [Thr^4Gly^7]OT which is highly selective for OTR.

small study of tuco-tucos (Beery et al. 2008a). Consistent with current data, social species may prove to share lower binding in the basolateral amygdala, lateral septum, BNST, or other brain regions (A. Beery, unpublished data). Of note, highly social naked mole-rats exhibit very sparse and low density receptor binding in most regions, across OTR and V1aRs (A. Beery, unpublished data) relative to other rodents with which we have experience, including voles, rats, and tuco-tucos. While oxytocin plays an important role in facilitating a wide range of social behaviors, the presence of more receptors in one species over another does not necessarily relate to the degree of particular social behaviors, for at least the majority of brain regions in which they may be present.

3.4.2 Stress and social behavior in caviomorphs

Animals respond to environmental, reproductive, and social challenges by producing glucocorticoid hormones (cortisol, corticosterone) that release energy stores for metabolism (Wingfield & Romero 2001; Bonier et al. 2009). In response to challenging conditions, individuals are expected to increase their GC secretion (Wingfield & Romero 2001), increasing baseline levels of GC (Romero 2004; Bonier et al. 2009). Short-term increases in circulating GCs are adaptive because they enhance survival and reproduction (Romero 2004; Bonier et al. 2009). In contrast, long-term elevation of GCs may have negative consequences such as drawing resources away from self-maintenance and growth and depressing immune function (Wingfield & Romero 2001; Dickens et al. 2009; Romero et al. 2009). Long-term elevations of GCs may reduce the responsiveness of the HPA axis, reducing an individual's ability to respond to new stressors and reducing survival and reproductive success (Rich & Romero 2005; Cyr & Romero 2007; Dickens et al. 2009). For example in female chinchillas, differences in GC metabolism under basal conditions are associated with both fur-chewing behavior and anxiety-related behaviors in behavioral tests (Ponzio et al. 2012).

The magnitude of an individual's stress response will depend on several intrinsic (e.g. physical condition) and extrinsic (e.g. ecological, social conditions) factors. Moreover, glucocorticoid hormone production is likely to be affected by life history traits (Bonier et al. 2009) or to influence them (Crespi et al. 2013). In recent years, researchers have determined some of the factors underlying variation in the neuroendocrine responses of caviomorph rodents. In particular, progress has been made in three important areas of research: (1) determining how social, environmental, life history, and reproductive conditions affect circulating stress hormone levels; (2) the influence of the early social environment on adult stress responses; and (3) the combined effect of stress and sex hormones (e.g. testosterone) on social and mating behaviors. In this section, we review the first major area of research. The latter areas of research (points 2 and 3) are addressed briefly. Extensive reviews of these themes are beyond the scope of this chapter and are the subject of recent comprehensive reviews (Colonnello et al. 2011; Hayes et al. 2011; Chapter 4 in this book).

Social conditions and circulating glucocorticoids

Research on two plurally breeding caviomorphs—degus and colonial-tucos—suggests that the neuroendocrine stress responses of adults are less sensitive to variation in group size than variation in group composition. In degus, the number of breeding females per group and total group size do not predict the baseline cortisol levels of lactating females (Ebensperger et al. 2011). However, in the lab, breeding females nesting with a male have higher plasma cortisol levels than breeding females nesting with a non-breeding female (but not solitary females) (Ebensperger et al. 2010). In the wild, the probability that degu offspring disperse

from natal nests increases with increasing number of offspring per group, though baseline cortisol does not increase with increasing group size and number of offspring at the natal nest (Quirici et al. 2011). The extent to which communal care of offspring influences the stress responses of offspring and is affected by the stress physiology of mothers is a topic of current investigation in degus (C. Bauer, L.M. Romero, L.D. Hayes & L.A. Ebensperger, unpublished data).

Similar to degus, the baseline levels of fecal corticosterone of free-living, yearling colonial tuco-tuco females (*C. socialibis*) do not vary with group size (Woodruff et al. 2013). Similar to social marmots (Hackländer et al. 2003), the stress responses of tuco-tuco females depend on the age composition of a group. Yearling tuco-tuco females living alone (dispersers) have significantly higher baseline fecal metabolites of corticosterone than yearling females living in groups or in pairs (Woodruff et al. 2013). Moreover, there is an inverted U-shaped relationship between the number of older females in a group and baseline fecal metabolites of corticosterone of females (Woodruff et al. 2013). This latter trend is not expected in degus, given their higher inter-annual mortality and lower reproductive rates.

The extent to which individuals are exposed to conspecifics during development may affect their stress responses to different social and mating situations (Chapter 4 in this book). For example, in the 1980s and 1990s, Sachser et al. (Sachser 1987; Sachser & Lick 1991) demonstrated that social experience (whether an individual is reared singly or in large groups), but not social status, influences the glucocorticoid levels of male guinea pigs under laboratory conditions. More recently, work on the socially monogamous yellow-toothed cavy (*Galea monasteriensis*) demonstrated a close connection between pair-bonding and stress, confirming previous work on other socially monogamous mammals (Adrian et al. 2008 and references within). The removal of a female from an established pair resulted in significant elevations of plasma cortisol in males (Adrian et al. 2008). In this study, male cortisol levels were reduced after the return of the female to the home enclosure.

Environmental and life history variation

Research on degus (Kenagy et al. 1999; Bauer et al. 2014) and tuco-tucos (*C. talarum*: Vera et al. 2011, 2013) suggests that circulating glucocorticoid levels vary by season, though these responses are confounded by different reproductive states associated with seasonality in these species (e.g. Bauer et al. 2014). In the degus, females exhibit the highest stress-induced cortisol during the austral winter-spring (which corresponds to gestation and lactation) (Bauer et al. 2014). Males exhibit higher stress-induced cortisol during the austral summer (non-breeding) and the late austral winter (late gestation for females) than the early austral winter (early gestation for females) (Bauer et al. 2014; see also Kenagy et al. 1999). Similarly, in tuco-tucos (*C. talarum*), the plasma cortisol levels (but not corticosterone) of males are statistically greater during the peak reproductive season and non-reproductive season than during the beginning of

the reproductive season (Vera et al. 2011). Baseline and stress-induced cortisol levels of *C. talarum* females are greater during the reproductive season than during the non-reproductive season (Vera et al. 2013). Together, these results suggest that a common thread in caviomorphs is that sex-specific stress responses reflect different life history challenges associated with seasonal reproduction.

Reproductive challenges

In mammals, investment in offspring—particularly during lactation—incurs a significant energetic cost on females (Thompson 1992). Glucocorticoids play an important role in sustaining lactation. Based on this premise, Bonier et al. (2009) proposed the cort-adaptation hypothesis, which predicts different relationships between glucocorticoid hormone levels and fitness during different reproductive states. Specifically, positive relationships between the concentration of glucocorticoids and reproductive success are predicted during late breeding (e.g. lactation) but not during pregnancy or mating. Support for this hypothesis comes from work on naturally occurring populations of degus. Ebensperger et al. (2011) observed that the baseline cortisol levels of lactating females (based on fecal metabolites of cortisol; Soto-Gamboa et al. 2009) were positively correlated with per capita number of offspring produced. Interestingly, in the same population, elevated baseline cortisol during a current breeding event was associated with reduced future reproduction (Ebensperger et al. 2013). In contrast to degus, the reproductive output of colonial tuco-tucos—based on the total and per capita number of offspring per burrow system—does not predict variation in baseline cortisol of lone and group-living females (Woodruff et al. 2013). These differences further support the idea that species-specific life history traits such as mortality, reproductive output (Ebensperger et al. 2013) and circadian patterns of behavior (Woodruff et al. 2013) play an important role in socially-mediated stress responses of caviomorph rodents.

3.4.3 Other approaches

Genetic approaches to social behavior are often slow to develop in non-traditional species, both because of a lack of transgenic animals, and—at a more basic level—the lack of published genomes. This is beginning to change with high throughput sequencing, and one study has begun the process of mapping gene expression changes with sociality in colonial tuco-tucos (*Ctenomys sociabilis*). As a first step, a reference transcriptome was created from hippocampal tissue from 10 individuals housed under different conditions; the authors propose to examine transcriptome variations associated with variation in group living in the future (MacManes & Lacey 2012).

At the same time, classic neuroscience manipulations such as brain lesions are being used to look at social behavior in some species. Although most studies of social behavior focus on regions such as the pre-frontal cortex, nucleus accumbens, and amygdala, some studies have indicated that the hippocampus may be important for social behavior. Social rodents that depend on recognition

and affiliative behaviors as a foundation for group living provide a special opportunity to examine impacts of this region on social behaviors. In a recent study, researchers found that both social recognition and related social behavior were impaired in degus following hippocampal lesions (Uekita & Okanoya 2011). The hippocampus may be an important crossroads for integrated sensory information about the social as well as the spatial environment.

3.5 Future directions

3.5.1 Caviomorphs as model organisms

As we approach the goal of examining the mechanisms supporting social behavior in broader taxonomic contrasts, caviomorph rodents provide many excellent opportunities. Caviomorphs exhibit variation in sociality outside the context of monogamy, and will allow us to better explore circuits and pathways that support non-sexual social behavior between peers. Comparisons between and within populations of variably social species will inform our understanding of how ecological conditions promote or impair groups with different characteristics, and shine some light on how life in groups affects organismal physiology. In a broader sense, the existence of varied behavior within and between species will allow us to understand how variation in neurobiology relates to evolutionary lineage and to social behavior. While research on social neurobiology continues to "dig deep" with model species such as mice and rats, we are also witnessing a rebirth of comparative studies as techniques become more scalable, and as the importance of "natural experiments" in social behavior is better appreciated.

3.5.2 Predicting behavior from neurochemistry

One ultimate goal of studies of the mechanisms supporting sociality would be to enable predictions of social structures on the basis of promoter structure, gene expression, and/or neuroanatomical patterning of receptors or their ligands. To date, patterns found in pairs of closely related species have not translated particularly well to other species in terms of specific binding patterns or genetic changes (reviewed in Beery et al. 2008a; Phelps et al. 2010). Animal societies are maintained by a variety of social interactions, ranging from general prosocial tendencies to highly specific attachments to particular individuals. Just as there are many different evolutionary paths to living in groups, so there are likely to be a variety of mechanisms that contribute to the different types of social relationships that maintain them. For example, meadow voles and colonial tuco-tucos share the tendency to form non-sexual social groups that include multiple same-sex individuals; even so, they may vary in how they achieve this end, with more specific attachment formation in meadow voles. Finding patterns supporting diverse behavior will require an increased level of sophistication in our specification of social behavior (Goodson 2013; Hofmann et al. 2014). On the other hand, while the behavioral impacts of specific neurochemicals acting in different circuits may

vary more than we currently understand, there is a high degree of conservation in the importance of particular molecules.

Some broad-scale efforts to associate behavioral and neurobiological data have met with success. In two neuroanatomical examples, neocortex volume was found to be associated with group size and social network size in primates (Kudo & Dunbar 2001) and telencephalon size was associated with monogamy in cichlid fish (Pollen et al. 2007) (see Table 3.1 for more examples). A characteristic of both of these studies is the examination of neurobiological data in a phylogenetic context. This sort of approach that melds evolutionary and neural data in search of fundamental commonalities is sorely needed (Goodson et al. 2005; Pollen & Hofmann 2008; O'Connell & Hofmann 2012; Hofmann et al. 2014; Taborsky et al. 2015). Fortunately, this type of research is becoming ever more possible as the ability to collect and analyze data operates at greater and greater scale.

To date, the recognition-reward-reinforcement pathways involved in maternal attachment and pair-bonding are the best understood areas within the realm of affiliative behavior, and these pathways are often extended as the basis for social behavior in general. There is no *a priori* reason to assume, however, that same-sex social bond formation utilizes the same mechanisms, and initial findings in both North and South American rodents suggest this is not the case. Absence of oxytocin receptors in the nucleus accumbens of colonial tuco-tucos provided the first sign that maintenance of same-sex sociality and opposite-sex bonding are not equally reliant on OT signaling in this brain region. This may indicate that sociality has little to do with traditional reward and reinforcement pathways in this species. Only through the discoveries of biological mechanisms contributing to monogamy and parenting has the door been opened for inquiry about other types of relationships; now it is time to examine other types of relationships that play an important role in the lives of caviomorph rodents.

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