

HOW THE BRAIN PROCESSES SOCIAL INFORMATION: Searching for the Social Brain*

Thomas R. Insel¹ and Russell D. Fernald²

¹*National Institute of Mental Health, Bethesda, Maryland 20892;*

email: insel@mail.nih.gov

²*Neuroscience Program, Stanford University, Stanford, California 94305;*

email: russ@psych.stanford.edu

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■ **Abstract** Because information about gender, kin, and social status are essential for reproduction and survival, it seems likely that specialized neural mechanisms have evolved to process social information. This review describes recent studies of four aspects of social information processing: (a) perception of social signals via the vomeronasal system, (b) formation of social memory via long-term filial imprinting and short-term recognition, (c) motivation for parental behavior and pair bonding, and (d) the neural consequences of social experience. Results from these studies and some recent functional imaging studies in human subjects begin to define the circuitry of a “social brain.” Such neurodevelopmental disorders as autism and schizophrenia are characterized by abnormal social cognition and corresponding deficits in social behavior; thus social neuroscience offers an important opportunity for translational research with an impact on public health.

INTRODUCTION

During the past decade a new field of research, social neuroscience, has emerged as molecular and cellular methods as well as neuroimaging tools have been used to investigate social behavior and social cognition. Social neuroscience has tackled problems as diverse as the neural basis of dominance, the molecular mechanisms of monogamy, and the organization of a “social brain.” The emergence of social neuroscience can be traced to three developments. First and perhaps most surprisingly, studies of certain social interactions such as reproductive behaviors or parental care have revealed some simple, yet robust, molecular and cellular mechanisms (Insel & Young 2001, Pfaff et al. 2002). One might expect that these ostensibly complicated behaviors would be the least likely to be reduced to

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simple neural mechanisms. However, social behavior is essential for reproduction, and therefore, the neural and hormonal processes subserving these behaviors are likely to be highly conserved. Second, there has been increasing recognition of the role abnormal social behavior plays in such human disorders as schizophrenia and autism (Lord et al. 2000). Studies in nonhuman animals may identify neural substrates of normal social behavior that could aid our understanding and treatment of abnormal human social behavior. Third, there is mounting evidence that social isolation and social separation are serious risk factors for medical disorders that may rival well-known traditional risk factors such as smoking and obesity (House et al. 1988). The powerful effect of loneliness on health begs the question of how social interaction protects against illness.

Although social neuroscience has emerged recently, its conceptual underpinnings reach back nearly a century. von Uexküll (1921) suggested that every species experiences life differently, living as it does in its own "Umwelt," or unique perceptual world. Lorenz (1935) expanded von Uexküll's idea of a perceptual world to include not only physical surroundings but also a social system. His landmark article "Companions as Factors in the Bird's Environment" suggests that an animal's perceptual world must include important information about the behavior of other individuals and even the group as a whole. Because successful social behavior requires recognition of key social interactions in their appropriate context, individual responses in social situations must have been important in shaping the species phenotype. However, in many species, little is known either about how such social perception occurs or about how it leads to the behavioral, physiological, cellular, and molecular changes needed for social behavior. Moreover, various epochs of an animal's life pose different requirements for successful and effective social behavior because distinct behavioral patterns may be important at different times. For example, affiliation, meaning contact with a conspecific, can be manifest as attachment during infancy, as maternal care postpartum, or as pair-bonding behavior in reproductive adults.

CONSTRAINTS ON ANALYZING SOCIALLY RELEVANT NEURAL SYSTEMS

Searching for specific neural substrates of social behavior sets important constraints on experimental methods. It is crucial that behavioral studies designed to understand the neural bases of specific behavioral patterns use realistic social situations where animals interact as they would in their natural habitat. Consequently, there are several important caveats for the most successful development of social neuroscience.

First, there is a tendency to use simple behavioral assays to probe complex behavioral patterns. Such assays are proxies for the real events and, although convenient for experimental purposes, can lead to over- or misinterpretation of results. For example, even though "approach" is often taken as a proxy for affiliative

behavior, one animal may approach another for many reasons depending critically on individual status, social context, and physiological state of the individuals involved. Therefore, using approach as a measure of affiliation can distort the value of experimental measurements (see Lederhendler & Shulkin 2000 for a more complete discussion of this issue).

Second, many studies make the tacit assumption that typical laboratory housing is appropriate for animals intended for use in the analysis of complex social behaviors. However, studies of rodents have shown the profound effects housing has on brain structures (Rosenzweig & Bennett 1996, van Praag et al. 2000) such that behavioral and genetic manipulations can be obscured by rearing conditions (Henderson 1970). Ethological information should guide decisions about the environmental factors needed to successfully mimic a natural situation. Wiedenmayer (1997) showed, for example, that gerbils develop stereotypies when their environment does not contain shelters that are appropriately based on their natural behavior. Perseveration of stereotypic behavior in captive animals can easily occur and may reflect stress-induced sensitization of dopamine systems (Cabib et al. 2000). These concerns are particularly important in the early experience of animals. Rearing animals in isolation can selectively disrupt higher-order cognitive function as well as sensory filtering (Hall 1998, Robbins et al. 1996). Thus, even relatively subtle changes in rearing can produce enhanced fearfulness in the animals in ways that could seriously confound experimental outcomes (Wurbel 2001).

Third, the failure to use ethologically relevant tasks can compromise the results of studies in which genetic or environmental challenges are used (Gerlai & Clayton 1999). Testing animals in a context irrelevant to the natural behavior of the animal can produce anomalous results for a variety of reasons. For example, the widely used Morris water maze, a spatial learning task, was developed for a rat species that inhabits wetlands (Morris 1981), although now it is used primarily to test mice that evolved to live in burrows in dry regions such as forests and grasslands. Tests that are not matched to natural behavior may subject the animal to significant stress, confounding what is intended to be a cognitive task with behavioral and endocrine responses to a threatening environment. Ideally a combination of field and laboratory studies might be used to structure experiments. Field observations can identify the capabilities of animals in their natural habitat, revealing processes that have been shaped by natural selection. These insights could then be used to frame laboratory procedures useful in controlled analyses of particular behaviors or cognitive tasks. When possible, several complementary tests should be used to assure that the overall outcome reflects the intended assessment.

Finally, growing evidence indicates that the social context can change neural pathways in individual animals. Whether we examine reproductive behavior (Fernald 2002), the size of a litter (Hofer et al. 1993), a companion for birdsong (Hessler & Doupe 1999), or simply group housing with an inevitable dominance hierarchy, it is important to recognize that social context matters. It is a challenge to discover not only how behavior is controlled via physiological processes, but also how social context influences physiological, cellular, and molecular events in the central nervous system.

SENSORY SPECIALIZATIONS FOR SOCIAL PERCEPTION

As noted above, different species have distinct sensory windows into the world and some sensory systems appear to have evolved especially for social behavior. This claim raises the more general issue of how to distinguish between the functioning of a neural system that is dedicated to processing social information and the functioning of a generic sensory system adapted for multimodal processing of complex stimuli such as social interactions.

Perhaps the best-known sensory system specialized for social behavior is that used for detecting pheromones, the compounds used for intraspecies communication (reviewed in Dulac & Torello 2003). All higher eukaryotes show a remarkable convergence toward two distinct olfactory systems. The main olfactory system, which detects volatile odorants that are inhaled via airways, is used to detect food, predators, and prey. Evolved to detect smells that cannot be predicted, it contains a sensory array able to detect a large number of odorants. In contrast, the accessory olfactory system detects a limited set of pheromones that are actively pumped into the interior of the vomeronasal organ where they are sensed by neurons that project to the accessory olfactory bulb (AOB). This system detects and recognizes species-specific olfactory signals that carry information about the sex, reproductive state, and location of possible mates as well as information about territory and social status that regulates various social behaviors. In contrast to the main olfactory system, which faces a large and unknown universe of odors, the accessory olfactory system has a limited and predictable set of signals to detect.

Progress in understanding the olfactory and pheromonal systems has been rapid, with many surprises. The mammalian main olfactory receptors are G protein-coupled receptors (GPCRs) with a conserved seven-transmembrane structure, which facilitated their discovery (Buck & Axel 1991), but it was unexpected that there would be more than 1000 genes encoding olfactory receptors in mammals. Olfactory receptors, (Mombaerts et al. 1996), the signaling cascade (Firestein 2001), and a remarkable spatial encoding of olfactory signals extending from the glomeruli to second-order neurons in the cortex (Zou et al. 2001) have all been well described. More important for social interactions is detection of semiochemicals or pheromones produced by conspecifics, although the issue of human pheromones is hotly contested in some quarters (Meredith 2001). Pheromonal detection via the AOB relies on receptors in the vomeronasal organ (VNO) that are evolutionarily unrelated to those in the primary olfactory system. VNO sensory neurons express receptor genes from three independent supergene families, V1r, V2r, and V3r, arrayed in segregated populations on the VNO neuroepithelium, and they express several immune complex genes including a multigene family, H2-Mv, that represents nonclassical class I members of the major histocompatibility complex (Ishii et al. 2003, Loconto et al. 2003). Cells in the VNO do not express the main components of the signaling cascade used for transducing activation of olfactory receptors (such as G_{olf}), but they do express *trp2*, a cation channel of the transient

receptor potential family. However, the VNO in humans is vestigial, disappearing before birth. All members of the human VNO gene family are pseudo genes except for one, and the ligand for this receptor is not known.

Histochemical and optical mapping suggest that there are two or more anatomical subdivisions of the AOB along the antero-posterior axis. The central representations of pheromone receptors differ from the precise spatial representations of the main olfactory system. Instead of the convergence of multiple neurons expressing a single olfactory receptor onto a single glomerulus as seen in the main olfactory bulb, there is a more diffuse topographic projection of pheromone receptors onto multiple glomeruli in the AOB with convergence in the mitral cell, second-order neurons (Del Punta et al. 2002). The significance of this difference between main and accessory bulb organization is not clear, although in both systems there is a high degree of anatomic specificity at this early level of sensory processing. Mitral cell projections also vary between main and accessory systems in the rodent brain, the former represented in the primary olfactory cortex and the latter distributed in the bed nuclei of the accessory olfactory tract and stria terminalis as well as in the vomeronasal amygdala, including aspects of the posteromedial cortical and medial nuclei. Projections from the vomeronasal amygdala are largely to the neuroendocrine hypothalamus, including the medial preoptic area (MPOA) and ventromedial nucleus.

How does the VNO-AOB pathway perceive social signals? Neurophysiological recordings in anesthetized mice and in VNO slices have revealed several interesting aspects of the segregation of information between the VNO and main olfactory bulb (Dulac 2000). Some odorants not known to be pheromones can stimulate neurons in the VNO (Sam et al. 2001, Trinh & Storm 2003), which leads to the speculation that volatile chemicals associated with food or other important environmental signals activate both systems. There is clearly a topography of response. Recording from VNO slices, Leinders-Zufall et al. (2000) found neurons exquisitely sensitive (e.g., 10^{-11} M) to putative pheromone signals in specific regions of the apical VNO. Holy et al. (2000) recorded from the excised VNO sensory system using an electrode array and found neurons sensitive to male or female mouse urine. These *in vitro* approaches are not able to exploit the fully functioning system, but they offer a view of some capabilities of the system. In an exciting *in vivo* approach, Luo et al. (2003) recorded from single neurons in the AOB of male mice engaged in natural behaviors. They observed that neuronal firing was modulated by physical contact with male and female anesthetized conspecifics. Their data suggest that pheromone sampling may require sniffing as a prerequisite for pheromonal signaling. Moreover, individual neurons were activated selectively by specific combinations of the sex and strain of conspecifics and failed to respond to an artificial mouse. Furthermore, the intact animals showed no response to chemicals used to stimulate the VNO in anesthetized mice and slices. Presumably, animals need to seek pheromonal sources and actively sample those of interest. An example of the neural recording and associated behavior can be viewed on the Web (<http://www.sciencemag.org/content/vol299/issue5610/images/data/1196/DC1/1082133S1.mov>).

Targeted mutagenesis has also revealed aspects of social perception via the VNO. Stowers et al. (2002) generated a knockout of the *trp2* gene, encoding the cation channel expressed exclusively in neurons of the VNO. In *trp2* knockout animals, copulation was unaffected, but the males apparently could not distinguish between sexes. Rather than attacking male intruders, as seen in wild-type mice, mutant males attempted to copulate with other males. This suggests that the VNO may be essential for gender discrimination, although the receptor family for this behavior is not clear because *trp2* is expressed throughout the VNO. Male mice with a null mutation of the $\beta 2m$ gene, expressed only in neurons that express the the V2R receptor family, do not show copulation with other males, but they lack aggression (Loconto et al. 2003). Thus, different classes of VNO receptors may be linked to specific behavioral responses.

Progress in understanding how the VNO detects social information has been remarkable. Future studies recording simultaneous behavioral and neural events should allow a sophisticated analysis of how the VNO-AOB processes social signals. Salient from the data produced thus far is that pheromonal signaling is different from main olfactory signaling: In pheromonal signaling, the animal appears to seek the signal to be detected, volatile stimuli may not be readily sensed by this system, and receptors in the VNO appear to be more finely tuned and more sensitive than the receptors in the main olfactory epithelium. Although there is a high degree of spatial and molecular organization in the accessory system, natural stimuli represent complex mixtures of pheromones that activate diverse areas in the brain. Rather than serving simply as releasers or activators of behavior or neuroendocrine responses, pheromonal signals may shape diverse sensory systems converging on the hypothalamus (Dulac & Torello 2003).

SOCIAL LEARNING: FROM PERCEPTION TO MEMORY

How does an individual make sense of social information? Social recognition can be considered at several levels: kin, status, gender, and individual. Here we describe two forms of learning about individual identity: imprinting, which is apparently permanently stored; and social recognition in adults, which appears to be short term. Studies in these two areas are beginning to identify some molecules and cells important for social recognition. Some systems or circuits for social recognition are best defined in fMRI studies of humans (described below).

Imprinting: Formation of Long-Term Social Preferences

How do young animals come to “know” their parents, siblings, and appropriate sexual partners? For infants of many species, learning about conspecifics generally and parents and siblings more specifically is achieved via specialized learning processes early in life. This learning is critically important for survival and reproduction. For this reason, it offers an unusual chance to understand how the nervous system evolved to support specialized learning for a social purpose.

Lorenz (1935) first described this specialized form of social learning. He observed that precocial birds (ducklings, goslings, and chicks) follow and become attached or socially bonded to the first moving object they encounter within hours after hatching, usually the mother. Lorenz (1935) discovered that if greylag geese were reared by him from the time of hatching, they would treat him like a parental bird, and upon reaching sexual maturity, they courted him in preference to conspecifics. Lorenz called this process imprinting after the German word “prägung” (printing) because he proposed that the important sensory object met by the newborn bird is stamped immediately and irreversibly onto its nervous system. He also recognized that there was a short, critical period following hatching during which the chick was sensitive to learning. We now distinguish two forms of imprinting: filial (identifying parental and species phenotypes) and sexual (identifying potential future sexual partners).

Imprinting has been extensively studied in the laboratory, in part because its features are a direct challenge to conventional ideas about learning (Hess 1972). Imprinting is fast, requires few trials, has an obligatory sensitive period, and is irreversible in natural situations—all contrary to classical rules of animal learning. As such, imprinting resembles conditioned taste aversion and fear conditioning, two other rapid and enduring forms of learning in adults. But unlike these other forms of single-trial learning, imprinting occurs within a developmentally restricted time window, providing a rich but largely unexplored area of investigation for linking neural changes to social experience. In a series of studies, Horn & McCabe (1984) proposed two distinct processes: (a) emergence of filial behavior toward a stimulus without prior exposure to that stimulus, which they called a predisposition, and (b) acquiring a preference for a stimulus through exposure to it. The claim that these are dissociable parts of imprinting is based on manipulations such as drug administration and lesions that affect the two phases differentially (Davies et al. 1985).

Predisposition to approach stimuli resembling conspecifics is independent of experience and occurs during a sensitive period (Bolhuis et al. 1985, Johnson et al. 1989b). This predisposition, at least for chicks, appears to depend on the complex structural or configural properties of the stimulus (Johnson & Horn 1988). These data suggest that the chick has inherited some kind of perceptual template that predisposes it to prefer the right class of objects for its attention. Evidence suggests this predisposition is then shaped by the subsequent experience of the animal (Hogan 1988). It is not clear how this evolutionarily essential sensory template is encoded in the brain or how animals match visual experience to such a template.

The second aspect of imprinting, acquiring a preference, has been extensively studied. On the basis of original ethological observations, Bolhuis & Honey (1998) found that the more complex and realistic the stimulus is (e.g., sound, motion, structure), the stronger the imprinting process is, which, in turn, is thought to contribute to formation of an integrated representation of the imprinting object. Are there particular sites in the brain responsible for imprinting? Horn and colleagues (for a

review see Horn 1985) have described the importance of a telencephalic midline region, the intermediate and medial hyperstriatum ventrale (IMHV), for imprinting in the chick. In a series of lesion studies, chicks that had their IMHV surgically removed on both sides could no longer retain imprinting and could not recognize the imprinting stimuli. However, lesioned chicks could learn externally rewarded stimuli. In addition, there is increased metabolic activity, *N*-methyl-D-aspartate (NMDA) receptor binding, and *c-fos* gene expression in IMHV during imprinting (McCabe & Horn 1994). Morphological studies have shown that imprinting is correlated with an increase in the length of the postsynaptic density of spine synapses in the IMHV but only in the left hemisphere. Significantly, there does not seem to be an increase in synapse number in the IMHV during imprinting. In a related series of experiments, Bock & Braun (1999) described changes that accompany auditory imprinting in the chick. Here the relevant regions are the mediorostral neostriatum/hyperstriatum ventrale and the dorso-caudal neostriatum. However, in contrast to the increase in the postsynaptic density described with visual imprinting, Bock & Braun (1999) note that auditory imprinting is associated with a loss of spines in these two regions.

In both visual and auditory imprinting, NMDA receptors appear important for experience-dependent plasticity. NMDA receptor antagonists block visual (McCabe & Horn 1991) and auditory (Bock & Braun 1999) imprinting and, in the latter case, prevent the learning-associated loss of spines specifically in the two regions identified as critical for learning. In other models of experience-dependent plasticity associated with sensitive periods (such as the formation of ocular dominance columns in the visual cortex, the formation of barrel fields in the somatosensory cortex, or song learning in the zebra finch), the end of the sensitive period is associated with developmental changes in NMDA receptor physiology along with decreased expression of the NR2B subunit and increased expression of the NR2A subunit within the NMDA receptor complex (Heinrich et al. 2002). In this context, imprinting may represent a specialized form of developmental learning that uses mechanisms adapted for long-term storage in the service of social recognition. However, in other models of developmental plasticity such as avian song learning, downregulation of the NR2B subunit is not sufficient to close the critical period (Heinrich et al. 2003), and in NR2A knockout mice there is no evidence of an extended critical period (Lu et al. 2001).

Imprinting offers an unusual opportunity to explore a well-defined, genetically modulated period of plasticity during which specific brain regions acquire information essential for survival of the individual. In birds this process is largely visual, in rodents imprinting is olfactory (see Sullivan & Wilson 2003), and in sheep, both visual and pheromonal signals may be critical (Kendrick et al. 1998). Two questions still need to be answered: (a) What are the neural substrates of the critical or sensitive period? and (b) What are the neural consequences of stimulation during this period? It seems likely that with the appropriate experimental paradigm and a careful delineation of the time course, techniques for profiling gene and protein expression will reveal the neural mechanism for the window of filial imprinting, analogous to the recent studies of avian song learning and ocular

dominance column formation. In contrast to the evanescent sensitive period, the neural consequences of imprinting are likely to reflect constitutive changes in gene expression possibly via epigenetic mechanisms. A beautiful example of one such mechanism has been described by Meaney and colleagues (Meaney et al. 1996, Champagne et al. 2003) in their studies of the long-term effects of high versus low maternal grooming of rat pups. Grooming apparently induces an epigenetic demethylation of the promoter of the hippocampal glucocorticoid receptor, exposing the promoter to transcription factors that induce gene expression in response to stress. As a result, pups who receive high levels of grooming have more hippocampal glucocorticoid receptors and, because these receptors serve as a brake on the hypothalamic stress response, these pups remain relatively less stress responsive throughout life.

Social Recognition

If imprinting confers an enduring memory that is important for recognizing parents or avoiding incest, how do we recognize familiar individuals encountered later in the life cycle? In rodents, recognizing conspecifics, unlike imprinting, appears to be a short-lived process. Adult social recognition rests on the observation that in a laboratory cage environment and, presumably, in the wild most rodents will enter into a “meet and greet” ritual when exposed to a novel intruder. In the field, rats live in colonies with a common pheromonal signature spread via grooming. When a resident male is exposed to an intruder male or a sexually receptive female, this ritual quickly evolves into either a threat display or an attempted mating bout, respectively, regulated by pheromone detection. But when a resident male is exposed to a juvenile or an ovariectomized female, the male predictably sniffs and grooms the intruder for at least 2 min (depending on the strain). If the intruder is then removed for 30 min before being placed again with the same resident male, the time for investigation falls by approximately 50%. This decrease in investigation has been assumed to reflect recognition of the intruder because (a) a novel intruder receives at least 2 min of investigation, (b) increasing intervals of separation between the initial and subsequent exposures to the same intruder results in increasing investigation time, and (c) drugs or interventions that impair memory formation increase investigation time on the recognition trial (Winslow & Camacho 1995). In male rats, after 90 min of separation there is little or no decrease in investigation time, presumably reflecting a loss of recognition.

In a series of studies dating back nearly two decades, intraventricular administration of the neuropeptide vasopressin (AVP) has been shown to increase social recognition in male rats (Engelmann et al. 1996). Landgraf and colleagues recently reported that a viral-vector-induced increase in the vasopressin V1a receptor specifically in the lateral septum increased social recognition (Landgraf et al. 2003). AVP in the rat lateral septum is much more abundant in males than in females (De Vries et al. 1992), possibly accounting for a gender difference and androgen dependence of social recognition. However, the full circuitry for AVP's effects in the rat brain remains to be described.

Ferguson et al. (2000) recently described mice with a null mutation of another member of the AVP peptide family, oxytocin, as socially amnesic. In the oxytocin-knockout (OT-KO) mouse most aspects of social behavior, such as sexual and maternal behavior, appear unchanged from those of controls (Nishimori et al. 1996, Winslow et al. 2000, Young et al. 1996). In the social recognition paradigm, the responses of male OT-KO and wild-type mice do not differ in an initial encounter with a novel intruder, each spending approximately 150 s investigating the novel mouse (Ferguson et al. 2000). However, when tested 30 min later, wild-type mice show the expected 50% decrease in investigation, whereas OT-KO mice exhibit no change from the initial trial (Ferguson et al. 2000). It is curious to note that OT-KO and wild-type mice do not differ on several tests of nonsocial memory nor do they differ in tests of olfactory function. Indeed, when tested with either a lemon-scented cotton ball or even a lemon-scented mouse, both OT-KO and wild-type mice appear to recognize the stimulus after 30 min of separation (Ferguson et al. 2002). The deficit in the male OT-KO mouse thus appears to be specific to the social domain (although, see also Tomizawa et al. 2003 for cognitive deficits in female OT-KO mice).

Oxytocin receptors are found throughout the main olfactory bulb, the AOB, as well as several telencephalic nuclei in the mouse brain (Insel et al. 1993). Although earlier pharmacological studies implicated the olfactory bulb as the likely site of action for oxytocin effects on social recognition (Dluzen et al. 1998), when Ferguson et al. (2001) compared regional activation in OT-KO and wild-type mice after a brief social exposure, Fos staining was increased in the main and accessory olfactory systems of both strains, with no differences apparent between OT-KO and wild-type mice. However, in contrast to the wild-type mice, the OT-KO mice failed to activate Fos in the medial nucleus of the amygdala and in downstream projections in the bed nucleus of the stria terminalis (BST) and the MPOA. Oxytocin injected into the medial nucleus of the amygdala (a region rich in oxytocin receptors) appeared to reinstate social recognition in the OT-KO mice, at a dose that was ineffective when given by the intracerebroventricular (icv) route.

Consistent with the role of the V1a receptor on social recognition in rats, mice with a null mutation of the V1a receptor (V1a-KO) also manifest a profound deficit in social memory (Bielsky et al. 2004). At first glance, the OT-KO and V1a-KO mice appear to have a murine equivalent of prosopagnosia, a clinical syndrome in which the ability to recognize faces is lost. However, careful consideration of the ethological significance of the behavior suggests that the experimental proxy used for social recognition in these mouse studies is not equivalent to our sense of individual recognition in humans. The grooming ritual in mice that is used to investigate an intruder includes delivery of a pheromonal signature. Thus, it seems possible that the recognition depends on the test mouse detecting his own familiar pheromone rather than recognizing any individual characteristics of the intruder mouse. Could the behavioral results observed in the OT-KO mouse be explained by a deficit in secreting the pheromone rather than an inability to make a social memory? This interpretation would suggest that activation of the medial

amygdala is associated with secretion rather than detection of pheromones. At present, we suggest that this social recognition test be used with controls that are attentive to changes or deficits in grooming or pheromone delivery to determine if any alteration in recognition is in fact a problem in information processing or retrieval. Results from other assays, such as the social transmission of food preference test, may be useful to confirm a deficit in social cognition (Wrenn et al. 2003).

SOCIAL MOTIVATION: FROM RECOGNITION TO ACTION

Social attachment, social affiliation, sex behavior, and parental care are among the most highly motivated social behaviors. The motivation for social interaction, as with other appetitive behaviors, can be quantified with operant techniques. For instance, Everitt (1990) has demonstrated that male rats will bar press for access to estrous females, and Lee et al. (1999) have shown that postpartum females will bar press for access to pups. In a recent confirmation of the importance of maternal motivation, postpartum female rats were found to prefer a cage associated with pups to a cage associated with cocaine (Mattson et al. 2001). The laboratory rat, widely used for studies of maternal care, is also useful for studies of maternal motivation (Numan 1994). Unlike many mammals, female rats show little interest in infants of their own species until just before parturition. Approximately one day prior to delivery they shift from avoiding pups to showing intense interest with avid nest building, retrieval, grooming, and defense of young. These behaviors persist through lactation, then abate with weaning. Rats, therefore, provide an opportunity to study two distinct aspects of maternal care: onset and maintenance. The onset of maternal care, switching from avoidance to intense interest, is of particular interest because of the magnitude of the increase in motivation.

The Onset of Rat Maternal Behavior

Given the abundant evidence that mesolimbic dopamine pathways are important for other forms of highly motivated behaviors, from feeding to psychostimulant self-administration (Kelley & Berridge 2002), it is not surprising that these same pathways have been implicated in appetitive social interactions. Maternal behavior is instructive in this regard because of the number of experiments showing the relationship between dopamine and maternal behavior in rats. For example, exposure to pups increases Fos activation (Lonstein et al. 1998) and dopamine release (Hansen et al. 1993) in the nucleus accumbens of maternal but not of nonmaternal females. Depletion of dopamine in the ventral tegmentum by chemical lesion during pregnancy blocks the development of maternal behavior (Hansen et al. 1991). Similar disruptions of maternal behavior result from systemic administration of the dopamine receptor antagonist haloperidol (Giordano et al. 1990, Stern & Keer

1999) and after acute and chronic administration of cocaine (Johns et al. 1997, Kinsley 1994). Either lesions or injections of dopamine antagonists into the nucleus accumbens inhibit selectively the active components of maternal behavior such as retrieval and pup licking, but not the more reflexive aspects such as nursing (Hansen et al. 1991, Keer & Stern 1999). In one study, 6-hydroxydopamine (6-OHDA) lesions of the nucleus accumbens on day 2 or 3 postpartum in primiparous rats markedly reduced retrieval of pups without reducing nest building, nursing, or maternal aggression (Hansen 1991). Lesioned females preferred food to pups, and these same females, tested later for sex behavior, showed no deficits in either proceptive or receptive behavior. Thus the deficit appeared specific to maternal interest. Curiously, after the lesioned females were separated from their pups for 3–6 h, they began to retrieve them, indicating that these females were capable of retrieval but needed some additional incentive to do so.

These experiments suggest dopamine in the nucleus accumbens is responsible for maternal motivation, consistent with research on feeding and sex. Why does the female retrieve her pups rather than respond to myriad other stimuli in her world, such as food and mates? There is increasing evidence that the neuropeptide oxytocin may be critical for linking pup signals to the mesolimbic dopamine stream involved in motivated behaviors. Several investigators have reported that oxytocin given centrally to estrogen-primed, nulliparous female rats facilitates the onset of maternal behavior (reviewed in Insel 1997). Perhaps even more remarkable, blockade of oxytocin neurotransmission results in a significant inhibition of the onset of maternal behavior but fails to affect maternal behavior once it has been established (reviewed in Insel 1997). These results support the notions that oxytocin is necessary for the transition from maternal avoidance to attachment to pups and that a central increase in oxytocin given under the appropriate gonadal steroid conditions facilitates the onset of maternal care. In a sense, the role of oxytocin in the uterus and mammary tissue for providing the physiologic support of the offspring is matched by its role in the brain for subserving the motivational changes essential for maternal care.

Physiological changes in gonadal steroids during pregnancy increase both the synthesis of the peptide and the number of receptors (Crowley et al. 1995, Insel et al. 1992). The changes in oxytocin receptors are not ubiquitous. Only those regions rich in estrogen receptors (e.g., BST and ventromedial nucleus of the hypothalamus) show increased oxytocin receptor binding, but in these regions the changes may be rapid and profound (up to 300% increases in hypothalamic binding in 72 h) (Johnson et al. 1989a).

Results from site-specific injections of an oxytocin antagonist suggest that this peptide may be particularly important for regulating dopaminergic function either by a direct action on the ventral tegmental area or by afferents in the MPOA or BST (Pedersen et al. 1994). A region including the medial aspect of the MPOA and ventral BST has been studied for more than four decades as a “hot spot” for maternal behavior. This region is rich in estrogen receptors, the onset of maternal behavior is associated with a pronounced increase in local estrogen receptor

gene expression, and exogenous administration of estrogen into the MPOA stimulates maternal behavior in nulliparous females (Numan & Insel 2003). Moreover, lesions of the MPOA inhibit maternal behavior, and pup stimuli increase the induction of Fos protein in this region, reflecting increased activity (Stack & Numan 2000). What is the connection between the MPOA/BST and the aforementioned dopamine regulation of maternal motivation? Numan & Smith (1984) showed that unilateral lesions of the MPOA (which do not inhibit maternal behavior) in conjunction with lesions of the ventral tegmental area greatly reduced maternal retrieval. A recent follow-up study is even more compelling (Stack et al. 2002). After exposure to pups for 6 h, postpartum rats with unilateral MPOA lesions showed an increase specifically in the nucleus accumbens shell, relative to females not exposed to pups. The Fos increase was unilateral, limited to the side that receives a projection from MPOA/BST, and was not found in the nucleus accumbens core. Taken together, the current evidence supports a model that pup stimuli processed via olfactory and amygdala pathways ultimately activate estrogen- and oxytocin-sensitive MPOA/BST neurons that in turn project to the mesolimbic dopamine pathway in the ventral tegmental area and/or the nucleus accumbens shell.

Null mutations of several genes, including prolactin-receptor, Fos-B, and the paternally imprinted Peg-1 and Peg-3 genes, have disrupted maternal behavior in mice (reviewed in Leckman & Herman 2001). Surprisingly, the OT-KO mouse shows no deficit in maternal behavior (although these mice fail to lactate). This paradox may be resolved by the recognition that most laboratory strains of mice, unlike rats, do not avoid pups and do not require pregnancy or parturition to exhibit maternal care (Russell & Leng 1998). As noted above, pup-directed behavior in rats transforms at parturition from avoidance to approach. Estrogen and oxytocin in the MPOA/BST appear to be essential for this induction of maternal motivation. In mice, none of these factors appear essential for maternal motivation, and there is not a discrete onset of maternal behavior as seen in rats. Therefore, the various mutations that reduce maternal behavior in mice may be influencing various aspects of maternal care, but we have no evidence at this point that they are reducing maternal motivation per se.

Formation of Partner Preferences

Pair bonding in monogamous species provides another interesting example of social motivation. The prairie vole (*Microtus ochrogaster*) is a mouse-sized rodent that manifests the classic features of monogamy: A breeding pair shares the same nest and territory where they are in frequent contact, males participate in parental care, and intruders of either sex are rejected. Getz et al. (1993) reported from field studies that following the death of one of the pair, a new mate is accepted only ~20% of the time (the rate is approximately the same whether the survivor is male or female). Prairie voles also demonstrate a curious pattern of reproductive development: Offspring remain sexually suppressed as long as they remain within the natal group. For females, puberty occurs not at a specific age but after

exposure to a chemosignal in the urine of an unrelated male (Carter et al. 1995). Within 24 h of exposure to this signal, the female becomes sexually receptive. She mates repeatedly with an unrelated male and, in the process, forms a selective and enduring preference or pair bond.

As with parturition in rats, mating in these voles is a transformational event resulting in long-term increases in partner preferences that can be quantified in laboratory tests. The available data are largely analogous to data described for rat maternal behavior. Dopamine is released in the nucleus accumbens with mating, dopamine agonists in this region facilitate partner preference formation, and dopamine D2 antagonists inhibit partner preference formation (Gingrich et al. 2000, Wang et al. 1999). However, abundant evidence indicates that mating activates dopamine in the nucleus accumbens in species that do not form a partner preference (Pfaus et al. 2001), so one might ask whether this change is related to pair bonding. Or more generally, what is mating doing in the monogamous brain to confer a preference for the partner?

Because of the evidence that oxytocin and vasopressin are released with sexual behavior (Witt 1995), prairie voles have been treated with these peptides (in the absence of mating) or with their selective antagonists (prior to mating). Both peptides facilitate partner preference formation, and conversely, antagonists reduce partner preference formation without reducing mating behavior (Insel et al. 2001). As with the studies of rat maternal care, much of the recent interest in this area has focused on identifying the neural circuit necessary for pair bonding. In contrast to closely related nonmonogamous voles (and other nonmonogamous rodents such as rats), prairie voles have a high density of oxytocin and AVP V1a receptors in either the nucleus accumbens and prelimbic cortex or the ventral pallidum, respectively (Insel et al. 2001, Lim et al. 2004). Are these receptors important for pair bonding? An oxytocin antagonist injected directly into the nucleus accumbens or prelimbic cortex blocks pair-bond formation in female prairie voles (Young et al. 2001). Increasing AVP V1a receptors via viral-vector administration directly into the ventral pallidum facilitates partner preference formation (Pitkow et al. 2001), but it remains to be shown that an antagonist injected into this region blocks the behavior (Liu et al. 2001).

Molecular studies of both oxytocin and vasopressin receptors suggest that species differences in distribution may result from hypervariable regions found in the promoters of both genes (Insel & Young 2000). Sequence differences in the V1a promoter alter expression *in vitro*, and mice with a prairie vole transgene, including this promoter, have a prairie vole-like pattern of V1a receptor distribution and exhibit increased social behavior in response to AVP (Hammock & Young 2002, Young et al. 1999). Whatever the mechanism, monogamous species like prairie voles and marmosets have abundant receptors for either oxytocin or vasopressin in mesolimbic pathways such as the nucleus accumbens and the ventral pallidum (Young et al. 2001). One current hypothesis is that these receptors link social information to reward circuits in the brain, providing a neurobiological mechanism for partner preference formation. In its simplest form, the release

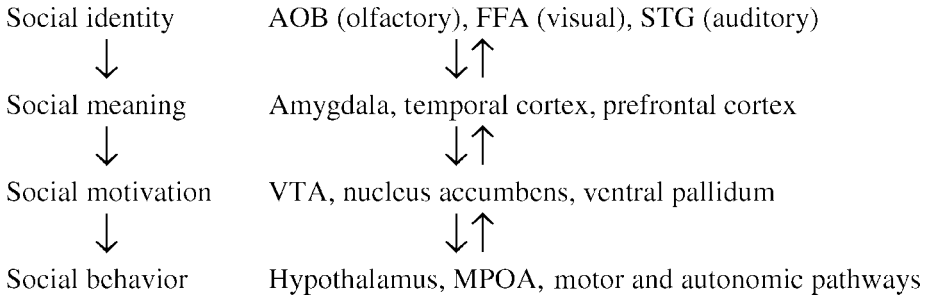


Figure 1 A simplified and highly theoretical model of social information processing in the mammalian brain. Sensory unimodal information is tagged as social in the accessory olfactory bulb (AOB), fusiform area (FFA), or superior temporal gyrus (STG). This signal becomes instantiated as significant or salient in a subsequent multimodal projection to poorly defined fields in the amygdala, temporal cortex, and prefrontal cortex, three regions where emotion, social status, or familiarity may be encoded. Social attachment (maternal behavior, pair bonding, and, potentially, infant attachment) involves recruitment of the mesolimbic dopamine pathway, including the ventral tegmental area, with development of individual preferences. Finally, social behavior involves activation of the neuroendocrine hypothalamus, including the medial preoptic area (MPOA), as well as motor and autonomic centers. The available data, although limited, suggest reciprocal activation between levels (see text for evidence that maternal behavior involves MPOA activation of the nucleus accumbens).

of oxytocin or vasopressin with mating would activate these reward pathways in monogamous species, resulting in a conditioned response or preference just as if the individual had received cocaine or amphetamine (see Figure 1). As noted above, mating activates dopamine release in both monogamous and nonmonogamous species. Therefore, this hypothesis rests on a specific role for oxytocin or vasopressin above and beyond dopamine release in the ventral striatum. Both peptides have been implicated in social recognition, presumably independent of effects on motivation. Recent reports of regional neurogenesis activated by mating in monogamous voles suggest another potential neural correlate of partner preference formation (Fowler et al. 2002).

SOCIAL BEHAVIOR THAT CHANGES THE BRAIN

It seems self-evident that the brain controls behavior, but can behavior also control the brain? Behavior influences specific aspects of brain structure and function in three different time frames. On an evolutionary timescale, the selective forces of the ecological niche of the animal are reflected in body shape, sensory and motor systems, and behavior. Similarly, on a developmental timescale, behavior acts in concert with the environment to establish structural changes in the brain that

influence an organism throughout its life. There is now evidence that in real time social behavior also causes changes in the brain of an adult animal. These alterations, caused by behavioral interactions, often are related to reproductive behavior and can be dramatic and reversible. Understanding the mechanisms responsible for such dynamic changes in the nervous systems of adult animals is a major challenge. How does behavior sculpt the brain and how are these changes controlled? To understand this requires a model system in which a complex social system can be manipulated and individuals can be analyzed at the physiological, cellular, and molecular level. A highly social cichlid fish provides one such model system.

In the African cichlid fish, *Haplochromis (Astatotilapia) burtoni*, there are two kinds of adult males: those with territories and those without (Fernald 1977). Territorial (T) males are brightly colored, with a dramatic black stripe through the eye, vertical black bars on the body, a black spot on the tip of the gill cover, and a large red patch just behind it. In contrast, nonterritorial (NT) males are cryptically colored, making them difficult to distinguish from the background and from females that are similarly camouflaged. Whether a male is T or NT depends on the social circumstances.

In their natural habitat, the shallow shorepools and river estuaries of Lake Tanganyika, *H. burtoni* live in a lek-like social system in which T males vigorously defend contiguous territories and solicit females to mate with them. If the female responds to these entreaties, he leads her into his pit where she lays her eggs at the bottom of the pit, collecting them in her mouth almost immediately. After she has laid several eggs, the male swims in front of her, displays the egglike spots on his anal fin (ocelli), and moves his body in a quivering motion (Fernald & Hirata 1977a,b). The male displays his anal fin because the spots may appear to the female to be eggs not yet collected (Wickler 1962). While attempting to "collect" the spots, the female ingests the milt ejected near them by the male, ensuring fertilization. On the other hand, NT males cannot spawn.

The natural behavior of *H. burtoni* reveals the extensive role of visual signals in social interactions and how much the social scene governs the behavior of individual animals. Each behavioral act influences the next. During the behavior, a great deal of information is exchanged between individuals. What does the animal attend to and what are the consequences?

Juvenile males raised with adults show suppressed gonadal maturation relative to those reared without adults (Davis & Fernald 1990). As well as having smaller testes, these animals have smaller gonadotropin-releasing hormone (GnRH)-containing neurons in the preoptic area, an area in the ventral telencephalon adjacent to the hypothalamus. These neurons project to the pituitary (Bushnik & Fernald 1995) where they release GnRH. The somata of GnRH neurons in T males are eight times larger than those in NT males, an effect that depends solely on social conditions. Because GnRH is the main signaling peptide that regulates reproductive maturity, the social control of maturation acts by changing structures in the brain.

Social status determines the physiology of the reproductive state, even in adult fish. Changing males from T to NT or vice versa has dramatic consequences. NT males who become T males have GnRH soma sizes similar to those of T males, whereas T males who become NT males have soma sizes comparable to those of NT males (Francis et al. 1993). The gonad sizes change accordingly. The same result has been shown for GnRH mRNAs using in situ hybridization with GnRH specific probes (White et al. 1995). Thus a change in social status alters brain structures essential for reproduction.

The socially induced GnRH-neuron size changes are remarkably asymmetric (White et al. 2002). Males ascending (NT→T) achieve large GnRH cell sizes in less than a week, whereas males descending (T→NT) have GnRH cell sizes that shrink slowly during a three-week period. This makes ecological sense because the chance to establish a territory may soon arise again, making the maintenance of an active reproductive physiology for a few weeks a reasonable adaptive strategy. Correspondingly, a newly ascended T male should mature sexually as quickly as possible because he may lose his territory sooner rather than later. Social status clearly determines both soma size of GnRH neurons in the preoptic area and relative gonad size, and these effects are reversible. The relatively large testes and GnRH neurons characteristic of T males are a consequence of their social dominance, and when this dominance advantage is lost, both neurons and testes shrink. Exactly how social information is transformed into changes in the brain remains unknown. There is, however, some evidence that visual information may be used to signal the state of individual animals.

Animals that have lost a territory (T→NT) grow more slowly and even shrink (Hofmann et al. 1999). Behavioral stress may play a role. Fox et al. (1997) showed that in *H. burtoni*, status switches in both directions can be accompanied by elevated levels of the major stress hormone cortisol, with the T→NT change showing the most pronounced increase. NT→T fish with increased cortisol levels usually did not maintain territoriality. Descending fish consistently showed high levels of cortisol, which may be elevated by losing a territory, thereby causing the downregulation of somatic growth. Taken together, these data show that social status can directly regulate neuron size, changing reproductive status as well as regulating growth. The complexity of the social interactions suggests that subtle signals from social encounters cause changes in the social brain of these cichlids.

SOCIAL SYSTEMS IN THE HUMAN BRAIN

Is there a social brain? Social perception in primates is largely visual, although auditory, somatosensory, and olfactory cues contribute to identifying kin, gender, and familiar individuals. Face perception has been the primary focus for much of human social neuroscience during the past few years, growing out of earlier neurophysiologic and recent neuroimaging studies that demonstrated cells or fields in the monkey temporal cortex respond to faces (Tsao et al. 2003). As fMRI studies

in humans have revealed the categorical nature of cortical processing of a range of visual stimuli, perhaps it is not surprising that the same technique would identify regions activated by faces. The specificity of regional activation for face processing remains unclear. For instance, the fusiform area in the occipital-temporal junction has been variously described as critical for face recognition or for expertise in processing categories with multiple elements, including birds for ornithologists, houses for realtors, or faces for most of us (Gauthier et al. 2000, Kanwisher et al. 1997). Lesions in this region have been associated with deficits in face recognition (prosopagnosia), and more recently, significant reductions in gray matter volume in this region have been reported in patients with chronic schizophrenia who also have difficulty with face recognition (Onitsuka et al. 2003).

An interesting approach to identifying the circuitry for social information has used fMRI to investigate regional brain activation in subjects watching animated vignettes of simple geometric shapes interacting either in a “social,” “mechanical,” or “random” fashion (Castelli et al. 2002, Martin & Weisberg 2004). These studies focus not on social objects such as faces but on how the brain responds while attributing social interaction to abstract images. These studies have identified a “social” circuit comprising the lateral segment of the fusiform gyrus, the superior temporal sulcus, the amygdala, and the ventromedial prefrontal cortex. Much of this circuit was recognized for social perception from studies in nonhuman primates (Brothers 1990) as well as social cognition in humans (reviewed in Adolphs 2001). For instance, previous evidence from lesion studies as well as functional imaging implicates the amygdala in the recognition of social emotions (guilt, arrogance) as well as perception of fear (Adolphs et al. 2002, but see Amaral et al. 2003). The ventromedial prefrontal cortex is strongly connected to the amygdala (Steffanacci & Amaral 2002) and has been linked to subjective pleasantness (Kringelbach et al. 2003), social judgment (Bechara et al. 1997), and processing of social vocalizations in nonhuman primates (Romanski & Goldman-Rakic 2002). What about extending this analysis from social recognition to social motivation? The first fMRI studies of love and loss in humans implicate the striatum, the medial insula, and the anterior cingulate cortex in romantic attachment (Bartels & Zeki 2000), as well as the anterior cingulate and the right ventral prefrontal cortex in the response to social exclusion (Eisenberger et al. 2003). The activation of the ventral striatum with social motivation in humans is generally consistent with the results from rodent studies presented above.

The identification of a social circuit in the human brain may prove important for identifying the neuropathology of autism (Lord et al. 2000). This neurodevelopmental disorder is defined by deficits in reciprocal social behavior and language as well as the presence of stereotypic behaviors. Children with autism appear to lack social motivation, as measured by eye contact and interest in looking at faces (Klin et al. 2002). Although there are no gross pathognomonic abnormalities in the autistic brain, fMRI studies have shown that people with autism do not activate the fusiform gyrus when presented with faces (Schultz et al. 2000). This could indicate simply a lack of attending to, or expertise with, faces, or the absence of

activation in this region may indicate a critical breakdown in the ability to process faces. Some individuals exhibit remarkable expertise with nonsocial categories of information, often in the form of savant skills such as calendar counting and idiosyncratic recall. Thus these individuals are capable of expertise, but apparently not in the social domain.

Studies of social information processing in nonhuman animals will likely point to where to look and what to look for in the brains of children with neurodevelopmental disorders such as autism and schizophrenia. Clinical studies report that children growing up with social deprivation exhibit autistic-like behavior and enduring deficits in attachment (O'Connor et al. 2003). As we understand the principles by which social experience supports normal brain development in animal studies, we may glimpse the process that fails for children with neurodevelopmental disorders who are exposed to healthy social environments yet seem unable to process this information for normal brain development. Much of the past decade has been devoted to searching for the genes, cells, and systems important for normal social behavior in animals. Currently, there is a broad search using linkage and association studies for genes associated with autism and schizophrenia. In the next decade these two approaches may converge by linking the genes that contribute to these clinical syndromes to the pathways that mediate social information, as is already happening with Fragile X (Brown et al. 2001) and Rett Syndrome (Shahbazian & Zoghbi 2002). Thus, we will likely borrow from discoveries in humans to design experiments in mice, just as we have been trying to build a clinical neuroscience based on research in rodents and other animals during this past decade.

CONCLUSION

This review focuses on a few examples from the emerging field of social neuroscience to ask how the brain makes sense of the social world. At the molecular level vomeronasal signals appear critical for perceiving social signals, and the nonapeptides such as oxytocin and vasopressin appear to be important for linking social signals to cognition and behavior. A central assumption in this approach is that the mechanisms for social learning and social motivation are built on well-known, generic neural systems for learning and motivation. It seems likely, although still unproven, that social memory requires many of the molecular steps involved in other forms of learning. Similarly, social preference formation, whether for offspring or a sexual partner, relies heavily on mesolimbic dopamine systems that confer the hedonic value of a wide range of stimuli. Unique to social learning (such as imprinting) and social motivation is (a) the rapid, apparently hard-wired nature of acquisition; (b) the strength of the response; and (c) the ostensible reliance on selective neuropeptides for linking perception to learning and motivation. Less clear is the relevance of these observations to the primate brain, where visual processing trumps vomeronasal signals and cortical networks may override the neuropeptide signals from the hypothalamus. Nevertheless, the search for the

molecular and cellular markers of the social brain should provide important insights into the mechanisms for autism, schizophrenia, and other vexing human disorders.

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