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Genetic Influences on Social Cognition

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ABSTRACT: Human social behavior develops under the influence of genetic, environmental, and cultural factors. Social cognition comprises our ability to understand and respond appropriately to other people's social approaches or responses. The concept embraces self-knowledge and theory of mind, or the ability to think about emotions and behavior from the perspective of another person. The neuropeptides oxytocin (OT) and vasopressin (AVP) are now known to play an important role, affecting individual differences in parenting behavior, social recognition, and affiliative behaviors. The processes of social cognition are also supported by reward circuitry, underpinned by the dopaminergic neurotransmitter system. Reward processes build social relationships, in parenting and pair-bonding, and influence social interactions that require trust, or display altruism. The impact of emotional regulation upon social behavior, including mood and anxiety, is also mediated through the serotonergic system. Variation in activity of serotonergic networks in the brain influences emotional responsivity, including subjective feelings, physiological responses, emotional expressions, and the tendency to become engaged in action as a consequence of a feeling state. Genetic variation in the receptors associated with OT, AVP, dopamine, and serotonin has been intensively studied in humans and animal models. Recent findings are building an increasingly coherent picture of regulatory mechanisms. **(*Pediatr Res* 69: 85R–91R, 2011)**

We, as humans, usually possess the ability to rapidly process social information about the thoughts and actions of other people and to interact in complex ways with them. Social cognition comprises a set of skills that enable us to understand thoughts and intentions that may differ from our own experiences or predispositions. As we develop through early childhood, we are increasingly capable of taking another person's perspective, and we develop self-knowledge. We can accurately predict how another person might behave in the future, from our social perceptions and experiences. We become capable of learning what motivates other people in their social interactions, even if these do not directly involve us. All these skills map onto schemas that are encoded in an associative network in memory and is orchestrated to ensure normal, skilled social adaptation (1).

The process by which we acquire social cognitive competence evolves with development and is modified in response to the environment. To begin with, infants cannot easily differentiate between themselves and other people, but they rapidly become aware that their actions have an impact on the physical and social world around them. In due course, they develop social understanding, language, and imitation. Eventually, most of us acquire the ability to "read the mind" of others. By this, we mean that it becomes possible for us to understand why other people behave the way they do and to respond appropriately to them in social situations. If we have not acquired this ability by adolescence, we may find ourselves becoming increasingly socially isolated and avoided by others in other than the most superficial social encounters.

A fully functioning social brain entails the development of a coordinated network of human cortical brain regions. These include the dorsomedial and dorsolateral prefrontal cortices, the paracingulate cortex, and the right and left temporoparietal junctions (2). The amygdala is also central to the neural circuitry underlying social cognition. It plays a key role in systems that associate social stimuli (auditory, visual, and olfactory) with value, it directs our unconscious responses during social encounters, and it arouses us to stimuli of relevance in our environment. The amygdala's reciprocal connections with the primary visual processing area in the inferior occipital gyrus facilitate the rapid analysis of socially salient information (3). Neural circuits of the social brain are activated by facial emotions, tone of voice, or olfactory cues and include the hippocampus, thus are linked to recognition memory. This complex network allows us to contextualize our perceptions and hence find answers to questions such as Do I know this person? Do I like him? Do I trust him?

In a recent review on the challenge of translation in social neuroscience, Insel (4) outlined the considerable progress being made in our understanding of how social information is processed by the brain. He points out that, despite our knowledge of sensory processing at the level of auditory, visual, and other perceptual cues, and our discovery of social behaviors such as affiliation in ever more simple organisms [*e.g. Caenorhabditis elegans* (5)], we have learned relatively little about how quite simple molecular mechanisms are translated into human social behavior. One promising path of research concerns the role played by neuropeptides and their receptors, of which around 100 have been described in the human brain, most of which are released from the hypothalamus. Our focus here is on the nonapeptides, oxytocin (OT) and vasopressin (AVP), that have been the subject of fascinating and important investigations in relation to their role in modulating social behavior for two decades (6).

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Abbreviations: AVP, vasopressin; **Avpr1a,** Arginine V1aR gene; **OT (R),** oxytocin (receptor); **V1aR,** AVP 1a receptor; **V1bR,** AVP 1b receptor

The Molecular Basis of Social Cognition: Role of OT and AVP

OT and AVP have both central and peripheral actions that have been implicated in the molecular basis of social cognition in animal models. Increasingly, a role for these neuropeptides in regulating human social cognition has been suggested. The OT and AVP proteins differ in structure by just two amino acids. The genes encoding the two proteins both occur on chromosome 20 and are thought to have arisen from a gene duplication event; the ancestral gene is estimated to be about 500 million years old (7).

The presence of nonapeptides similar to OT and AVP has been described in diverse species, from birds to mammals. Their relative similarity suggests that they have been conserved during evolution. Both molecules have widespread receptor-mediated effects on behavior and physiology (4). In mammals, estrogens modulate both the synthesis of and receptors for oxytocin. Androgens act similarly on AVP (although some species-specific differences exist). Accordingly, to a degree, these neuropeptides influence sexually dimorphic social behaviors (8).

Oxytocin

OT has both peripheral and central actions. Peripherally, OT acts as a hormone that has a critical role in parturition and lactation, whereas centrally, it acts as a neuromodulator *via* a G-coupled protein receptor. It is produced from two sources. First, from the magnocellular neurosecretory cells located in the supraoptic and paraventricular nuclei of the hypothalamus. Magnocellular neurons project exclusively to the posterior pituitary. Recent evidence suggests that OT is released into the brain from its dendrites into extracellular space, and this more generalized release mechanism can be regulated independently of the pituitary system (9). Formerly, the paraventricular neurons were thought to play the major role in the behavioral functions of the neuropeptide; there are centrally acting projections to limbic-system (hippocampus, amygdala, striatum, hypothalamus, and nucleus accumbens) and mid- and hind-brain nuclei (10). Peripheral OT does not cross the blood-brain barrier easily, although it is observed in human cerebrospinal fluid (CSF) just minutes after intranasal administration (11).

OT has been given experimentally to humans both by i.v. injection and by nasal administration. It seems to influence a variety of social and behavioral responses, as witnessed by a variety of studies in recent years (12). These effects include a) anxiolysis by decreasing peripheral cortisol and altering corresponding behavior; b) alterations in parenting behavior (13); c) increases in prosocial behavior as measured by trust, generosity, altruism, and betrayal aversion, in behavioral and/or functional MRI (fMRI) studies (14–16); d) alterations in face perception, based on fMRI studies highlighting differential amygdala activity; e) changed eye-movement patterns with more fixation to the eyes; f) improved "mind reading" or mentalization (probably linked with more fixation to the eyes) (17), particularly in disorders like autism; and g) alterations in social memory.

OT, Social Recognition, and the Response to Threat

The action of OT in increasing trust and prosocial behavior is apparently mediated, at least in part, through influence on general social appraisal including perception of interpersonal threat. A key player in the detection of relevant stimuli in our environment, including our response to apparent threat, is the amygdala, which is activated by excitatory pathways that connect the central amygdala nucleus to the midbrain, and thence to the autonomic nervous system. Excessive amygdala activation during social encounters raises anxiety, leading to social withdrawal (18). In humans, such activation is potently increased by direct eye contact (19,20). There is evidence that exogenous OT acts to reduce activation of the amygdala, midbrain regions, and the dorsal striatum, postulated to be as a consequence of influence on reflexive visual attention mechanisms (12), reducing uncertainty regarding the predictive value of social stimuli (21) or increasing the perceived salience of social cues (22). This reduction in the physiological and psychological reaction to threat accounts, at least in part, for the increase in prosocial behavior.

OT and Autism

Autism is an early neurodevelopmental disorder presenting in childhood, with deficits in social cognition and communication and rigid and repetitive patterns of behavior central to the presentation. Genetic variations in genes related to OT and its receptor have been variably reported as being associated with autism susceptibility (see below). Plasma levels of OT are low in autistic individuals (23) and tend to normalize with the administration of exogenous OT (24). The use of exogenously administered OT to treat autistic behaviors is a subject of growing interest. A reduction in repetitive behaviors was reported by Hollander *et al.* (25) after OT infusion, and this pioneering study was followed by others, which claimed that it increased retention of social cognition (26) and empathy (27).

Autism affects four times as many males as females. Male vulnerability to this quintessential disorder of social cognition has been attributed to testosterone exposure, especially *in utero*, but this controversial theory has not been proven (28). Estrogen affects the synthesis of OT (29) and enhances activity of the OT receptor (OTR) (7). Thus, it is possible that higher levels of OT might be protective of females, whatever independent predisposing factors lead to autism risk. Accordingly, hypothetically, in females, neuropeptidergic regulation of neural circuitry influencing social cognition could prevent autistic behavior being fully expressed phenotypically.

OT and Genetic Influences on Regulation

Only a single type of OTR has been identified (30) and it is located at chromosome 3p26.2. It can be found in many different tissues in the body, but its distribution is highly variable, both within and between species. The potential for environmental influences on the functioning of OT and related proteins exists. Regions of high GC content (CpG islands) upstream of the transcription start site of the OTR gene suggest that it may be susceptible to regulation through dif-

ferential methylation, which could potentially influence the pattern of tissue expression. By this means, lifelong differences in the sensitivity of the receptor could be subject to epigenetic influences, consequent upon environmental circumstances of upbringing (31). By analogy, receptor expression in the hypothalamic-pituitary-adrenal (HPA) axis may be reduced by adversity, such as the quality of early maternal care (32).

Variations in a specific polymorphism of the OTR gene (rs53576) have been linked to variations in behavioral style among typical individuals, including empathy and stress reactivity (33), loneliness (34), prosocial temperament (35), and maternal sensitivity to their offspring (36). Not all studies have found this association (37). Conversely, Tost *et al.* (35) not only found an allelic association with temperament but also, in the course of a substantial neuroimaging study, discovered that activation and inter-regional coupling of the amgydala with the hypothalamus during facial emotion processing was affected too.

There may also be an association between the gene variant and susceptibility to develop an autistic disorder, although the finding has not been consistent across studies. Although the association that Wu *et al.* (38) reported was replicated (39), no such association with this allele has been found by others (40,41).

A potential role for the CD38 gene in the regulation of OT release has been suggested by recent investigations (42). CD38 is a multifunctional molecule that plays a key role in a wide variety of tissue-related activities including migration, adhesion, and secretion. It is highly expressed in the brain in both glial cells and neurons. If the gene is knocked out in mice, there is over-storage of OT and reduced release, resulting in low plasma OT levels and reduced social behavior (9). However, at this time, we do not know whether these findings in mice are replicable in primates, including humans, although the role of the CD38 system in regulating OT release is clearly of considerable interest to those seeking a pharmacological intervention that could ameliorate autistic behavior.

Could the response to OT by autistic subjects in treatment studies be modified by differential sensitivity of the OTR? As discussed, a genetic variant of the OTR gene has a sexually dimorphic impact upon social responsiveness in typical adults (35) and apparently influences nonautistic individuals in their theory of mind skills, empathic tendencies (33), and the ability to sustain eye gaze (43). We also know from the few studies that have administered OT to autistic subjects that there are substantial variations in response to exogenous OT, both within group and within individuals, according to the nature of the task (24).

Vasopressin

AVP synthesis occurs in the hypothalamus, but it is released into general circulation from the pituitary. AVP acts as a hormone regulating water balance in the periphery, and it also has neuropeptidergic actions in the CNS. Androgen-dependent synthesis occurs in parvocellular neurons within the paraventricular nuclei, the bed nucleus of the stria terminalis, the medial amygdala, and suprachiasmatic nucleus (44).

Three distinct AVP receptor subtypes have been described. The V1a receptor (V1aR) is expressed widely in the brain, as well as in the liver, kidney, and peripheral vasculature. The V1b receptor (V1bR) is expressed in the brain and also peripherally (kidney, thymus, heart, lung, spleen, uterus, and breast). The V2 receptor is expressed primarily in the kidneys. AVP has the capacity to bind not only to AVP receptors but also to the OTR, indicating that it has the potential to modulate the activity of various subtypes (4). Most research has focused on the V1bR, which has been subject to evolutionary selection pressure in humans (45).

Relatively little is known about the influences on AVP expression in the human brain. Evidence from animal studies indicates that expression may show sexual dimorphism and may be modulated by as yet unidentified genes on the X- or Y-chromosomes (46). Studies in mouse knockouts of the AVP receptor 1a have demonstrated that anxiety-like behavior reported in males, but assumed to be present in both males and females, is in fact sex-specific (47). Possible mechanisms underlying this sexual dimorphism have not been clarified and could relate to either genetic or sex-steroidal regulation. Unfortunately, we know relatively little about gender differences affecting individual variation in gene expression or neuropeptide regulation in the human brain. Inevitably much of what follows is taken from research with animal models, although some human evidence is emerging from postmortem studies (48).

Behavioral effects of AVP have been described mainly in males, in animal models. They include the promotion of both aggression and affiliation, in addition to other aspects of social interaction including parental care. AVP can act to enhance social recognition, nonspatial learning and memory, and the emotional response to stress (49). There have been attempts to demonstrate an impact of AVP on social behavior in humans, and these have taken the form of two main experimental techniques. One approach has been to administer AVP as a spray intranasally to normal males. This increases the subjective impression of threat to neutral social stimuli (50) and, by implication, the risk of an aggressive response.

A sparse literature concerning the influence of AVP on human behavior has indicated a correlation between CSF AVP levels and a lifetime history of aggression in individuals with personality disorder (51). Thompson *et al.* (50) suggested that AVP might influence aggression in human males by biasing responses to emotionally ambiguous stimuli as if they were threatening or aggressive. The same authors later demonstrated sexually dimorphic effects; males and females viewing unfamiliar faces after intranasal AVP attributed them as unfriendly and friendly, respectively (52).

Activation of the V1a receptor increases male anxiety and facilitates aggression in animal models (53). The degree of behavioral response depends upon early social experience. The V1bR also has a role to play in modulating aggression in males (54). Aggressive behavior in females is not normally observed in response to AVP (55). Gender differences in behavioral response, due to receptor sensitivity, could be the consequence of a neonatal surge in OT, which is found to have sexually dimorphic effects on the later expression of AVP receptors (56). Thus, some sexually dimorphic behavior in adult males could reflect a synergistic interaction between AVP receptor sensitivity to androgens and AVP, as a consequence of neonatal OT exposure.

There is cross-receptor reactivity between OT and AVP in early life. The OT surge leads to increased AVP receptor binding in the ventral pallidum, the lateral septum, and cingulate cortex in males. In contrast, in females, it leads to less AVP receptor binding in the equivalent sites. The impact of AVP on behavior is not merely to increase aggression, at least in some animal models. In rats, males with a higher density of V1aRs in the lateral septum are more likely to provide paternal behavior; AVP receptors in the medial preoptic area and bed nucleus of the stria terminalis also play a role in stimulating maternal care (55).

AVP-Related Genes

Animal knockouts of *Avpr1a* (Arginine V1aR gene) are associated with impairment of social memory, reduced anxiety-like behavior, and selective social amnesia in male knockouts, but these deficits can be corrected by re-expressing the gene (57). In contrast, over-expression of *Avpr1a* in the lateral septum of males facilitates social memory formation and hence social recognition. The effect of AVP on social memory seems to be specific to this brain region (58), where there is the highest density of V1aR binding in the human and animal brain (59).

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Variability in the genomic structure of the V1aR has been associated with differences in personality or behavior in normal males. The focus has been on two microsatellites, which are upstream of the gene, that are designated RS1 and RS3. The more interesting of the two is RS3, which has variable length within the promoter region. In a pioneering study, Knafo *et al.* (48) demonstrated that funds allocated in the Dictator Game (an economic game in which the first player is given a sum which they can choose to share with an anonymous partner or keep it without penalty) were correlated with the RS3 variant. The sample was mixed-sex, and participants with longer alleles shared a greater proportion of their money than those with shorter alleles. Somewhat surprisingly, there was no main effect of gender.

In a study based on the observation that variations in the microsatellite length in the promoter region of the V1aR influence pair-bonding formation in closely related vole species (60), Walum *et al.* (61) reported a unique finding in a sample of the North American population. There was a modest correlation between parental bonding and RS3 length in men only, not in women. Shorter alleles were associated with more marital crises; homozygosity for the 334 allele (affecting 5–15% of the male population) was associated with a doubling of risk. The mechanism by which this remarkable (and as yet unreplicated) finding has come about is unknown, but it is worth noting that the same short variant is associated with greater activation of the amygdala in response to a fearful face emotion-recognition task (62). Perhaps those males with longer alleles for RS3 are more socially sensitive to their spouse's emotional state and were therefore less likely to engage in behaviors that upset their marital partnership.

A recent study has also demonstrated lower levels of promoter activity associated with the shorter allele of RS1 in humans, this shorter allele being overtransmitted to probands in families with an autistic child (63). Shorter alleles of RS1 are therefore potentially associated with reduced transcription of *Avpr1a*.

Because AVP seems to have its major behavioral impact on males, AVP-related genes have been investigated in autism. Preliminary evidence from several studies suggests a role for polymorphisms in the *Avpr1a* in autism susceptibility (6,64,65). The Avpr1b receptor has also been implicated in the formation of social memories (66), but knowledge about this receptor is still relatively patchy. There is prominent Avpr1b expression in the hippocampal field CA2 pyramidal neurons, which facilitates the contexualization, *via* memory, of novel social encounters (67).

Neuropeptide-Dopaminergic Interactions

AVP facilitates affiliation and social attachment by modulating processes associated with reward and motivation, engaging dopamine-regulated circuits in the nucleus accumbens. The postulated interaction between the neural systems plays a major role in the regulation of pair-bond formation (68). OT and AVP also shape the neural representation of the partner by building a profile through olfactory cues, which remains stable (69). For rodents, at least, the odor of the partner comes to be associated with a pleasurable and rewarding encounter (70). Zeki (69) suggests that human adaptations of the same essential mechanisms underlie romantic and maternal love. Falling in love requires us not only to activate neural circuits that facilitate attachment but also to deactivate defensive circuits: physical proximity to strangers would normally trigger aversive reactions.

The relationship between OT modulated behaviors and the dopaminergic systems that regulate mood and behavior has not been very fully investigated (71). Evidence is nevertheless emerging that implicate dopamine-OT interactions in the modulation of neural circuits that influence affiliative behaviors. Skuse and Gallagher (8) showed that the receptor binding sites of the nonapeptide OT and of dopamine tend to coexist in several brain regions, including the dorsal striatum (caudate and putamen), the medial prefrontal cortex, the ventral tegmental area, and the substantia nigra (Fig. 1) (69). They are also in close apposition in the ventral tegmental area, the nucleus accumbens, and the ventral pallidum. In this way, it is at least feasible that they coregulate activity of reward related circuitry such as the corticostriatal pathway. The role played by this circuitry in humans is uncertain, but there is good evidence that in animal models, mating results in a release of OT that activates a mesolimbic circuit in the ventral tegmental area that is itself modulated by dopamine receptors, and that there is consequent dopamine surge in the nucleus accumbens, linking sexual activity with the formation of partner-bonds (4).

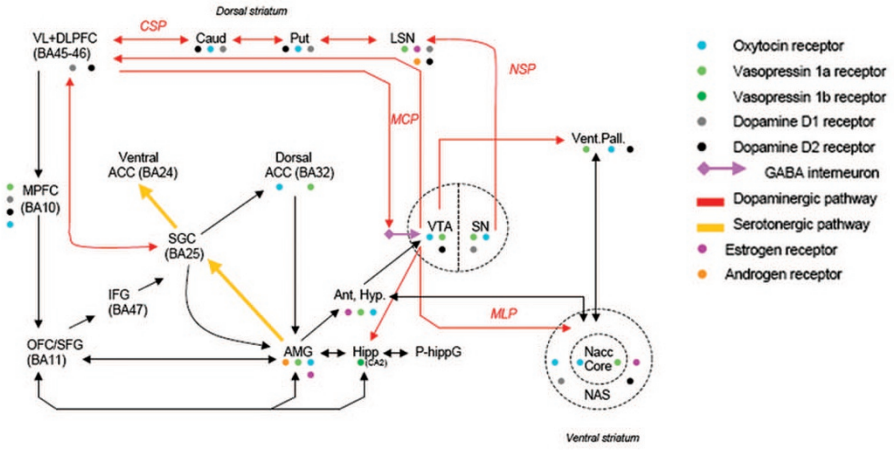

Figure 1. Neural circuits contributing to the social brain. A simplified account of neural circuits believed to contribute to the regulation of the "social brain," showing a subset of interconnections between brain regions involved in socioemotional processing and perceptions. The figure illustrates colocalization of oxytocin, vasopressin, dopaminergic, and serotonergic receptors. Sex hormone receptors are also indicated. "Reward" circuitry encompasses the corticostriatal pathway (CSP), the nigrostriatal pathway (NSP), the mesocortical pathway (MCP), and the mesolimbic pathway (MLP). These dopaminergic circuits link the dorsal and ventral striatum to the prefrontal cortex, and components of the striatum have somewhat different roles. Oxytocin and vasopressin can potentially enhance the hedonic value of social interactions, by activating areas that are rich in dopamine receptors, including the substantia nigra (SN), the globus pallidus, the nucleus of Meynert, the bed nucleus of the stria terminalis, and the ventral tegmental area (VTA).

There is also considerable evidence that these influences are important for the development of normal parent-infant relationships, although they have been suggested to be more relevant to the establishment of maternal than paternal care (72). Conversely, a recent longitudinal study of plasma OT levels among new parents with their first infant found there were increasing plasma OT levels over the first 6 months regardless of parental gender (13).

Serotonergic Influences on Social Cognition

Social cognition is not solely a function of stable personality traits. There are state-dependent influences too, including moods such as anxiety, which are susceptible to changes in serotonergic neurotransmission. The serotonergic system is the largest efferent system in the brain. It has wide-ranging functions, including behavioral inhibition, appetite, aggression, mood, social affiliation, and sleep, in addition to social decision-making (73). In primate studies, experimentally elevated serotonin decreases aggression and increases cooperativeness and social potency. Contrastingly, reduced serotonin activity leads to increased aggression and deterioration of cooperativeness (74). Studies in both animals and humans have found that greater serotonin activity positively influences social interaction and cooperation, while low serotonin activity has the opposite effect (75).

Serotonergic Interaction With AVP and OT

An association exists between OT and AVP and the serotonergic system, through the HPA axis. Functions of the paraventricular nucleus of the hypothalamus are regulated by serotonin, and serotonin receptor subtypes influence release of OT and AVP (76). During development, excess serotonin may be as detrimental as too little. Excess serotonin (in thrombocytes) has been reported in a substantial minority (up to 30%) of individuals with autism (77). Animals exposed to elevated serotonin during early development have reduced OT expression and loss of OT-containing cells in the paraventricular nucleus in adulthood. This reduction is associated with reduced maternal bonding and socially explorative behaviors (78).

Serotonin also desensitizes the AVP receptor, which could reduce affiliative behavior in adult males (79). The V1aR and a subtype of serotonin receptor colocalize in the anterior hypothalamus; therefore, it is possible that serotonergic synapses on AVP neurons carry the potential for serotonin to influence behavioral aggression, which is mediated by the AVP receptor (80). In general, interactions between the serotonergic and AVP systems are not well understood, and more research is needed.

Conclusions

A reductionist view of genetic influences suggests that variation within genes influencing activity in the social brain could account for individual differences in human social cognition. We are increasingly aware of the evidence that complex behaviors are rarely influenced by a single locus of main effect (81) and are subject to the influence of environment (82). Nevertheless, increasing evidence suggests the systems outlined in this review are potentially major players in human and animal models of social behavior.

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