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Solitary Mammals Provide an Animal Model for Autism Spectrum Disorders

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Species of solitary mammals are known to exhibit specialized, neurological adaptations that prepare them to focus working memory on food procurement and survival rather than on social interaction. Solitary and nonmonogamous mammals, which do not form strong social bonds, have been documented to exhibit behaviors and biomarkers that are similar to endophenotypes in autism. Both individuals on the autism spectrum and certain solitary mammals have been reported to be low on measures of affiliative need, bodily expressiveness, bonding and attachment, direct and shared gazing, emotional engagement, conspecific recognition, partner preference, separation distress, and social approach behavior. Solitary mammals also exhibit certain biomarkers that are characteristic of autism, including diminished oxytocin and vasopressin signaling, dysregulation of the endogenous opioid system, increased Hypothalamic-pituitary-adrenal axis (HPA) activity to social encounters, and reduced HPA activity to separation and isolation. The extent of these similarities suggests that solitary mammals may offer a useful model of autism spectrum disorders and an opportunity for investigating genetic and epigenetic etiological factors. If the brain in autism can be shown to exhibit distinct homologous or homoplastic similarities to the brains of solitary animals, it will reveal that they may be central to the phenotype and should be targeted for further investigation. Research of the neurological, cellular, and molecular basis of these specializations in other mammals may provide insight for behavioral analysis, communication intervention, and psychopharmacology for autism.

Keywords: autism, solitary, monogamous, oxytocin, vasopressin

Autism is a developmental disorder defined by behavioral symptoms across three general areas: social reciprocity, communication, and restricted and repetitive interests (American Psychiatric Association, 2000). It is diagnosed through behavioral observation using standardized tools as well as clinical judgment (Piven, 2000). The diagnostic indicators are behavioral symptoms rather than definitive neurological markers. Proposed biomarkers include gene expression profiling, proteomic profiling, metabolomic profiling, head size, brain structure, neurotransmission, and eye movement (Walsh, Elsabbagh, Bolton, & Singh, 2011). Multiple etiologies are involved in autism and autism spectrum disorders (ASDs), including genetic susceptibility, multigenic interactions, and interactions between genetic and environmental factors (Cantor, 2009). Because of the broad range of biomarkers and etiological factors, well-defined animal models that can recapitulate core symptoms of the disorder are essential for research on the nature of the neurological aberrations. Currently, mouse models are the most widely utilized because of the extensive knowledgebase available for mouse genetics and neurology, and because of the availability of detailed behavioral phenotyping data available for many mouse strains (Halladay et al., 2009).

Rodent models of autism typically involve mice with specific lesions, mice that are genetically engineered to carry certain genes,

or panels of inbred mouse strains carrying naturally occurring genetic polymorphisms. Advances have included the establishment and evaluation of mouse models capable of reflecting disease symptoms such as impaired social interaction, communication deficits, and repetitive behaviors. Large-scale data sets and biobanks have linked multiple genes to ASDs, and genetic linkage and association studies in humans have begun to inform the design of mouse models. Transgenic rodent mutants with deletions, truncations, and overexpression of these autism candidate genes have helped to model the disorder (Moy & Nadler, 2008). However, the rodents used for these models are primarily social animals that are engineered to have symptoms characteristic of social deficits. The present article attempts to place emphasis on the potential importance of naturally occurring phenotypes found in solitary species in modeling autism. There is a large knowledge base in zoology and behavioral neuroscience of naturally existing variation in social capacities found between mammalian species that can be harnessed as a tool to inform the development of future animal models and to provide insight on the biology of autism.

Most animals, many mammals, and several species of primates are solitary (Alcock, 2001). Solitary species are known to have specialized behavioral adaptations that prepare them mentally to live alone (Decety, 2011). These behavioral adaptations have been shown to have neural underpinnings (Young, 2009). Adjustments to neural social circuits and associated neurotransmitters, neuromodulators, and their receptors fine-tune solitary animals to direct cognition toward foraging and self-preservation rather than on interaction with conspecifics (Alcock, 2001). Not all solitary mammals exhibit the same suite of adjustments. This is because indi-

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vidual species respond to diverse social concerns particular to their unique environments. There does, however, seem to be a large amount of convergence in many of these adjustments (Adolphs, 2001). Social neuroscientists have begun to elucidate specific neurological pathways that underlie specializations involved in prosocial behavior, attachment, and bonding. Researchers are also beginning to compare the pathways found in social animals with those in solitary animals (Shapiro & Insel, 1990), and to identify traits that correlate with group size and social necessity (Dunbar, 1988, 1998). Even though this research is in its nascent stages and the pathways involved are currently not well resolved, continued experimental research may have important implications for ASDs, because individuals on the autism spectrum share a variety of traits with solitary species (Reser, 2011a, 2011b). In an effort to promote this comparative approach, the present article reviews the literature that points to comparable traits.

Our understanding of the social nervous system has been driven by studies analyzing specific biological markers in species that parent, species that are socially monogamous, species capable of developing extended families, and those capable of selective social camaraderie (Porges & Carter, 2010). Comparisons of the species-typical mating and affiliative strategies between the socially monogamous prairie vole (*Microtus ochrogaster*) and the closely related but nonmonogamous (promiscuous or polygamous) montane vole (*Microtus montanus*) has served as the primary model for the mapping of the neurocircuitry of social behavior in mammals (Carter, DeVries, & Getz, 1995). These voles have been closely studied, and they exhibit divergent traits in the neuroscience of bonding and attachment. These and other closely related, but socially discrepant, pairs of species are discussed in an effort to build a comparative paradigm.

Individuals on the autism spectrum exhibit both behaviors and biological markers that are common in solitary and nonmonogamous mammals (Reser, 2011a). Both solitary mammals and autistic individuals have been reported to demonstrate lower measures of affiliative need, bodily expressiveness, bonding and attachment, conspecific recognition, emotional engagement, gregariousness, partner preference, separation distress, and social approach behavior. Individuals with autism also exhibit certain biological markers that are characteristic of solitary mammals, including diminished oxytocin (OXT) and vasopressin (AVP) action, dysregulation of the endogenous opioid system, increased Hypothalamic-pituitary-adrenal axis (HPA) activity to social events, and reduced HPA activity to separation, and isolation owing to anomalies in vagal tone and parasympathetic response (some of these mechanisms may be ontogenetically prior to others). Tables 1 and 2 show

matched comparisons between (a) neurotypical humans and humans with autism, and (b) the nonmonogamous montane vole and the monogamous prairie vole. Are the similarities in these shared behaviors sufficient to warrant the pursuit of a solitary mammal model of autism? Before this question can be answered, these purported similarities must be investigated in a variety of species with differing bonding and attachment strategies.

There are currently no animal models that reflect the entire range of behavioral and neurological phenotypes in autism; however, some researchers have advised that studies of the neurobiology of normal social cognition may provide clarification for understanding the mechanisms responsible for autism (Hammock & Young, 2006). This article extends this argument, advising that studies of the neurobiology of solitary cognition may provide further insight and clarification. Regardless of whether the similarities between the brains of solitary/nonmonogamous mammals and individuals on the autism spectrum are coincidental or are partly due to adaptive convergence to similar ecological demands (as proposed and outlined in Reser, 2011a), they may help to elucidate the neurobiological and molecular underpinnings of ASD.

Hammock and Young (2006, p. 2187) posit that

basic research into ethologically relevant behavior of the prairie vole has allowed us to gain insight into some of the underlying neural and genetic mechanisms of social-bonding behavior in mammals. Humans may share some of these mechanisms and when these mechanisms are disrupted, either by genetic, environmental or interactive causes, extreme phenotypes such as autism may be revealed. These studies illustrate the power of the comparative neuroethological approach for understanding human neurobiology and suggest that examining the neurobiological bases of complex social behavior in divergent species is a valuable approach to gaining insight on human pathologies.

Mammals That Forage Solitarily

Some animal species are obligately social, some are obligately solitary, and others are facultatively social, and can transition between social and solitary lifestyles. Species that are obligately social form groups even under very low population densities (Bothma & Walker, 1999), whereas some species like whistling rats (*Paratomys brantsii*) maintain solitary living even under very high population densities (Jackson, 1999). Obligate solitary living is rare in birds, but common in mammals, reptiles, amphibians, and invertebrates. Among the many mammals that have been categorized as solitary are well-known animals such as armadillos, opossums, orangutans, red pandas, red squirrels, Tasmanian devils, as

Table 1
Behavioral Predispositions in Autism and Montane Voles

Reduced behaviors	Individuals with autism relative to those without	Montane voles relative to prairie voles
Affiliative need, gregariousness, and social approach	Baron-Cohen et al., 2000; Bora et al., 2009; Mundy, 1995	Lim et al., 2004; Shapiro & Insel, 1990
Bodily expressiveness and communicativeness	Peppé et al., 2007; Yirmiya et al., 1989	Hammock & Young, 2006; Marler, 1968
Bonding and attachment	Rutgers et al., 2004; Sigman & Ungerer, 1984	Hammock & Young, 2006; Marler, 1968
Conspecific recognition	Dalton et al., 2005; Pierce & Redcay, 2008	Lim et al., 2004; Young, 2002
Social preference	Buitelaar, 1995; Depue & Morrone-Strupinsky, 2005	Lim et al., 2004; Young, 2009

Table 2
Neurological Presentations in Autism and Montane Voles

Presentations	Humans with autism	Montane relative to prairie voles
Reduced action of oxytocin and vasopressin	Green et al., 2001; Hollander et al., 2003	Marler, 1968; Shapiro and Insel, 1990
Dysregulation of the endogenous opioid system	Gilberg, 1995; Machin & Dunbar, 2011	Shapiro et al., 1989
Anomalies in vagal tone and parasympathetic response	Porges, 2005; Porges & Carter, 2010	Grippe et al., 2007, 2008; Shapiro & Insel, 2004
HPA hyperactivity in social situations	Baron-Cohen et al., 2000; Sahley & Panksepp, 1987	Hammock and Young, 2006; Shapiro and Insel, 1990

well as most bears, cougars, tigers, and skunks. Table 3 provides a more extensive list that includes a diverse assortment of mammals from orders, including primates, lagomorpha, rodentia, carnivora, insectivora, artiodactyla, perissodactyla, soricomorpha, xenarthra, and also marsupials and monotremes.

Behavioral genetics has demonstrated that both social (subsocial, parasocial, presocial, eusocial, etc.) and asocial tendencies have both genetic and neural underpinnings (Trivers, 1985). Furthermore, these traits can show considerable variability both between and within animal species (Frank, 1998). Significant intraspecific variation in social propensities has been observed in more than one hundred vertebrate species (Lott, 1991). It is not clear if the variation within species is due to genetic differences between individuals, differential responses to environmental circumstances, or gene–environment interactions. Likewise, it is not clear why there might be variation in social propensities and abilities within our own species (Baron-Cohen, 1995). However, it is thought that much variation between species is genetic. Perhaps both intra- and interspecific diversity can be utilized to investigate the autism spectrum; however, the data concerning interspecific diversity is currently much stronger. Even closely related species can have vastly divergent social predispositions. In fact, phylogenetic inertia is thought to be strong for general physiology but not for social behavior, that is, closely related species can have very different social organization if they live in different habitats or eat different foods (Zuk, 2002).

Placed together in a large room, several species of rodents, such as nonmonogamous montane voles, are content to be loners and

will spread out uniformly, attempting to maximize the distance between themselves and their conspecifics. Social rodents like monogamous prairie voles, if placed in the same room, will prefer to huddle together and affiliate in close proximity (Shapiro & Insel, 1990). It is thought that the wide discrepancy in social behavior between these voles reflects adaptation to two very different physical and social environments (Adolphs, 2001). In prairie and pine voles, the males and females form long-term pair bonds, establish a nest site, and rear their offspring together. In contrast, montane and meadow voles do not form pair bonds, and only the females take part in rearing the young. This is true in the wild and in captivity. It is believed that this diversity in behavior is maintained by selection favoring one of two male spatial/paternity strategies: (a) maintain a small home range and actively defend the female that one is monogamous with from other males (breeder), or (b) maximize range by wandering in order to maximize the rate at which unguarded females are encountered (roamer; Phelps, 2010).

Nonmonogamous montane and meadow voles do not show partner preferences that prairie and pine voles do after experimentally induced pair bonds are instigated by cohabitation (Lim et al., 2004). This may be likened to the situation in autism in which social bonding and secure attachment behavior is diminished (Sigman & Ungerer, 1984). Pups of the monogamous prairie vole, but not the nonmonogamous montane vole, show a robust stress response to maternal separation along with increased vocalization and increased serum corticosterone levels (Shapiro & Insel, 1990). This behavioral pattern is highly analogous to the diminished separation distress evident in autistic infants and children. In fact, children with autism show diminished (but existent) preferential proximity seeking and reunion behavior in the Strange Situation Test and other measures (Buitelaar, 1995; Naber et al., 2008).

Because of small size and easy maintenance in the laboratory, the neurobiology of the social differences between these two species of vole has been carefully examined. The differences are thought to be largely governed by the regulation of the neuro-modulators OXT and AVP (Churchland, 2011). In fact, neuropeptides like OXT, AVP, and endogenous opioids are known to regulate complex social behaviors, in conjunction with monoaminergic neurotransmitter systems (Miller, 2005). Interestingly, the same neuropeptides have been shown to be affected in autism (Gilberg, 1995; Green et al., 2001; Hollander et al., 2003; Machin & Dunbar, 2011). In fact, preliminary data suggest that allelic variants of genes necessary for the development of parental and affiliative behaviors in other species (especially the genes for the OXT and prolactin receptors) are associated with ASD (Yrigollen et al., 2008).

Table 3
Abridged List of Solitary Mammals

<p>Armadillo, Baikal seal, Bamboo rat, Bear, Black rhinoceros, Black-footed cat, Blind mole rat, Brown-throated sloth, Bushbuck, Bushy-tailed opossum, Clouded leopard, Coast mole, Cougar, Dusky-footed woodrat, Eastern pygmy possum, European mink, European Polecat, Fishing Cat, Four-horned Antelope, Four-toed Hedgehog, Giant Anteater, Grizzly bear, Hog-nosed skunk, Honey badger, Jaguar, Japanese hare, Javan rhinoceros, Lemming leopard, Maned sloth, Marbled polecat, Marten, Mountain weasel, Montane vole, Meadow vole, Musk deer, Neotropical otter, Northern bettong, Opossum, Orangutan, Paca, Philippine mouse-deer, Philippine tarsier, Polar bear, Pudú, Red brocket, Red panda, Red squirrel, Rhinoceros, Ringed seal, Scaly-tailed possum, Short-beaked echidna, Siberian chipmunk, Skunk, Solenodon, Southern tamandua, Spotted skunk, Steppe polecat, Striped hog-nosed skunk, Striped polecat, Sumatran rhinoceros, Tapeti, Tasmanian devil, Tiger, Vagrant shrew, Water deer, Zokor</p>
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It will be interesting to perform further comparative analyses, but it is not completely clear which genes or which brain systems should be interrogated. A relevant model of neurobiological regulation of affiliation in mammals (Depue & Morrone-Strupinsky, 2005) suggests that dopamine plays an important role in incentive–reward motivational processes associated with the appetitive phase of affiliation, that endogenous opioids are involved in the consummatory phase of socialization, and that OXT and AVP enhance the perception and memory of affiliative stimuli. To begin to make the appropriate comparisons, let us first take a look at the role of OXT signaling in nonmonogamous rodents, and in autism.

OXT Signaling

OXT is a peptide hormone and neuromodulator involved in reproduction, social recognition, and pair bonding in mammals. Animal species that rely on pair bonds and social attachment exhibit higher levels of plasma OXT, especially when it is behaviorally relevant, like during monogamous sex, childbirth, and lactation (Campbell, 2008). Not surprisingly, interspecific, seasonal, and reproductive variation in OXT concentrations have been attributed adaptive significance. High levels are associated with mating, continued proximity, trust, and pair bonding in a large number of mammals (Adolphs, 2001). OXT is capable of down-regulating or buffering the response to stressors, especially social ones (acting at the level of the hypothalamus, among other areas). It is released during positive social interactions, and appears to facilitate capacity for being trusting and socially perceptive (Porges & Carter, 2010). OXT knockout mice show deficiencies in social recognition and social memory, and also in the ability to manage emotional reactivity due to stress (Pedersen, Vadlamudi, Boccia, & Amico, 2006; Takayanagi et al., 2005).

After being synthesized in magnocellular neurons in the paraventricular and supraoptic nuclei of the hypothalamus, and processed along axonal projections to the posterior lobe of the pituitary, OXT and AVP are released into the extracellular space, resulting in both local action and diffusion throughout the brain. OXT and AVP are also synthesized by parvocellular neurons of the hypothalamus, and from here travel directly, via hypothalamic projections, to different brain areas, including the amygdala, hippocampus, striatum, suprachiasmatic nucleus, bed nucleus of the stria terminalis, and brain stem, where they take different actions, dependent on the receptors they bind to. It is not clear if the areas that synthesize, process, and distribute OXT and AVP are affected in autism or in solitary animals, although this should be a topic of future research. It is known that the anatomical sites of OXT synthesis and their projections are highly conserved in mammalian species (Hammock & Young, 2006), but their quantitative properties may be divergent. On the other hand, there are significant differences in OXT receptor distribution patterns between monogamous and nonmonogamous mammals.

Prairie voles and montane voles have very different OXT receptor profiles. The montane vole, relative to the prairie vole, has a much smaller number of receptors in the brain for OXT and, unlike the amorous prairie voles, they do not form pair bonds (Marler, 1968). The montane voles have fewer receptors and thus are less responsive to OXT, making them more wary, suspicious, and more easily frightened of other members of their species (Marler, 1968).

When the two are compared, monogamous species have higher densities of OXT receptors in the caudate, putamen, amygdala, orbitofrontal cortex, and nucleus accumbens (Hammock & Young, 2006). This may indicate that these brain regions, and their quality of OXT receptivity, should be attended to in autism. The shell region of the nucleus accumbens is especially abundant in OXT receptors in socially monogamous species and prairie voles, but not in nonmonogamous voles (Insel, 2010). OXT receptor antagonists applied directly to the nucleus accumbens of female prairie voles inhibit mating-induced partner preference formation, indicating that activation of OXT receptors in this area of the brain is necessary for bonding and attachment (Young, Lim, Gingrich, & Insel, 2001). Other nonmonogamous species, such as marmoset monkeys, rhesus monkeys, titi monkeys, the California deer mouse, and the white-footed mouse, have OXT and AVP receptor distributions that are highly similar to that of the montane vole (Bales et al., 2007; Z. Wang et al., 1997). These comparisons suggest that autism research should be focused on the nucleus accumbens and its role in social motivation. It would be interesting to compare the details of OXT action, such as receptor number and distribution pattern, in solitary animals with that of people with autism, but again, this research has not been done. The comparable data about receptor density and distribution in humans has not been determined because injection methods to tag receptors cannot be done in living humans for ethical reasons, and do not yield results when performed on the brains of cadavers.

Results interpreted as supporting the hypothesis that baseline cerebrospinal fluid (CSF) OXT concentrations are related to species-typical social/affective behavior patterns comes from comparisons between bonnet macaques (*Macaca radiata*) and pigtail macaques (*Macaca nemestrina*). The bonnet macaques, which have significantly higher levels of CSF concentrations of OXT when laboratory-born than the pigtail macaques, are described as gregarious affiliative and affectively stable, whereas pigtail macaques are described as socially distant and temperamentally unstable (Rosenblum et al., 2002). Furthermore, the pigtail macaques exhibited elevations in CSF corticotropin-releasing factor, elevations of which promote social vigilance in both solitary and territorial mammals. Within a species, the early environment may play a role. When rhesus macaques (*Macaca mulatta*) are separated from their mothers at birth and reared with peers in a small cage, they develop a wide range of behavioral abnormalities that have been associated with autistic symptoms. These monkeys exhibit low affiliation, high aggression, and high self-directed and repetitive activities. These genetically very social monkeys also had significantly lower concentrations of CSF OXT (Winslow, Noble, Lyons, Sterk, & Insel, 2003).

OXT, the neuropeptide thought to enhance social learning, social expressiveness, direct eye gaze, and the ability to remember faces in humans (Savaskan, Ehrhardt, Schulz, Walter, & Schachniger, 2008), is reduced in the blood plasma of autism subjects. Diminished circulating levels of OXT may play a large role in retuning multiple social brain modules in autism, and increasing fear and avoidance responses to social stimuli (Green et al., 2001). It has been shown that intravenous OXT produces a significant reduction in stereotypic behaviors in adult autism subjects, and increases empathy and generosity in people without autism (Hollander et al., 2003). After treatment with intranasally inhaled OXT, autistic patients have been reported to exhibit more appropriate

social behavior (Andari et al., 2010), increased attention to the eye region of faces (Andari et al., 2010), increased emotion recognition (Guastella et al., 2010), diminished repetitive behavior (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005), and diminished social fear (Kirsch et al., 2005). Likewise, OXT infusions into the brain increase side-by-side contact and decreased aggressive behavior in female prairie voles (Witt, Carter, & Walton, 1990), increased social contact in male rats (Witt, Winslow, & Insel, 1992), and in squirrel monkeys (Winslow & Insel, 1991). Although this research is promising, further clinical trials are necessary to demonstrate potential benefits and side effects in the treatment of autism (Bartz & Hollander, 2008).

Humans and all eutherian mammals have only one receptor for OXT, OXTR, but humans have several alleles for the receptor that differ in their binding effectiveness. Individuals homozygous for the G allele (which produces the high affinity receptor), when compared with carriers of the A allele, show higher empathy, lower overall stress response, as well as lower prevalence of autism (Rodrigues, Saslow, Garcia, John, & Keltner, 2009). Two single nucleotide polymorphisms in the third intron of the OXT receptor have emerged as candidate genes for autism. In fact, several studies have shown that these polymorphisms were overtransmitted by families to offspring with ASD (Wermter et al., 2010; Wu et al., 2005). Other genes seem to be involved as well. Recent work on CD38, a transmembrane protein that is involved in OXT secretion in the brain, has shown that several genetic variants of the gene show a significant association with high functioning autism (Munesue et al., 2010). Although several studies point to function of the OXT receptor (Jacob et al., 2007; Wermter et al., 2010), the underlying problem with OXT signaling in autism remains unclear.

AVP Signaling

Arginine AVP is a peptide hormone found in most mammals that plays a key role in homeostasis and the regulation of water, glucose, and salts in the blood. Stored in vesicles in the posterior pituitary, most AVP is released into the bloodstream, although some AVP is released directly into the brain, where it plays a significant role in social behavior and bonding. Humans and all eutherian mammals have three receptors AVP: AVP receptor 1A (AVPR1A), AVP receptor 1B, and AVP receptor 2. Experimental studies in several species have indicated that the precise distribution of AVP receptors in the brain is associated with species-typical patterns of social behavior. Specifically, there are consistent differences between monogamous and nonmonogamous voles in the distribution of AVP receptors and the distribution of AVP-containing axons (Young, 2009). AVP release during social interaction and mating in prairie voles leads to increased activation of brain areas with high levels of AVP receptors, such as the ventral pallidum. High density of receptors in the ventral pallidum is also found in the monogamous marmoset, evincing convergent evolution among rodents and primates. Activation of the pallidum, a key area in mammalian reward circuitry, is thought to reinforce affiliative behavior, leading to conditioned partner preference and initiation of pair bonding (Pitkow et al., 2001).

In male prairie voles, infusions of AVP directly into the brain facilitate partner preference formation and receptor antagonists block it. Altering receptor density also makes a difference. Exper-

imentally increasing the AVP receptor (V1aR) levels in the ventral pallidum of nonmonogamous meadow voles, using the injection of a viral vector directly in the ventral pallidum, resulted in the formation of strong partner preferences. Hammock and Young (2006, p. 2193) describe this experiment in the following way: "Therefore, even though these two species diverged long ago, this simple change in the expression of a single gene replicated a hypothetical evolutionary event that may have ultimately led to the development of monogamy."

AVP receptors in the lateral septum (which projects directly to the nucleus accumbens) have been shown—by studies using site-specific injections of a V1aR-specific antagonist—to be critical for social recognition in male mice (Bielsky, Hu, Ren, Terwilliger, & Young, 2005). Further, these authors found that a viral vector causing reexpression of V1aR in the lateral septum of V1aR knockout mice resulted in a complete rescue of social recognition. Knowledge of the role of the ventral pallidum, the lateral septum, and the nucleus accumbens in this circuit offers clues as to where to look and what brain areas to target in autism. In fact, the receptivity of these areas to AVP in autism remains undefined. These findings further substantiate the importance of attaining receptor distribution profiles in autism, so that specific brain areas and their receptors can be manipulated for therapeutic purposes.

There is also evidence for a role of the gene that codes for the human AVP receptor, AVPR1A, in ASD. This evidence comes from genetic studies of the polymorphic microsatellite repeats in the 5' flanking region of the gene (3,625 base pairs upstream of the transcription start site of AVPR1A). Of these repeats, overtransmission of RS3 and undertransmission of RS1 has been associated with ASD (Wassink et al., 2004; Yirmiya et al., 2006). Fascinatingly, similar microsatellite repeats have also been found in *avpr1a* in prairie voles, and have been viewed as instrumental in regulating social behavior. Some, but not all, studies have found an association of these repeats with social behaviors in voles (Hammock & Young, 2005; Mabry, Streatfeild, Keane, & Solomon, 2011). Hammock and Young (2005) have done extensive experimentation suggesting that the AVPR1A locus may be such a tuning knob, while relating their findings to autism.

Endogenous Opioids

Endogenous opioids are opiate-like peptides that bind to opioid receptors in the central and peripheral nervous system and the gastrointestinal tract. In the brain, this binding has an analgesic effect, due to decreased perception of pain, decreased reaction to pain, and increased pain tolerance. Endogenous opioids are thought to be heavily involved in the consummatory phase of affiliation (Depue & Morrone-Strupinsky, 2005). Their release and action during social intercourse is thought to make social encounters pleasurable and reinforcing. Blockade of endogenous opioid receptors by an opioid antagonist increases the need for social attachment and therefore the solicitation of affiliative behavior from social partners (Martel, Nevison, Simpson, & Keverne, 1995). Acute treatment with nonsedative doses of morphine significantly decreases clinging behavior and grooming solicitations in primates, as well as decreasing grooming performed. Morphine also reduces huddling duration and social activity in prairie voles (Shapiro, Meyer, & Dewsbury, 1989). Because low levels of opioids increase seeking for affiliative comfort in mammals, and

high levels decrease it, it has been suspected that high levels are associated with autism, and this seems to be the case (Machin & Dunbar, 2011). Perhaps presumed high action of opioids in the autistic brain keeps these individuals from seeking social contact, and the presumed absence of phasic opioid release during affiliation keeps social encounters from being rewarding.

In a review on this topic, Sahley and Panksepp (1987) point out that a growing body of evidence points out that: (a) autistic-like symptoms can be induced in animals with the administration of exogenous opioids, (b) human individuals addicted to opiates exhibit autistic-like symptoms, (c) autistic-like symptoms in the severely mentally retarded can be attenuated by opioid blockade, and (d) the many brain areas that have been suggested to be dysfunctional in autism have high concentrations of opioids. The following quote from Panksepp (1994, p. 44) illustrates that the role of opioids in autism is complicated but potentially informative:

Thus opioid blockade with naltrexone can reduce maternal competence in animals, while at the same time increasing maternal motivation. Opioid blockade likewise appears to increase the social motivation of rat pups, but reduces the reinforcing quality of interaction with the mother, suggesting that opioids provide feedback concerning the pleasurable qualities of social interaction in both mothers and infants. The clinical implications of this knowledge are not straightforward, but they generally suggest that clinically deficient social bonding might be capable of being strengthened via manipulation of brain opioid systems.

Autistic children lack the normal motivation to engage others socially, as indicated by their poor social skills and lack of spontaneous communication. They seem to lack emotional interest in other people, leading to a decreased initiative to affiliate (Sahley & Panksepp, 1987). Autism has been speculated to be associated with higher opioid levels and higher opioid receptor activation, which may underlie the reluctance to engage (Gilberg, 1995), although this has not been clearly demonstrated and many details remain unclear. Further research on the effects of opioids in social behavior and their role in autism should prove informative. Specific pathways stand out as having promise. Studies in animals indicate that of the different families of opiate receptors, the μ -opiate receptor family seems to be the most directly implicated in the regulation of social behavior, and that the β -endorphin has high affinity for those receptors. It is generally thought that interactions between μ -opiate receptors and dopamine neurons in the ventral tegmental area of the hypothalamus produce the experience of reward associated with the appetitive and consummatory phases of social contact (Gilberg, 1995). This pathway should be interrogated by future autism research. OXT and AVP also facilitate the effects of endogenous opioids. In rodents, OXT neurons in the paraventricular nucleus of the hypothalamus project to the neurons in the arcuate nucleus and phasically increase the release of opioids there (Csiffáry et al., 1992). Endogenous opioids have been shown to play a role in diminishing the release of OXT and AVP, as well as a role in regulating the hypothalamic pituitary adrenal axis. The details about how these systems interact remain to be described.

There is a close functional relationship between endogenous opioid and serotonergic systems in the brain. In fact, serotonin pathways modulate both enkephalin and morphine analgesia. Se-

rotonergic input to the hypothalamus via the raphe nuclei may result in reduced arousal and facilitation of opioid-mediated feelings of affiliative gratification (Depue & Morrone-Strupinsky, 2005). Thus, high and dysregulated levels of serotonin observed in autism may also play a role in dampening the need for certain forms of social contact (Anderson, 2005). In fact, administration of the anorexigenic drug fenfluramine has been shown to lower elevated serotonin levels and partially ameliorate several symptoms in autism (Clineschmidt et al., 1978). Social network analysis has shown that patterns of grooming and aggressive behavior in rhesus macaques can be partially explained by repeat polymorphisms associated with the serotonin system (Brent et al., 2011). Rhesus macaques that carry a copy of the short allele in the serotonin transporter-linked repeat polymorphism direct less attention to the eyes and are less likely to look at a face than a nonface image (Watson, Ghodasra, & Platt, 2009). Allelic heterogeneity at the serotonin transporter locus has been similarly implicated in autism as well (Sutcliffe et al., 2005).

Alterations in Amygdalar, Vagus, and Parasympathetic Responses

Highly social animals share with humans the capacity to form long-lasting social relationships and thus provide an opportunity to examine the physiological effects of social isolation. In prairie voles, isolation from a partner for a few days produces behavioral responses that significantly mimic depression and anxiety in humans. The prairie vole, for instance, has an autonomic nervous system that is relatively humanlike, with high levels of parasympathetic-vagal activity (Grippe et al., 2007). These animals exhibit increases in heart rate, decreases in parasympathetic function, and increased behavioral reactivity to social isolation and social stressors. Socially isolated prairie voles explore less, show increases in anhedonia, and are more likely to display immobility in response to a stressor (Grippe et al., 2008), whereas montane voles are relatively inured. Also like solitary mammals, individuals with autism are less sympathetically responsive to social separation and isolation (Buitelaar, 1995; Naber et al., 2008).

It is thought that social mammals uniquely have the ability to regulate an autonomic state of calmness while regulating communicative functions, including the musculature of the face and neck necessary to produce prosocial facial expressions, vocalizations, and head gestures (Porges & Carter, 2010). These capacities are limited in autism, suggesting that parasympathetic function may be involved. The primary nerve of the parasympathetic branch of the autonomic nervous system exits the brain stem as the vagus or 10th cranial nerve. This nerve has both motor-efferent and sensory-afferent components. Many of these afferent sensory fibers carry information from the viscera to a brain stem region known as the nucleus tractus solitarius. Stephen Porges (2005) has documented alterations in vagus morphology and parasympathetic tone in autism that are consonant with phenotypes found in nonsocial species. He points out that social contact in autism leads to sympathetic activation and fight-flight arousal states that induce a drive to diminish contact or withdraw. Individuals with autism have been widely reported to have increased fear activity in the amygdala and high levels of sympathetic function during social interaction (Baron-Cohen et al., 2000). Autonomic arousal is linked to social stimuli for solitary animals, because it is important

that solitary animals protect their foraging space and actively avoid threatening conspecifics. Animals that are solitary are often territorial and find the presence of another animal in their territory aversive, especially an animal of their own species (Harcourt, 1989).

Alterations in Brain Regions Involved in Social Processing

The brain abnormalities in autism do not seem to constitute indiscriminate pathological abnormalities, as one might expect if autism were simply a disease. The most conspicuous brain abnormalities seem to consistently affect the areas of the brain that have been associated with social cognition (Adolphs, 2001). The amygdala, the anterior cingulate cortex, the orbito and medial frontal cortex, and the mirror neuron system have all been strongly associated with social cognition (Dapretto, Davies, & Pfeifer, 2006), and also have been shown to be the same areas that exhibit the prominent anomalies in autism (Williams, Whiten, Suddendorf, & Perrett, 2001). Unfortunately, despite some hopeful research (i.e., Bell, Pellis, & Kolb, 2010; Pellis et al., 2006), little is known about the social cortex in mammals, especially solitary ones.

The brain in autism has shown underactivity in nearly every brain region associated with the empathy circuit (Di Martino et al., 2009). When individuals with autism attempt to make judgments about the intentions, motives, or state of mind of another, they show reduced activity in the dorsomedial prefrontal cortex (dmPFC; Happe et al., 1996; A. T. Wang, Lee, Sigman, & Dapretto, 2007). When asked to infer emotional state from pictures of people's faces, they demonstrate underactivity in the frontal operculum, amygdala, and anterior insula (Baron-Cohen & Hammer, 1997; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001). When individuals with autism are asked to rate how they feel after viewing emotionally charged pictures, they show less activity within a number of regions in the empathy circuit, including the dmPFC, the posterior cingulate cortex, and the temporal pole (Silani et al., 2008). Not only are areas involved in empathy underactive during empathy tasks, but the dmPFC and ventromedial prefrontal cortex (vmPFC) show atypical baseline activity during rest (Kennedy & Courchesne, 2008; Kennedy, Redcay, & Courchesne, 2006). In fact, social impairment in autism is correlated positively with degree of atypical vmPFC response (Lombardo, Barnes, Wheelwright, & Baron-Cohen, 2007; Lombardo et al., 2010). The corresponding studies in nonhuman animals have not been performed, but it might be expected that solitary or nonmonogamous species exhibit the same neuroanatomical irregularities in homologous cortical areas and the motor neuron system. Analogues of the relevant prefrontal areas may not be present in rodents but are in other primates. Existent, yet limited, empathic abilities have been documented in apes and cortical regions that correspond to human social cortical regions are thought to be instrumental (Dunbar, 2010; Joffe & Dunbar, 1997; Povinelli, 1994).

It has been suggested that empathizing and systemizing of physical systems are contingent on separate brain modules (Baron-Cohen, 1995), but both may in fact be made possible by the same architecture for systemizing, namely, the pathways involved in immediate and working memory. In other words, empathy may

involve systemizing another's perceived mental state using mirror neurons and social schemas derived from social learning experiences. Perhaps social mammals naturally find stimuli coming from conspecifics captivating and will automatically attempt to systemize this information unless fear sets in first. Phasic increases in dopamine neurotransmission in the PFC are thought to underlie the ability to internally represent, maintain, and update contextual information about salient external and internal stimuli (Braver & Cohen, 1999). Stimuli that are deemed novel, surprising, or appetitive are given priority. Seamans and Robbins (2010) have proposed that this dopaminergic process regulates the access of salient contextual representations and maintains them online in active memory so that systemization and modeling of these representations can take place. Perhaps the brains of solitary mammals are fine-tuned to perceive incoming social stimuli as fearful and not appetitive or novel in order to keep these stimuli from entering working memory. Aberrations in the receptivity of subcortical motivational areas to neurochemicals such as OXT and AVP are likely to be the prior or proximate causes of altered cognition in autism. These low-level aberrations likely influence and give rise to the emergent aberrations in cortical areas, which should be considered the high-level targets for cognitive/behavioral interventions.

Natural selection cannot act on behavior directly but instead acts on the neural substrates that generate the psychological mechanisms that create the behavior (Buss, 2005). These brain modules were naturally selected to be sensitive to a narrow range of perceptual information, preparing the organism to learn about or solve particular adaptive problems. Tuning differences in domain-specific mechanisms or modules may underlie the differences in autistic cognition and, like other differences seen in nature, may have been created by natural selection to help solitary foragers face their particular set of recurrent or ecologically relevant threats and opportunities. High-level behaviors affected by these processes may include eye contact, facial expressiveness, and facial recognition.

Averted gaze and poor eye contact are very common in autism (Hutt & Ounsted, 1966). Autistic individuals describe eye contact as uncomfortable and even threatening. Interestingly, eye contact is also very rare in the vast majority of solitary species, including orangutans, who actively avoid both direct gazing and even facing (Yamagiwa, 1992). Chimpanzees and gorillas share gazes and use the eyes for communication frequently, just like most humans (Gómez, 1996). Staring between unfamiliar apes is often interpreted as a threat signal; therefore, it is best for the solitary orangutan to avoid both eye contact and direct gazing in order to forestall an attack (Gómez, 1996). Solitary orangutans actively avoid gazing and eye contact, and this tendency, very common among solitary animals, has been explicitly interpreted as adaptive for their solitary foraging niche (Yamagiwa, 1992). Instead of face-to-face direct viewing, orangutans, like individuals with autism, glance momentarily at others sideways, with the head turned away (Kaplan & Rogers, 2002). The neurological substrates (including amygdalar sensitivity) that underlie this very specific and prominent tendency may have evolved for the same adaptive, defensive reasons in both autism and the orangutan.

Studies have shown that autistic individuals are less expressive, especially with respect to facial communication. They make fewer facial expressions and are rated as more flat or neutral in affect by

observers (Yirmiya, Kasari, Sigman, & Mundy, 1989). This absence of facial responsiveness is probably due to underlying neuronal mechanisms, and there is evidence that the facial motor nucleus is significantly reduced in size in autism (Rodier, Ingram, Tisdale, Nelson, & Romano, 1996). Fascinatingly, the size of the facial motor nucleus is thought to vary predictably in total volume as a function of group size in monkeys and apes. The larger the average group size, the more important facial expressiveness is and the larger the facial motor nucleus must be (Sherwood, 2005). It should be informative to analyze the anatomical organization of the autistic facial motor nucleus, taking note of the general size, the placement of motor neurons, the distribution of neuron types, and the general topography of muscle representation.

Face processing, a key factor in the development of social perception, is severely impaired in autism (Dalton et al., 2005). The area responsible for face recognition, the fusiform face area, in particular, has demonstrated reduced activation in autism during facial discrimination tasks (Pierce & Redcay, 2008), indicating that in autism, like in many solitary animal species (Cosmides & Tooby, 1992), identity recognition may not be as valuable.

Epigenetics and Phenotypic Plasticity

Research in the field of phenotypic plasticity and epigenetics has shown that many organisms, from plants to flies to people, demonstrate predictive adaptive responses to particular environmental stressors (Auld, Agrawal, & Relyea, 2010). There are many examples of predictive adaptive responses in nature, and they allow organisms to use specific, early, environmental cues to influence their developmental trajectory (Via & Lande, 1985). Study of these predictive, adaptive responses have shown that virtually all species can be reprogrammed by portending environmental cues, that the morphological changes are brought about by alterations in gene expression, and that this potential for change allows members of a species to conform to occasional, but regularly recurring, environmental pressures (DeWitt & Scheiner, 2004). It may be possible that some social mammals are receptive to certain foreboding environmental cues that give them information about the social environment that they can expect after birth. Cues indicative of social attenuation might be used by developing mammals to alter their social neurochemistry. It is already known that rats and humans respond in a similar way to cues about stress in a behavioral response referred to as *social referencing* (Francis, Diorio, Liu, & Meaney, 1999). Researchers such as Michael Meaney at McGill University have documented that stress responsiveness can be largely programmed in young rats. The frequency of early cues indicative of maternal care (such as the extent of early maternal stress, arched back nursing, licking, and grooming) modulate the expression of genes that regulate behavioral and neuroendocrine responses to stressors (Zhang, Parent, Weaver, & Meaney, 2004). In other words, mammals stressed in utero and beyond genetically modify themselves to ensure that they are better prepared for a threatening environment (Reser, 2006, 2007).

Some mammals have been documented to exhibit adaptive social flexibility or plasticity to changing social environments. Both sexes of African striped mouse (*Rhabdomys pumilio*) have been shown to exhibit such resilience by changing their reproductive tactics facultatively (Schradin et al., 2012). In mammals, high population density favors philopatry and group living, whereas

reproductive competition, absence of surviving female relatives, high predation pressure, infanticide, and low food availability favor dispersal and solitary living (Randall, Rogovin, Parker, & Eimes, 2005; Schradin et al., 2012). Ecological constraints in the prevailing environment determine which strategy will contribute the most to evolutionary fitness. Phenotypic flexibility, in the form of endocrine adjustments, has been documented in the African striped mouse, and the phenotypic flexibility is attributed to epigenetic changes and a broad reaction norm, not to polymorphism. Ongoing research has shown that specific endocrine changes underlie these proclivities, including higher testosterone, lower prolactin, and lower glucocorticoid levels (Schradin et al., 2012). Interestingly, there is also evidence of aberrations in each of these three hormones in humans with autism. Similar plasticity has been documented in adult male primates. First-time and experienced father marmosets who had spent a considerable amount of time carrying infants had a greater number of AVP V1a receptors in the prefrontal cortex than adult male nonfathers living in similar social conditions (Kozorovitskiy, Hughes, Lee, & Gould, 2006).

Recent research has underscored the large environmental influences in autism. These studies have confirmed that autism is not only driven by genetics, but can be strongly associated with particular environmental scenarios. Research has even revealed that autism may be associated with aberrant epigenetic methylation of the OXT receptor (Gregory et al., 2009). Autism may be linked with specific environmental cues that are predictive of the quality of the social environment that the fetus is "expecting" to be born into. The questions to ask are (a) Could epidemiological factors that predispose an individual to autism, or some facet related to them, offer information to a fetus about the condition of the social environment that its mother is experiencing?; and (b) Are there other cues that the fetus could intercept and respond to that indicate how valuable social cognition has proven to be to its parents? This perspective could influence geneticists and epidemiologists to reinterpret the epigenetic contributions to autism, change how they look for environmental effects, and cause them to hone in on specific molecular pathways responsible for changes in gene expression.

The Social/Solitary Dichotomy in Nonhuman Primates

Nonhuman primate models may be preferable to rodent models because primates are more closely related to humans, have complex social structures, rely on vision for social signaling, and have deep homology in brain circuitry mediating the computation of reward sensitivity and social value. On the other hand, they have only infrequently been used to model autism, as primates are more expensive to manage than rodents, are not appropriate for invasive studies due to ethical concerns, are "low throughput" due to much longer gestation times, and are not ideal for knock-in, knock-out, or optogenetic studies. Primates, and especially apes, are relatively social mammals, but each species can be shown to lie on a spectrum. Nocturnal prosimians, such as mouse lemurs, dwarf lemurs, bush babies, and lorises, are solitary foragers and do not live in groups, but they do exhibit some social networking faculties (Bearder, 1987). Interestingly, these "stem primates" are thought to represent the ancestral pattern of primate social organization (Müller & Thalmann, 2000; Shultz, Opie, & Atkinson, 2011).

Orangutans, socially cautious and introverted, are known to eat, sleep, hunt, and forage on their own, and are thought to spend around 95% of their time in the wild alone (Delgado & van Schaik, 2000; van Schaik, 1999). Orangutans have low interaction and association rates, and only infrequently meet up with conspecifics, often only to mate (van Schaik & van Hoof, 1996). Chimpanzees are gregarious, yet have fluid, fission–fusion societies, in which group members split up into small groups during daily excursions and later reconvene in response to changes in food distribution. Chimps usually forage in groups but are known to forage solitarily when food becomes scarce (de Waal, 1982). Bonobos and savanna baboons tend to form significantly larger, more socially cohesive groups and both primarily forage together. Despite these dramatic differences in the behavior of these primates, it has not yet been made clear if these discrepancies are attributable to ecological factors, neurological factors, or both.

Polymorphism in the repetitive microsatellite locus for the AVP receptor is present in both humans and bonobos. Chimpanzees, which are thought to exhibit slightly lower levels of social reciprocity, empathy, and sociosexual bonding relative to bonobos, do not have this microsatellite locus, and Hammock and Young (2005) have suggested that this is reminiscent of the genetic differences between montane and prairie voles at this same locus. It is thought that bonobos are more social and easy going because their foraging territory south of the Congo River is much richer in large fruiting trees than that of chimpanzees north of the Congo. Thus reduced foraging competition seems to facilitate social life in bonobos (Hare, Melis, Woods, Hastings, & Wrangham, 2007; Wrangham, 1986) and may have resulted in a human-like AVP expression profile. Recall that autism, on the other hand, has been strongly associated with a very different AVP expression profile and with overtransmission of specific microsatellite repeats in this same gene (Wassink et al., 2004; Yirmiya et al., 2006).

Pair living is relatively rare in primates, but group living is not. The most common type of social organization in nonhuman primates consists of relatively promiscuous multimale/multifemale social groups, but even though there is no pair bonding, group members bond. There is a paucity of research on this topic, though, and the influence of social neuropeptides on primate group structure has been largely neglected. In anthropoid primates, same-sex relationships have much in common with sexual relationships in mammals that form monogamous pairs. They both involve high

levels of coordination, behavioral synchronization, and compromise (Machin & Dunbar, 2011), and both involve a central role of OXT (Dunbar, 2010). Thus, even though voles provide a strong foundation for social neuroscience, further research on primate social neurochemistry should be highly informative.

Discussion

This review has attempted, in an exploratory manner, to consider parallels in neurophysiology between ASD and solitary mammals. Preliminary comparative studies juxtaposing the neurobiology of social mammals with that of solitary mammals have been done, but the pertinent comparisons with autism have only begun. The review suggests that basic and translational research on social cognition in solitary mammals, and the brain alterations that underlie it, could lead to advancements in understanding and, ultimately, treating autism. The pertinent literature also seems to suggest that research on the neurophysiology of solitary mammals may contribute to the identification of more specific biomarkers and the development of more precise animal models. The similarities noted here may be numerous and fine-grained enough to suggest that they are not superficial or coincidental. However, the extent to which these animal studies can be directly extrapolated to autism is very unclear.

This line of research points to four major dichotomies that might help to model autism, listed in Table 4. There is a monogamous/nonmonogamous dichotomy, a group/solitary dichotomy, and a domestic/wild dichotomy. There may also be a relevant female/male dichotomy as well, as there is evidence of significant sexual dimorphism in many, if not all, of the neurobiological systems discussed (Baron-Cohen, 2003; Hammock & Young, 2006). The biodiversity underlying these dichotomies should be interrogated from the perspective of comparative psychology and biology.

An important question remains: Are the neurobiological mechanisms found in solitary and nonmonogamous mammals sufficient to capture the nuanced social impairments featured in the autism diagnosis? Because of the various—genetic and environmental—etiological contributions to autism (Cantor, 2009), it is clear that only a fraction of what is known as autism could be accurately modeled by cognitive specializations for solitary living in other mammals. The modern, nosological entity of autism is a mixture of phenotypes with separate causes lumped together by clinicians,

Table 4
Species Whose Social Inclinations Can Be Meaningfully Compared

Monogamous vs. Nonmonogamous	Group adapted vs. Solitary	Domesticated vs. Wild
Prairie voles (<i>Microtus ochrogaster</i>) vs. Montane voles (<i>Microtus montanus</i>)	Spotted hyenas (<i>Crocutta crocutta</i>) vs. Striped hyenas (<i>Hyaena hyaena</i>)	Domesticated dogs (<i>Canis lupus familiaris</i>) vs. Wolves (<i>Canis lupus</i>)
Marten (family Martes) vs. Agouti (family Dasyprocta)	Lions (<i>Panthera leo</i>) vs. Tigers (<i>Panthera tigris</i>)	Domesticated silver fox vs. Wild red fox (<i>Vulpes vulpes</i>)
California deer mouse (<i>Peromyscus californicus</i>) vs. white-footed mouse (<i>Peromyscus leucopus</i>)	Pigtail macaque (<i>Macaca nemestrina</i>) vs. Bonnet macaque (<i>Macaca radiata</i>)	Domesticated goat (<i>Capra aegagrus hircus</i>) vs. Wild goat (<i>Capra aegagrus</i>)
Marmoset (family Callitrichidae) vs. Rhesus macaque (<i>Macaca mulatta</i>)	Chimpanzees (<i>Pan troglodytes</i>) vs. Orangutans (<i>Pongo pygmaeus</i>)	Humans (<i>Homo sapiens sapiens</i>) vs. Chimps (<i>Pan troglodytes</i>)
Pine voles (<i>Microtus pinetorum</i>) vs. Meadow voles (<i>Microtus pennsylvanicus</i>)	Ringtailed lemurs (<i>Lemur catta</i>) vs. Mongoos lemur (<i>Eulemur mongoz</i>)	Chicken (<i>Gallus gallus</i>) vs. Quail (family Galliformes)

and a large proportion of it may represent disease that cannot be reliably compared with naturally occurring phenotypes in animals. Based on the paucity of basic research and the absence of consensus in the literature, the present line of research necessitates further critical examination as well as questioning of the methodology, and even the structuring assumptions. Ultimately, understanding ASD will probably require synthesis across several different models, which, together, should offer complementary and convergent conclusions.

This model, unlike most animal models, does not detail how to alter or program a laboratory animal to mimic aspects of autism. The pronouncements here have not made considerations for immediate application but are much more general and expository. Normally, diseases with discrete, recognized causes, such as Rett syndrome, Down syndrome, and Fragile X syndrome, are best amenable to animal modeling and immediately suggest treatment options. Highly polygenic disorders that also involve phenotypic plasticity, and de novo mutations, such as autism, are more difficult to model and the models are more difficult to assess. The utility of animal models for autism is commonly assessed using three criteria: (a) face validity (resemblance to human symptoms), (b) construct validity (similarity to the underlying causes of the disease), and (c) predictive validity (expected similar responses to treatments). It is currently not possible to meaningfully assess the validity or value of the present model.

Not only could the study of solitary mammals affect the study of autism, but research in autism could help to elucidate phenomena in social neuroscience and social psychology. Traits associated with autism, aside from those listed in Tables 1 and 2, should be investigated in a variety of solitary mammals, including joint attention, pretend play, facial expressiveness, communicative intent, empathy, the mirror neuron system, fusiform recognition areas, and other social cortical areas. In addition, this research

should have implications for understanding other disorders marked by alterations in related social pathways, such as borderline personality disorder, insecure attachment disorder, psychopathy, and William's syndrome. Robert Plomin, author of the leading textbook *Behavioral Genetics* writes, "[We predict that] when genes are found for common disorders such as mild mental retardation or learning disabilities, the same genes will be associated with variation throughout the normal distribution of intelligence, including the high end of the distribution" (Plomin et al., 2008). Could something similar be true throughout the normal distribution of sociality, including social deficits, ASDs, and other disorders of bonding, attachment, and empathy?

Convergent evolution is pervasive, and the similarities between autism and solitary animals may extend beyond superficial resemblances. An article by Reser (2011) reviews etiological and comparative evidence supporting the hypothesis that some genes associated with the autism spectrum were naturally selected and represent the adaptive benefits of being cognitively suited for solitary foraging. People on the autism spectrum are conceptualized here as potentially ecologically competent. The article suggests that upon independence from their mothers, young individuals on the autism spectrum may have been psychologically predisposed toward a different life-history strategy, common among mammals and even some primates, to hunt and gather primarily on their own. This may have resulted from periodic or geographic disruptions in the efficacy of group foraging in the ancestral past, or from reduced adaptive value of sociocultural information sharing. The resulting evolutionary pressures may have driven the selection of genes that created social processing deficits, making their bearers resistant to the transference of units of cultural information (memes). Many of the behavioral and cognitive tendencies that autistic individuals exhibit are viewed as adaptations that would have comple-

Table 5
Behavioral Inclinations in Autism, Then and Now

Trait or symptom of autism	Psychological consequences	Implications for moderns	Implications for solitary foragers
High systemizing ability	A tendency to systematically explore the laws governing nonsocial processes (Baron-Cohen, 2003, 2006)	Eccentric or narrow but substantial knowledge and skills (Treffer, 2000)	An impetus guiding the acquisition of food procurement techniques
Obsessive, repetitious tendencies	Perseveration in behavior and thought (Piven, 2000)	Repetitious play and need for sameness (Kelly et al., 2008)	Order, structure, and autonomous self-regulation
Gaze aversion and absence of shared eye contact	Minimal eye contact and diminished attention to the faces of others (Piven, 2000)	Unfortunate social hurdle (Hutt & Ounsted, 1966)	Instinctually prepared not to challenge or provoke conspecifics
Low oxytocin and vasopressin activity	Reduced social interest, learning, and expressiveness (Green et al., 2001)	Unfortunately hindered social cognition (Hollander et al., 2003)	Programmed for a socially impoverished environment
Anomalies in anterior cingulate cortex, orbito and medial frontal cortex	Reduced social learning (Adolphs, 2001)	Hindered social cognition, imitation, and empathy (Dapretto et al., 2006)	Decreased reliance on others
Amygdala hyperactivity	Potential of innate and conditioned fears (Dapretto, 2006)	Excessive anxiety and withdrawal from social world (Baron-Cohen et al., 2000)	Healthy caution and fear of unfamiliar conspecifics

mented a solitary lifestyle. Table 5 presents some of these tendencies, their implications for modern individuals, and their implications for prehistoric, solitary foragers. The article emphasizes that individuals on the autism spectrum may have only been partially solitary, that natural selection may have only favored subclinical autistic traits, and that the most severe cases of autism may be due to assortative mating.

Perhaps components of the autism spectrum can be understood in terms of behavioral ecology and evolutionary medicine, but this does not necessarily mean that autism is an ecological anachronism. Several scientists and many autism advocacy groups promote the idea that autism has compensatory advantages, even in modern society (Baron-Cohen, 2006; Grandin & Panek, 2013). Individuals on the autism spectrum have been shown to exhibit extremely high levels of achievement in systemizing domains, such as mathematics, physics, and computer science (Baron-Cohen et al., 1999), and this is referred to as the *autism advantage* in popular autism advocacy.

The contemporary, postgenomic age allows molecular methods that were practically inconceivable before genome sequencing was possible. The emerging field of evolutionary cognitive genetics makes it clear that there can now be confluence and integration between fields such as brain genomics, human population genetics, and molecular anthropology. The methodology of this field may be applicable here. In order to use modern methods to study the present relationships, it might be helpful to (a) perform large-scale comparisons of genes across several strategically selected species in a search for social dimorphisms or social genes with highly elevated rates of evolution in mammals or primates, (b) determine if the alleles for these genes are associated with specific social phenotypes using in vitro and in vivo lab studies, and (c) subject the candidate genes to polymorphism and association studies in humans.

The analytical tools that social neuroscientists use to study social capacity in other vertebrates can, with appropriate caution, be used to study social capability in humans. Other species have found myriad ways to reduce social contact for ecological purposes, and understanding how this is accomplished may provide insight on prosocial pharmacotherapeutics or even gene therapy for autism. How can the present comparative, neuroethological approach help with autism? In this author's opinion, the way it can help the most is through comparative neurobiology. It will be interesting to see if neuroanatomical receptor distribution patterns of OXT, vasopressin, endogenous opioids, prolactin, serotonin, and dopamine in the brains of solitary mammals resembles those observed in autism. If there are significant resemblances, it will be important for scientists to compare the distributions patterns of these receptors in different animals to help determine which areas in the autism brain feature a paucity of receptor expression, so that these specific areas can be targeted. It may be possible to test drugs, and even behavioral interventions, in solitary or nonmonogamous animals to determine if these have the capacity to reverse social interaction deficits. The model may allow an alternate vantage point into the autistic brain, which can only be studied in limited ways because of technical limitations and ethical concerns.

References

- Adolphs, R. (2001). The neurobiology of social cognition. *Current Opinion in Neurobiology*, 11, 231–239. doi:10.1016/S0959-4388(00)00202-6
- Alcock, J. (2001). *Animal behavior: An evolutionary approach*. Sunderland, MA: Sinauer.
- American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th ed., text rev.). Washington, DC: Author.
- Andari, E., Duhamel, J. R., Zalla, T., Herbrecht, E., Leboyer, M., & Sirigu, A. (2010). Promoting social behavior with oxytocin in high-functioning autism spectrum disorders. *PNAS Proceedings of the National Academy of Sciences of the United States of America*, 107, 4389–4394. doi:10.1073/pnas.0910249107
- Anderson, G. M. (2005). Serotonin in autism. In M. L. Bauman & T. L. Kemper (Eds.), *The neurobiology of autism* (pp. 303–318). Baltimore, MD: John Hopkins University Press.
- Auld, J. R., Agrawal, A. A., & Relyea, R. A. (2010). Re-evaluating the costs and limits of adaptive phenotypic plasticity. *Proceedings. Biological Sciences/The Royal Society*, 277, 503–511.
- Bales, K. L., Van Westerhuyzen, J. A., Lewis-Reese, A. D., Grotte, N. D., Lanter, J. A., & Carter, C. S. (2007). Oxytocin has dose-dependent developmental effects on pair-bonding and alloparental care in female prairie voles. *Hormones and Behavior*, 52, 274–279. doi:10.1016/j.yhbeh.2007.05.004
- Baron-Cohen, S. (1995). *Mindblindness: An essay on autism and theory of mind*. Boston, MA: MIT Press/Bradford Books.
- Baron-Cohen, S. (2003). *The essential difference: The truth about the male and female brain*. New York, NY: Basic Books.
- Baron-Cohen, S. (2006). The hyper-systemizing, assortative mating theory of autism. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, 30, 865–872. doi:10.1016/j.pnpbp.2006.01.010
- Baron-Cohen, S., & Hammer, J. (1997). Parents of children with Asperger syndrome: What is the cognitive phenotype? *Journal of Cognitive Neuroscience*, 9, 548–554. doi:10.1162/jocn.1997.9.4.548
- Baron-Cohen, S., Ring, H. A., Bullmore, E. T., Wheelwright, S., Ashwin, C., & Williams, S. C. R. (2000). The amygdala theory of autism. *Neuroscience and Biobehavioral Reviews*, 24, 355–364. doi:10.1016/S0149-7634(00)00011-7
- Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., & Plumb, I. (2001). The “Reading the Mind in the Eyes” test revised version: A study with normal adults, and adults with Asperger syndrome or high-functioning autism. *Journal of Child Psychology and Psychiatry*, 42, 241–251. doi:10.1111/1469-7610.00715
- Baron-Cohen, S., Wheelwright, S., Stone, V., & Rutherford, M. (1999). A mathematician, a physicist, and a computer scientist with Asperger Syndrome: performance on folk psychology and folk physics test. *Neurocase*, 5, 475–483.
- Bart, J. A., & Hollander, E. (2008). Oxytocin and experimental therapeutics in autism spectrum disorders. *Progress in Brain Research*, 170, 451–462. doi:10.1016/S0079-6123(08)00435-4
- Bearder, S. K. (1987). Lorises, bushbabies, and tarsiers: Diverse societies in solitary foragers. In B. Smuts, D. Cheney, R. Seyfarth, R. Wrangham, & T. Struhsaker (Eds.), *Primate societies* (pp. 12–24). Chicago, IL: University of Chicago Press.
- Bell, H. C., Pellis, S. M., & Kolb, B. (2010). Juvenile peer play experience and development of the orbitofrontal and medial prefrontal cortices. *Behavioural Brain Research*, 207, 7–13. doi:10.1016/j.bbr.2009.09.029
- Bielsky, I. F., Hu, S., Ren, X., Terwilliger, E. F., & Young, L. J. (2005). The V1a vasopressin receptor is necessary and sufficient for normal social recognition: A gene replacement study. *Neuron*, 47, 503–513. doi:10.1016/j.neuron.2005.06.031
- Bora, E., Murat, Y., & Nicholas, A. (2009). Neurobiology of human affiliative behavior: Implications for psychiatric disorders. *Current Opinion in Psychiatry*, 22, 320–325. doi:10.1097/YCO.0b013e328329e970

- Bothma, J., du, P., & Walker, C. (1999). *Larger carnivores of the African savannas*. Pretoria, South Africa: J. L. van Schaik. doi:10.1007/978-3-662-03766-9
- Braver, T. S., & Cohen, J. D. (1999). Dopamine, cognitive control, and schizophrenia: The gating model. *Progress in Brain Research*, 121, 327–349. doi:10.1016/S0079-6123(08)63082-4
- Brent, L. J., Heilbronner, S. R., Horvath, J. E., Gonzalez-Martinez, J., Ruiz-Lambides, A. V., Robinson, A., . . . Platt, M. L. (2011). *Genetics of social network position in free-ranging rhesus macaques*. Neuroscience 2011 Abstracts. (p. 18) Washington, DC: Society for Neuroscience.
- Buitelaar, J. K. (1995). Attachment and social withdrawal in autism: Hypotheses and findings. *Behaviour*, 132, 319–350. doi:10.1163/156853995X00595
- Buss, D. M. (2005). *The handbook of evolutionary psychology*. New York, NY: Wiley.
- Campbell, A. (2008). Attachment, aggression and affiliation: The role of oxytocin in female social behavior. *Biological Psychology*, 77, 1–10. doi:10.1016/j.biopsycho.2007.09.001
- Cantor, R. M. (2009). Molecular genetics of autism. *Current Psychiatry Reports*, 11, 137–142. doi:10.1007/s11920-009-0021-1
- Carter, C. S., DeVries, C. A., & Getz, L. L. (1995). Physiological substrates of mammalian monogamy: The prairie vole model. *Neuroscience and Biobehavioral Reviews*, 19, 303–314. doi:10.1016/0149-7634(94)00070-H
- Churchland, P. S. (2011). *Braintrust*. Princeton, NJ: Princeton University Press.
- Clineschmidt, B. V., Zacchei, A. G., Totaro, J. A., Pflueger, A. B., McGuffin, J. C., & Wishousky, T. I. (1978). Fenfluramine and Brain Serotonin. *Annals of The New York Academy of Sciences*, 305, 222–241.
- Cosmides, L., & Tooby, J. (1992). Cognitive adaptations for social exchange. In J. H. Barkow, L. Cosmides, & J. Tooby (Eds.), *The adapted mind: Evolutionary psychology and the generation of culture* (pp. 127–148). New York, NY: Oxford University Press.
- Csiffáry, A., Ruttner, Z., Toth, Z., & Palkovits, M. (1992). Oxytocin nerve fibers innervate β -endorphin neurons in the arcuate nucleus of the rat hypothalamus. *Neuroendocrinology*, 56, 429–435. doi:10.1159/000126259
- Dalton, K. M., Nacewicz, B. M., Johnstone, T., Schaefer, H. S., Gernsbacher, M. A., Goldsmith, H. H., . . . Davidson, R. J. (2005). Gaze fixation and the neural circuitry of face processing in autism. *Nature Neuroscience*, 8, 519–526.
- Dapretto, M., Davies, M. S., & Pfeifer, J. H. (2006). Understanding emotions in others: Mirror neuron dysfunction in children with autism spectrum disorders. *Nature Neuroscience*, 9, 28–30. doi:10.1038/nn1611
- Decety, J. (2011). The neuroevolution of empathy. *Annals of the New York Academy of Sciences*, 1231, 35–45. doi:10.1111/j.1749-6632.2011.06027.x
- Delgado, R., & van Schaik, C. P. (2000). The behavioral ecology and conservation of the orangutan (*Pongo pygmaeus*): A tale of two islands. *Evolutionary Anthropology*, 9, 201–218. doi:10.1002/1520-6505(2000)9:5<201::AID-EVAN2>3.0.CO;2-Y
- Depue, R. A., & Morrongiello, J. V. (2005). A neurobehavioral model of affiliative bonding: Implications for conceptualizing a human trait of affiliation. *Behavioral and Brain Sciences*, 28, 313–350; discussion 350–395. doi:10.1017/S0140525X05000063
- de Waal, F. (1982). *Chimpanzee politics: Power and sex among apes*. London, UK: Jonathan Cape.
- DeWitt, T. J., & Scheiner, S. M. (2004). *Phenotypic plasticity: Functional and conceptual approaches*. Oxford, UK: Oxford University Press.
- Di Martino, A., Ross, K., Uddin, L. Q., Sklar, A. B., Castellanos, F. X., & Milham, M. P. (2009). Functional brain correlates of social and nonsocial processes in autism spectrum disorders: An activation likelihood estimation meta-analysis. *Biological Psychiatry*, 65, 63–74. doi:10.1016/j.biopsycho.2008.09.022
- Dunbar, R. I. M. (1988). *Primate social systems*. London, UK: Chapman & Hall. doi:10.1007/978-1-4684-6694-2
- Dunbar, R. I. M. (1998). The social brain hypothesis. *Evolutionary Anthropology*, 6, 178–190. doi:10.1002/(SICI)1520-6505(1998)6:5<178::AID-EVAN5>3.0.CO;2-8
- Dunbar, R. I. M. (2010). The social role of touch in humans and primates: Behavioral function and neurobiological mechanisms. *Neuroscience and Biobehavioral Reviews*, 34, 260–268. doi:10.1016/j.neubiorev.2008.07.001
- Francis, D., Diorio, J., Liu, D., & Meaney, M. J. (1999). Nongenomic transmission across generations of maternal behavior and stress responses in the rat. *Science*, 286, 1155–1158.
- Frank, S. A. (1998). *Foundations of social evolution*. Princeton, NJ: Princeton University Press.
- Gilberg, C. (1995). Endogenous opioids and opiate antagonists in autism: brief review of empirical findings and implications for clinicians. *Developmental Medicine and Child Neurology*, 37, 239–245.
- Gómez, J. C. (1996). Ostensive behavior in great apes: The role of eye contact. In A. E. Russon, K. A. Bard, & S. T. Parker (Eds.), *Reaching into thought: The minds of the great apes* (pp. 131–151). Cambridge, UK: Cambridge University Press.
- Grandin, T., & Panek, R. (2013). *The autistic brain: Thinking across the spectrum*. New York, NY: Houghton Mifflin.
- Green, L., Fein, D., Modahl, C., Feinstein, C., Waterhouse, L., & Morris, M. (2001). Oxytocin and autistic disorder: Alterations in peptide forms. *Biological Psychiatry*, 50, 609–613. doi:10.1016/S0006-3223(01)01139-8
- Gregory, S. G., Connelly, J. J., Towers, A. J., Johnson, J., Biscocho, D., Markunas, C. A., . . . Pericak-Vance, M. A. (2009). Genomic and epigenetic evidence for oxytocin receptor deficiency in autism. *BMC Medicine*, 7, 62. doi:10.1186/1741-7015-7-62
- Grippe, A. J., Gerena, D., Huang, J., Kumar, N., Shah, M., Ughreja, R., & Carter, C. S. (2007). Social isolation induces behavioral and neuroendocrine disturbances relevant to depression in female and male prairie voles. *Psychoneuroendocrinology*, 32, 966–980.
- Grippe, A. J., Wu, K. D., Hassan, I., & Carter, C. S. (2008). Social isolation in prairie voles induces behavioral relevant to negative affect: towards the development of a rodent model focused on co-occurring depression and anxiety. *Depression and Anxiety*, 25, E17–E26.
- Guastella, A. J., Einfeld, E. L., Gray, K., Rinehart, N., Tonge, B., Lambert, T. J., & Hickie, I. B. (2010, April). Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. *Biological Psychiatry*, 67, 692–694. doi:10.1016/j.biopsycho.2009.09.020
- Halladay, A. K., Amaral, D., Aschner, M., Bolivar, V. J., Bowman, A., DiCicco-Bloom, E., . . . Threadgill, D. W. (2009). Animal models of autism spectrum disorders: Information for neurotoxicologists. *Neurotoxicology*, 30, 811–821. doi:10.1016/j.neuro.2009.07.002
- Happé, F., Ehlers, S., Fletcher, P., Frith, U., Johansson, M., Gillberg, C., Dolan, R., Frackowiak, R., & Frith, C. (1996). “Theory of mind” in the brain: Evidence from a PET scan study of Asperger Syndrome. *Neuroreport*, 8, 197–201.
- Hammock, E. A. D., & Young, L. J. (2005). Microsatellite instability generates diversity in brain and sociobehavioral traits. *Science*, 308, 1630–1634. doi:10.1126/science.1111427
- Hammock, E. A. D., & Young, L. J. (2006). Oxytocin, vasopressin and pair bonding: Implications for autism. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, 361, 2187–2198. doi:10.1098/rstb.2006.1939
- Harcourt, A. H. (1989). Sociality and competition in primates and non-primates. In V. Standen & R. Foley (Eds.), *Comparative socioecology* (pp. 223–242). Oxford, UK: Blackwell Scientific.

- Hare, B., Melis, A. P., Woods, V., Hastings, S., & Wrangham, R. (2007). Tolerance allows bonobos to outperform chimpanzees on a cooperative task. *Current Biology*, 17, 619–623. doi:10.1016/j.cub.2007.02.040
- Hollander, E., Novotny, S., Hanratty, M., Yaffe, R., DeCaria, C. M., Aronowitz, B. R., & Moscovich, S. (2003). Oxytocin infusion reduces repetitive behaviors in adults with autistic and Asperger's disorders. *Neuropsychopharmacology*, 28, 193–198. doi:10.1038/sj.npp.1300021
- Hutt, C., & Ounsted, C. (1966). The biological significance of gaze aversion with particular reference to the syndrome of infantile autism. *Behavioral Science*, 11, 346–356. doi:10.1002/bs.3830110504
- Insel, T. R. (2010). The challenge of translation in social neuroscience: A review of oxytocin, vasopressin and affiliative behavior. *Neuron*, 65, 768–779. doi:10.1016/j.neuron.2010.03.005
- Jackson, T. P. (1999). The social organization and breeding system of Brant's whistling rat (*Parotomys brantsii*). *Journal of Zoology*, 247, 323–331. doi:10.1111/j.1469-7998.1999.tb00995.x
- Jacob, S., Brune, C. W., Carter, C. S., Leventhal, B. L., Lord, C., & Cook, E. H. (2007, April). Association of the oxytocin receptor gene (OXTR) in Caucasian children and adolescents with autism. *Neuroscience Letters*, 417, 6–9. doi:10.1016/j.neulet.2007.02.001
- Joffe, T. H., & Dunbar, R. I. M. (1997). Visual and socio-cognitive information processing in primate brain evolution. *Proceedings. Biological Sciences/The Royal Society*, 264, 1303–1307. doi:10.1098/rspb.1997.0180
- Kaplan, G., & Rogers, L. J. (2002). Patterns of Gazing in Orangutans (*Pongo pygmaeus*). *International Journal of Primatology*, 23, 501–526.
- Kelly, A. B., Garnett, M. S., Attwood, T., & Peterson, C. (2008). Autism spectrum symptomatology in children: The impact of family and peer relationships. *Journal of Abnormal Child Psychology*, 36, 1069–1081. doi:10.1007/s10802-008-9234-8
- Kennedy, D. P., & Courchesne, E. (2008). The intrinsic functional organization of the brain is altered in autism. *NeuroImage*, 39, 1877–1885. doi:10.1016/j.neuroimage.2007.10.052
- Kennedy, D. P., Redcay, E., & Courchesne, E. (2006). Failing to deactivate: Resting functional abnormalities in autism. *PNAS Proceedings of the National Academy of Sciences of the United States of America*, 103, 8275–8280. doi:10.1073/pnas.0600674103
- Kirsch, P., Esslinger, C., Chen, Q., Mier, D., Lis, S., Siddhanti, S., . . . Meyer-Lindenberg, A. (2005). Oxytocin modulates neural circuitry for social cognition and fear in humans. *The Journal of Neuroscience*, 25, 11489–11493. doi:10.1523/JNEUROSCI.3984-05.2005
- Kosfeld, M., Heinrichs, M., Zak, P. J., Fischbacher, U., & Fehr, E. (2005, June). Oxytocin increases trust in humans. *Nature*, 435, 673–676. doi:10.1038/nature03701
- Kozorovitskiy, Y., Hughes, M., Lee, K., & Gould, E. (2006). Fatherhood affects dendritic spines and vasopressin V1a receptors in the primate prefrontal cortex. *Nature Neuroscience*, 9, 1094–1095. doi:10.1038/nn1753
- Lim, M. M., Wang, Z., Olazabal, D. E., Ren, X., Terwilliger, E. F., & Young, L. J. (2004). Enhanced partner preference in promiscuous species by manipulating the expression of a single gene. *Nature*, 429, 754–757. doi:10.1038/nature02539
- Lombardo, M. V., Barnes, J. L., Wheelwright, S., & Baron-Cohen, S. (2007). Self-referential cognition and empathy in autism. *PLoS One*, 2, e883.
- Lombardo, M. V., Chakrabarti, B., Bullmore, E. T., Sadek, S. A., Pasco, G., Wheelwright, S. J., . . . Baron-Cohen, S. (2010). Atypical neural self-representation in autism. *Brain*, 133, 611–624. doi:10.1093/brain/awp306
- Lott, D. F. (1991). *Intraspecific variation in the social systems of wild vertebrates*. New York, NY: Cambridge University Press.
- Mabry, K. E., Streatfeild, C. A., Keane, B., & Solomon, N. G. (2011). Avpr1a length polymorphism is not associated with either social or genetic monogamy in free-living prairie voles. *Animal Behaviour*, 81, 11–18. doi:10.1016/j.anbehav.2010.09.021
- Machin, A. J., & Dunbar, R. I. M. (2011). The brain opioid theory of social attachment: A review of the evidence. *Behaviour*, 148, 985–1025. doi:10.1163/000579511X596624
- Marler, P. (1968). Aggression and dispersal: Two functions in primate communication. In P. C. Jay (Ed.), *Primates: Studies in adaptation and variability* (pp. 223–245). New York, NY: Holt, Rinehart and Winston.
- Martel, F. L., Nevison, C. M., Simpson, M. J. A., & Keverne, E. B. (1995). Effects of opioid receptor blockade on the social behavior of rhesus monkeys living in large family groups. *Developmental Psychobiology*, 28, 71–84. doi:10.1002/dev.420280202
- Miller, W. B. (2005). Affiliative reward and the ontogenetic bonding system. *Behavioral and Brain Sciences*, 28, 357–358. doi:10.1017/S0140525X05290064
- Moy, S. S., & Nadler, J. J. (2008). Advances in behavioral genetics: Mouse models of autism. *Molecular Psychiatry*, 13, 4–26. doi:10.1038/sj.mp.4002082
- Müller, A. E., & Thalmann, U. (2000). Origin and evolution of primate social organization: A reconstruction. *Biological Reviews*, 75, 405–435. doi:10.1017/S0006323100005533
- Mundy, P. (1995). Joint attention and social-emotional approach behavior in children with autism. *Development and Psychopathology*, 7, 63–82. doi:10.1017/S0954579400006349
- Munesue, T., Yokoyama, S., Nakamura, K., Anitha, A., Yamada, K., Hayashi, K., . . . Higashida, H. (2010). Two genetic variants of CD38 in subjects with autism spectrum disorders and controls. *Neuroscience Research*, 67, 181–191. doi:10.1016/j.neures.2010.03.004
- Naber, F. B. A., Bakermans-Kranenburg, M. J., van IJzendoorn, M. H., Swinkels, S. H. N., Buitelaar, J. K., Dietz, C., . . . Van Engeland, H. (2008). Play behavior and attachment in toddlers with autism. *Journal of Autism and Developmental Disorders*, 38, 857–866. doi:10.1007/s10803-007-0454-5
- Panksepp, J., Nelson, E., & Siviy, S. (1994). Brain opioids and mother-infant social motivation. *Acta Paediatrica*, 83, 40–46.
- Pedersen, C. A., Vadlamudi, S. V., Boccia, M. L., & Amico, J. A. (2006). Maternal behavior deficits in nulliparous oxytocin knockout mice. *Genes, Brain & Behavior*, 5, 274–281. doi:10.1111/j.1601-183X.2005.00162.x
- Pellis, S. M., Hastings, E., Shimizu, T., Kamitakahara, H., Komorowska, J., Forgie, M. L., & Kolb, B. (2006). The effects of orbital frontal cortex damage on the modulation of defensive responses by rats in playful and non-playful social contexts. *Behavioral Neuroscience*, 120, 72–84. doi:10.1037/0735-7044.120.1.72
- Peppé, S., McCann, J., Gibbon, F., O'Hare, A., & Rutherford, M. (2007). Receptive and expressive prosodic ability in children with high-functioning autism. *Journal of Speech, Language, and Hearing Research*, 50, 1015–1028. doi:10.1044/1092-4388(2007/071)
- Phelps, S. M. (2010). From endophenotypes to evolution: Social attachment, sexual fidelity and the avpr1a locus. *Current Opinion in Neurobiology*, 20, 795–802. doi:10.1016/j.conb.2010.09.002
- Pierce, K., & Redcay, E. (2008). Fusiform function in children with an autism spectrum disorder is a matter of “who”. *Biological Psychiatry*, 64, 552–560. doi:10.1016/j.biopsych.2008.05.013
- Pitkow, L. J., Sharer, C. A., Ren, X., Insel, T. R., Terwilliger, E. F., & Young, L. J. (2001). Facilitation of affiliation and pair-bond formation by vasopressin receptor gene transfer into the ventral forebrain of a monogamous vole. *The Journal of Neuroscience*, 21, 7392–7396.
- Piven, J. (2000). The broad autism phenotype. In P. J. Accardo, C. Magnusen, & A. J. Capute (Eds.), *Autism: Clinical and research issues* (pp. 214–224). Baltimore, MD: York Press.
- Plomin, R., DeFries, J. C., McClearn, G. E., & McGuffin, P. (2008). *Behavioral Genetics* (p.), New York, NY: Worth Publishers.
- Porges, S. W. (2005). The vagus: A mediator of behavioral and physiologic

- features associated with autism. In M. L. Bauman & T. L. Kemper (Eds.), *The neurobiology of autism* (pp. 65–78). Baltimore, MD: John Hopkins University Press.
- Porges, S. W., & Carter, C. S. (2010). *Neurobiological bases of social behavior across the life span. The handbook of life-span development*. Hoboken, NJ: Wiley.
- Povinelli, D. J. (1994). What chimpanzees (might) know about the mind. In R. Wrangham, W. McGrew, F. de Waal, & P. Heltne (Eds.), *Chimpanzee cultures* (pp. 285–300). Cambridge, UK: Harvard University Press.
- Randall, J. A., Rogovin, K., Parker, P. G., & Eimes, J. A. (2005). Flexible social structure of a desert rodent, *Rhombomys opimus*: Philopatry, kinship, and ecological constraints. *Behavioral Ecology*, 16, 961–973. doi:10.1093/beheco/ari078
- Reser, J. E. (2006). Evolutionary neuropathology and congenital mental retardation: Environmental cues predictive of maternal deprivation influence the fetus to minimize cerebral metabolism in order to express bioenergetic thrift. *Medical Hypotheses*, 67, 529–544. doi:10.1016/j.mehy.2006.03.005
- Reser, J. E. (2007). Schizophrenia and phenotypic plasticity: Schizophrenia may represent a predictive, adaptive response to severe environmental adversity that allows both bioenergetic thrift and a defensive behavioral strategy. *Medical Hypotheses*, 69, 383–394. doi:10.1016/j.mehy.2006.12.031
- Reser, J. E. (2011a). Conceptualizing the autism spectrum in terms of natural selection and behavioral ecology: The solitary forager hypothesis. *Evolutionary Psychology*, 9, 207–238.
- Reser, J. E. (2011b). *Solitary mammals provide an animal model for autism spectrum disorders*. Poster session presented at the annual Cell Symposium on Autism, Washington, DC.
- Rodier, P. M., Ingram, J. L., Tisdale, B., Nelson, S., & Romano, J. (1996). Embryological origins for autism: Developmental anomalies of the cranial nerve nuclei. *Journal of Computational Neurology*, 370, 247–261. doi:10.1002/(SICI)1096-9861(19960624)370:2<247::AID-CNE8>3.0.CO;2-2
- Rodrigues, S. M., Saslow, L. R., Garcia, N., John, O. P., & Keltner, D. (2009). Oxytocin receptor genetic variation relates to empathy and stress reactivity in humans. *PNAS Proceedings of the National Academy of Sciences of the United States of America*, 106, 21437–21441. doi:10.1073/pnas.0909579106
- Rosenblum, L. A., Smith, E. L. P., Altemus, M., Scharf, B. A., Owens, M. J., & Nemeroff, C. B., . . . Copland, J. D. (2002). Differing concentrations of corticotropin releasing factor and oxytocin in the cerebrospinal fluid of bonnet and pigtail macaques. *Psychoneuroendocrinology*, 27, 651–660. doi:10.1016/S0306-4530(01)00056-7
- Rutgers, A. H., Bakermans-Kranenburg, M. J., van Ijzendoorn, M. H., & van Berckelaer-Onnes, I. A. (2004). Autism and attachment: A meta-analytic review. *Journal of Child Psychology and Psychiatry*, 45, 1123–1134. doi:10.1111/j.1469-7610.2004.t01-1-00305.x
- Sahley, T. L., & Panksepp, J. (1987). Brain opioids and autism: An updated analysis of possible linkages. *Journal of Autism and Developmental Disorders*, 17, 201–216. doi:10.1007/BF01495056
- Savaskan, E., Ehrhardt, R., Schulz, A., Walter, M., & Schachniger, H. (2008). Post-learning intranasal oxytocin modulates human memory for facial identity. *Psychoneuroendocrinology*, 33, 368–374. doi:10.1016/j.psyneuen.2007.12.004
- Schradin, C., Lindholm, A. K., Johannsen, J., Schoepf, I., Yuen, C., Konig, B., & Pillay, N. (2012). Social flexibility and social evolution in mammals: A case study of the African striped mouse (*Rhabdomys pumilio*). *Molecular Ecology*, 21, 541–543. doi:10.1111/j.1365-294X.2011.05256.x
- Seamans, J. K., & Robbins, T. W. (2010). Dopamine modulation of the prefrontal cortex and cognitive function. In K. A. Neve (Ed.), *The dopamine receptors* (2nd ed., pp. 373–398). New York, NY: Humana Press. doi:10.1007/978-1-60327-333-6_14
- Shapiro, L. E., & Insel, T. R. (1990). Infant's response to social separation reflects adult differences in affiliative behavior: A comparative developmental study in prairie and montane voles. *Developmental Psychology*, 23, 375–393. doi:10.1002/dev.420230502
- Shapiro, L. E., Meyer, M. E., & Dewsbury, D. A. (1989). Affiliative behavior in voles: Effects of morphine, naloxone, and cross-fostering. *Physiology & Behavior*, 46, 719–723. doi:10.1016/0031-9384(89)90357-0
- Sherwood, C. C. (2005). Comparative anatomy of the facial motor nucleus in mammals, with an analysis of neuron numbers in primates. *The Anatomical Record. Part A, Discoveries in Molecular, Cellular, and Evolutionary Biology*, 287, 1067–1079. doi:10.1002/ar.a.20259
- Shultz, S., Opie, C., & Atkinson, Q. D. (2011). Stepwise evolution of stable sociality in primates. *Nature*, 479, 219–222. doi:10.1038/nature10601
- Sigman, M., & Ungerer, J. A. (1984). Attachment behaviors in autistic children. *Journal of Autism and Developmental Disorders*, 14, 231–244. doi:10.1007/BF02409576
- Silani, G., Bird, G., Brindley, R., Singer, T., Frith, C., & Frith, U. (2008). Levels of emotional awareness and autism: An fMRI study. *Social Neuroscience*, 3, 97–112. doi:10.1080/17470910701577020
- Sutcliffe, J. S., Delahanty, R. J., Prasad, H. C., McCauley, J. L., Han, Q., Jian, L., . . . Blakely, R. D. (2005). Allelic heterogeneity at the serotonin transporter locus (SLC6A4) confers susceptibility to autism and rigid-compulsive behaviors. *American Journal of Human Genetics*, 77, 265–279.
- Takayanagi, Y., Yoshida, M., Bielsky, I. F., Ross, H. E., Kawamata, M., Onaka, T., . . . Nishimori, K. (2005). Pervasive social deficits, but normal parturition, in oxytocin receptor-deficient mice. *PNAS Proceedings of the National Academy of Sciences of the United States of America*, 102, 16096–16101. doi:10.1073/pnas.0505312102
- Treffert, D. A. (2000). The savant syndrome in autism. In P. J. Accardo, C. Magnusen, & A. J. Capute (Eds.), *Autism: Clinical and research issues* (pp. 193–214). Baltimore, MD: York Press.
- Trivers, R. (1985). *Social evolution*. Menlo Park, CA: Benjamin Cummings.
- van Schaik, C. P. (1999). The socioecology of fission–fusion sociality in orangutans. *Primates*, 40, 69–86. doi:10.1007/BF02557703
- van Schaik, C. P., & van Hoof, J. A. (1996). Toward an understanding of the orangutan's social system. In W. C. McGrew, L. F. Marchant, & T. Nishida (Eds.), *Great ape societies* (pp. 127–148). London, UK: Cambridge University Press. doi:10.1017/CBO9780511752414.003
- Via, S., & Lande, R. (1985). Genotype–environment interaction and the evolution of phenotypic plasticity. *Evolution*, 39, 505–522. doi:10.2307/2408649
- Walsh, P., Elsabbagh, M., Bolton, P., & Singh, I. (2011). In search of biomarkers for autism: Scientific, social and ethical challenges. *Nature Reviews Neuroscience*, 12, 603–612. doi:10.1038/nrn3113
- Wang, A. T., Lee, S. S., Sigman, M., & Dapretto, M. (2007). Reading affect in the face and voice: Neural correlates of interpreting communicative intent in children and adolescents with autism spectrum disorders. *Archives of General Psychiatry*, 64, 698–708.
- Wang, Z., Toloczko, D., Young, L. J., Moody, K., Newman, J. D., & Insel, T. R. (1997). Vasopressin in the forebrain of common marmosets (*Callicebus jacchus*): Studies with in situ hybridization, immunocytochemistry, and receptor autoradiography. *Brain Research*, 768, 147–156. doi:10.1016/S0006-8993(97)00636-7
- Wassink, T. H., Piven, J., Vieland, V. J., Pietila, J., Goedken, R. J., Folstein, S. E., & Sheffield, V. C. (2004). Examination of AVPR1a as an autism susceptibility gene. *Molecular Psychiatry*, 9, 968–972.

- Watson, K. K., Ghodasra, J. H., & Platt, M. L. (2009). Serotonin transporter genotype modulates social reward and punishment in rhesus macaques. *PLoS One*, 4, e4156. doi:10.1371/journal.pone.0004156
- Wermter, A. K., Kamp-Becker, I., Hesse, P., Schulte-Körne, G., Strauch, K., & Remschmidt, H. (2010). Evidence for the involvement of genetic variation in the oxytocin receptor gene (OXTR) in the etiology of autistic disorders on high-functioning level. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics*, 153, 629–639.
- Williams, J. H. G., Whiten, A., Suddendorf, T., & Perrett, D. I. (2001). Imitation, mirror neurons and autism. *Neuroscience and Biobehavioral Reviews*, 25, 287–295. doi:10.1016/S0149-7634(01)00014-8
- Winslow, J. T., & Insel, T. R. (1991). Social status in pairs of squirrel monkeys determines the behavioral response to central oxytocin administration. *Journal of Neuroscience*, 11, 2032–2038.
- Winslow, J. T., Noble, P. L., Lyons, C. K., Sterk, S. M., & Insel, T. R. (2003). Rearing effects on cerebrospinal fluid oxytocin concentration on social buffering in rhesus monkeys. *Neuropsychopharmacology*, 28, 910–918.
- Witt, D. M., Carter, C. S., & Walton, D. M. (1990). Central and peripheral effects of oxytocin administration in prairie voles (*Microtus ochrogaster*). *Pharmacology, Biochemistry and Behavior*, 37, 63–69. doi:10.1016/0091-3057(90)90042-G
- Witt, D. M., Winslow, J. T., & Insel, T. R. (1992). Enhanced social interactions in rats following chronic, centrally infused oxytocin. *Pharmacology, Biochemistry and Behavior*, 43, 855–861. doi:10.1016/0091-3057(92)90418-F
- Wrangham, R. W. (1986). Ecology and social relationships in two species of chimpanzees. In D. Rubenstein and R. Wrangham, *Ecological aspects of social evolution* (pp. 352–378). Princeton, NJ: Princeton University Press.
- Wu, S., Jia, M., Ruan, Y., Liu, J., Guo, Y., Shuang, M., . . . Zhang, D. (2005). Positive association of the oxytocin receptor gene (OXTR) with autism in the Chinese Han population. *Biological Psychiatry*, 1, 74–77. doi:10.1016/j.biopsych.2005.03.013
- Yamagiwa, J. (1992). Functional analysis of social staring behavior in an all-male group of mountain gorillas. *Primates*, 33, 523–544. doi:10.1007/BF02381153
- Yirmiya, N., Kasari, C., Sigman, M., & Mundy, P. (1989). Facial expressions of affect in autistic, mentally retarded and normal children. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, 30, 725–735. doi:10.1111/j.1469-7610.1989.tb00785.x
- Yirmiya, N., Rosenberg, C., Levi, S., Salomon, S., Shulman, C., Nemanov, L., . . . Ebstein, R. P. (2006). Association between the arginine vasopressin 1a receptor (AVPR1A) gene and autism in a family-based study: Mediation by socialization skills. *Molecular Psychiatry*, 11, 488–494. doi:10.1038/sj.mp.4001812
- Young, L. J. (2002). The neurobiology of social recognition, approach, and avoidance. *Biological Psychiatry*, 51, 18–26. doi:10.1016/S0006-3223(01)01268-9
- Young, L. J. (2009). The neuroendocrinology of the social brain. *Frontiers in Neuroendocrinology*, 30, 425–428. doi:10.1016/j.yfrne.2009.06.002
- Young, L. J., Lim, M., Gingrich, B., & Insel, T. R. (2001). Cellular mechanisms of social attachment. *Hormones and Behavior*, 40, 133–138. doi:10.1006/hbeh.2001.1691
- Yrigollen, C. M., Han, S. S., Kochetkova, A., Babitz, A., Chang, J. T., Volkmar, F. R., . . . Grigorenko, L. (2008). Genes controlling affiliative behavior as candidate genes for autism. *Biological Psychiatry*, 63, 911–916. doi:10.1016/j.biopsych.2007.11.015
- Zhang, T. Y., Parent, C., Weaver, I., & Meaney, M. (2004). Maternal programming of individual differences in defensive responses in the rat. *Annals of the New York Academy of Sciences*, 1032, 85–103. doi:10.1196/annals.1314.007
- Zuk, M. (2002). *Sexual selections: What we can and can't learn about sex from animals*. Los Angeles, CA: University of California Press.

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