Published in final edited form as:
Horm Behav. 2012 March ; 61(3): 400–409. doi:10.1016/j.yhbeh.2012.01.016.

Human Neuroimaging of Oxytocin and Vasopressin in Social Cognition

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Abstract

The neuropeptides oxytocin and vasopressin have increasingly been identified as modulators of human social behaviors and associated with neuropsychiatric disorders characterized by social dysfunction, such as autism. Identifying the human brain regions that are impacted by oxytocin and vasopressin in a social context is essential to fully characterize the role of oxytocin and vasopressin in complex human social cognition. Advances in human non-invasive neuroimaging techniques and genetics have enabled scientists to begin to elucidate the neurobiological basis of the influence of oxytocin and vasopressin on human social behaviors. Here we review the findings to-date from investigations of the acute and chronic effects of oxytocin and vasopressin on neural activity underlying social cognitive processes using “pharmacological fMRI” and “imaging genetics”, respectively.

Introduction

Oxytocin and arginine-vasopressin are highly evolutionarily conserved, molecularly similar neuropeptides known, in part, for their prominent role in mammalian social behavior and social cognition (Donaldson and Young, 2008). Historically, the social functions of oxytocin and vasopressin have primarily been elucidated in animal studies; receptor knockout, antagonism, and agonism have determined a role for oxytocin (Neumann, 2008) and vasopressin (Caldwell et al., 2008) in social affiliative and aggressive behavior (Insel, 2010), social memory and recognition (Bielsky and Young, 2004), and social stress and anxiety (Carter et al., 2008), as well as provided insight into the involvement of particular neural systems and brain regions underlying the social effects of oxytocin and vasopressin such as the amygdala, lateral septum, and nucleus accumbens (Raggenbass, 2008; Ross et al., 2009; Veenema and Neumann, 2008).

Parallel studies in humans are challenged by ethical constraints and the complexity of human sociality; however, both the discovery that the intranasal administration of neuropeptides is successful in getting them into the brain (Born et al., 2002) and advances in the mapping of human genetic variation have allowed researchers to investigate how increasing brain oxytocin and vasopressin concentrations and how genetic variation in oxytocin and vasopressin receptor genes modulate human social behavior. These

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investigations have revealed a role for oxytocin and/or vasopressin in a variety of human social cognitive processes, including social memory and recognition, emotion perception, empathy, trust, cooperation, fear and aggression, and social stress (for reviews see (Bartz et al., 2011; Bos et al., 2011; Ebstein et al., 2010)). While providing valuable information regarding the role of these prosocial neuropeptides in human social behavior, the aforementioned behavioral human studies do not reveal the neural systems underlying the effects of oxytocin and vasopressin on human social behavior. Given evidence that the distribution of oxytocin and vasopressin receptors in the human brain differs from that in rodents (Loup et al., 1991), as well as the species-specific differences in sensory systems critically involved in social perception/interactions (i.e., rodents rely mostly on olfactory cues, while humans rely primarily on auditory and visual cues), neural mechanisms of the influence of oxytocin and vasopressin on human sociality are likely to be, at least in part, different than in animals. As such, identifying the human brain regions that are impacted by oxytocin and vasopressin in a social context is essential to fully characterize the role of oxytocin and vasopressin in complex human social cognition.

The advent of non-invasive neuroimaging, and its increasing presence in mainstream human research, has enabled scientists to begin to elucidate the neurobiological basis of the influence of oxytocin and vasopressin on human social behaviors. While several neuroimaging techniques exist, virtually all investigations pertinent to the current review (i.e., specific to understanding the impact of oxytocin and vasopressin on neural activity and morphology related to social processes in particular) have made use of structural and functional magnetic resonance imaging (MRI and fMRI, respectively). Whereas structural MRI conveys morphological information (e.g., local gray matter volume), fMRI provides regional signals representing an indirect measure of synaptic activity by virtue of activity-dependent changes in local hemodynamics (Logothetis and Wandell, 2004). Specifically, the research highlighted in the current review utilizes “pharmacological fMRI” and “imaging genetics” to assess acute or chronic influences, respectively, of oxytocin and vasopressin on neural circuitry underlying social behaviors. Pharmacological fMRI entails the combination of drug administration with fMRI to assess the influence of a drug on task-related brain activity (Honey and Bullmore, 2004). To that end, here we present pharmacological fMRI investigations of the acute effect that intranasal oxytocin and vasopressin administration has on neural activity during engagement in particular social cognitive processes. Imaging genetics is the investigation of how a particular genetic variant chronically impacts neural activity or morphology (Hariri and Weinberger, 2003). Here, we present imaging genetic studies on the consequences of human genetic variants related to oxytocin and vasopressin receptor genes on brain activity and gray matter volume in socially-relevant brain regions.

In the following sections, we review relevant pharmacological fMRI and imaging genetics studies for oxytocin and vasopressin separately, limiting our discussion to studies specifically directed at determining the influence of oxytocin/vasopressin on neural circuitry underlying some aspect of social cognition (Table 1). The studies are performed on healthy men and women, however, in a subsequent section we discuss the implications for mental disorders characterized by social dysfunction, including a review of relevant research in particular psychiatric populations. Finally, we will end with concluding remarks and a discussion of future research directions and remaining questions.

Oxytocin

Pharmacological fMRI Studies: Effects of Intranasal Oxytocin Administration

To identify neural correlates underlying the influence of oxytocin on human social cognitive processes, the pharmacological fMRI studies highlighted in this section implemented double-blinded, placebo-controlled (either within and between subjects) procedures

involving intranasal administration of OT at a dose of 24–32 IU, which has become the norm in human studies of OT administration (Bos et al., 2011). Despite the potential for fMRI to provide researchers with a snapshot of neural activity in the entire brain at a given moment, pharmacological fMRI studies using oxytocin administration have overwhelmingly focused in on the amygdala. The reason for this amygdala region of interest (ROI) approach is three fold; first, the amygdala has been shown to play a pivotal role in human social cognition (Adolphs, 2010), particularly in extracting information from faces (Adolphs and Spezio, 2006), second, there is evidence to support oxytocin release and binding in the amygdala (Huber et al., 2005; Landgraf and Neumann, 2004), and third, in animals, activation of oxytocin receptors in the amygdala appears to underlie oxytocin's role in certain elements of social cognition, particularly conspecific recognition (Ferguson et al., 2001). Usually, whole-brain results, when reported in the literature, have been subjected to more lenient statistical thresholds for exploratory purposes; when available, we will include such findings in our discussion.

Human social cognition is an undisputedly complex construct, both behaviorally and neurally, made up of multiple distinct elements and principles. One of the most basic cornerstones of human sociality is the ability to process and extract information (e.g., emotions and intent) from facial expressions. Oxytocin pharmacological fMRI studies have begun to elucidate the neural circuitry modulated by oxytocin during the implicit and explicit processing of emotional faces. These studies were initiated with an investigation conducted by Kirsch et al. (2005) in which, under oxytocin and placebo, men were subjected to a well-validated matching task during fMRI that involved matching faces with fear or anger expressions, negative non-social scenes, or geometric shapes (Hariri et al., 2002). As previously demonstrated (Hariri et al., 2002), under placebo, the amygdala was engaged during both face and scene matching compared to shape matching. Oxytocin significantly attenuated left amygdala activity during exposure to both social negative emotion on faces and negative non-social scenes. While no oxytocin effect on behavior (perhaps due to ceiling effect) during this implicit processing of negative social affect were reported, the findings shed light on the neural basis for oxytocin's capability to increase trust (Kosfeld et al., 2005; Mikolajczak et al., 2010) and decrease aversion (Evans et al., 2010) and arousal (Norman et al., 2010) towards threatening social stimuli, as amygdala reactivity has been associated with perceived untrustworthiness (Winston et al., 2002) and social threat arousal of faces (Williams et al., 2001). Additionally, as further support for this interpretation, Kirsch et al. (Kirsch et al., 2005) assessed the impact of oxytocin on amygdala-brainstem functional connectivity (i.e., covariation or correlation of activity between regions) and found that oxytocin reduced coupling between amygdala and brainstem, a connection critical for fear reactions (LeDoux, 2000). Similar effects of oxytocin on amygdala efferents to brainstem have been found in rodent studies (Huber et al., 2005).

Kirsch et al. (Kirsch et al., 2005) established a role of the amygdala underlying the influence of oxytocin on social behavior; however, the use of solely negative valence stimuli in their study begged the question whether or not the findings extend to positive valence (i.e., happy) facial stimuli. A subsequent oxytocin pharmacological fMRI investigation answered this question using a different, but also implicit (i.e. gender identification task), facial emotion processing task which included happy facial expressions, in addition to fearful and angry (Domes et al., 2007a). As expected, oxytocin diminished amygdala reactivity to fear and anger faces in men, but, and perhaps somewhat surprisingly given the known pro-social effects of oxytocin, oxytocin also dampened right amygdala activity associated with processing happy faces compared to neutral, suggesting oxytocin may reduce arousal to affective social stimuli in general via modulation of amygdala activity. Of note, an exploratory whole-brain analysis also revealed that during emotional face processing (particularly happy and fearful faces) oxytocin, relative to placebo, decreased activity in the

temporal lobes, including the temporoparietal junction (TPJ) and temporal poles, areas known for their integral role in social cognition, particularly related to the tracking of emotions and intentions of others (Frith, 2007). These decreases in both amygdala and TPJ activity may provide a neural basis for oxytocin's capability to decrease arousal toward social stimuli and increase trust (Kosfeld et al., 2005; Mikolajczak et al., 2010; Norman et al., 2010). While the aforementioned studies provide strong evidence that oxytocin attenuates amygdala reactivity during the relatively simple social cognitive process of emotion perception, subsequent studies suggest the impact of oxytocin on amygdala activity may be more complicated, perhaps depending on laterality and subregions of the amygdala, explicity of emotion processing, and gender, as outlined below.

An oxytocin pharmacological fMRI investigation of explicit emotion classification replicated an oxytocin-driven decrease in amygdala reactivity to fearful face stimuli, but found that oxytocin increased left anterior amygdala activity when processing happy faces (Gamer et al., 2010), a finding seemingly at odds with that of previous report with regards to positively valenced social stimuli (Domes et al., 2007a). These inconsistencies may illuminate a laterality-specific effect, as the oxytocin-driven *decrease* in amygdala reactivity to happy faces was restricted to the *right* hemisphere (Domes et al., 2007a), whereas the oxytocin-driven *increase* in amygdala activity only reached significance in the *left* hemisphere (Gamer et al., 2010). Alternatively, the differential findings regarding directionality of oxytocin's influence on amygdala activity during positive valence social emotion processing may be due to the implementation of an explicit emotion identification task, rather than implicit emotion processing; however, the likelihood that task explicitness is solely responsible is lessened by the fact that both explicit and implicit emotion processing engage the amygdala, and while evidence suggests such engagement is greater with explicit emotion processing (Habel et al., 2007), other evidence points to greater amygdala involvement in implicit emotion processing (Critchley et al., 2000). While it is clear that oxytocin modulates amygdala reactivity to all emotional faces, future studies will be necessary to conclusively determine the potential context- and valence-dependent directionality of this oxytocin neural effect in humans.

We have described the encoding of emotional facial stimuli as a relatively simple social cognitive process; however, proper extraction of emotion information from faces relies on proper direction of attention to relevant facial features. Accurate identification of fearful facial expressions is contingent on preferential attention to the eyes region and is mediated by the amygdala (Adolphs et al., 2005). Interestingly, making use of higher-resolution fMRI to better image the amygdala, research suggests that oxytocin modulation of amygdala activity related to social emotion valence (as described above) and the directing of social attention during face processing occurs in distinct amygdala subregions. Specifically, oxytocin effects on the amygdala's response to social valence (i.e., positive and negative emotions compared to neutral) were localized in the dorsal and lateral anterior amygdala (possibly corresponding to the corticomedial nuclear group and lateral amygdaloid nucleus). On the other hand, oxytocin enhanced activity in a posterior amygdala subregion (likely corresponding to the basal nucleus) when face stimuli triggered a redirection of social attention to the eyes, irrespective of the emotional valence (Gamer et al., 2010). Moreover, when subjects' initial fixation was directed at the mouth region of a face, thereby requiring a redirection of social attention to view the eye region, the superior colliculus, a brainstem structure strongly associated with initiating saccades (Ignashchenkova et al., 2004), was more engaged under oxytocin than placebo. Furthermore, oxytocin enhanced functional coupling between the superior colliculi and the posterior, rather than anterior, amygdala subregion (Gamer et al., 2010). Together these findings may providing a neural mechanism by which oxytocin increases gaze to the eye region of faces (Guastella et al., 2008),

increases facial fear recognition (Fischer-Shofty et al., 2010), and increases the ability to infer affective mental states of others from the eyes (Domes et al., 2007b).

Up to this point, the oxytocin pharmacological fMRI investigations reviewed in this section have all been performed using male subjects, but do the findings extend to females? In congruence with the sex-dimorphic influence of oxytocin on social behavior in animals (Carter, 2007; de Vries, 2008), the influence of oxytocin on social emotion processing in amygdala – as well as certain cortical regions – appears to depend, at least in part or in certain circumstances, on gender. In the first study of oxytocin effects on neural circuitry underlying social emotion perception in women, while undergoing fMRI, female subjects rated the emotional arousal of fearful, angry and happy facial expressions presented in blocks. Unlike what was previously found in male subjects (Domes et al., 2007a; Gamer et al., 2010; Kirsch et al., 2005), relative to placebo, oxytocin significantly increased left amygdala and brainstem responses to fearful faces and did not affect amygdala or brainstem activity to angry or happy faces, irrespective of where social attention was directed (Domes et al., 2010). In females, activity was also increased by oxytocin in several other regions, as demonstrated in an exploratory whole-brain analysis; while in men activity in the temporal poles was dampened by oxytocin when processing happy and fearful faces (Domes et al., 2007a), in females, oxytocin enhanced activity in the temporal poles, as well as superior temporal gyrus, fusiform gyrus, and insula (Domes et al., 2010), brain areas highly involved with face perception and emotion encoding (Haxby et al., 2000) and empathy (Decety, 2010). The effect of oxytocin on neural activity evoked by angry faces was mostly localized to the prefrontal cortex. These findings highlight a strikingly different profile in women compared to men, characterized by oxytocin-induced increases in brain activation where a decrease was evoked in men (e.g., amygdala, brainstem, temporal poles) during emotional face processing. While Domes at al. (2010) provide evidence that estradiol and progesterone levels are not responsible for the findings in females, the underlying factor(s) driving this gender difference remain unknown. Despite being unable to pinpoint the exact cause, the revealed gender differences underscore the importance of investigating oxytocin effects on social cognition-related neural activity both in females and males, preferably within the same paradigm, which as of yet has not been done and is necessary to confirm the preliminary sexually dimorphic nature of oxytocin modulation of neural social emotion perception. In fact, the aforementioned oxytocin-driven enhancement of amygdala activity in females during exposure to fearful faces, even if replicated, may be specific to facial emotion processing; another oxytocin pharmacological fMRI study demonstrated a decrease of right amygdala activity during exposure to the sounds of babies crying in women who had received oxytocin compared to those who received placebo (Riem et al., 2011), stressing that, at least in females, the impact of oxytocin on amygdala reactivity is strongly contingent on the specific social cognitive process being employed. Interestingly, while the influence of oxytocin on amygdala activity in females appear to be task-dependent, oxytocin generated an augmented insula/inferior frontal gyrus responses to both emotional face processing (Domes et al., 2010) and exposure to infant crying (Riem et al., 2011). This oxytocin-induced heightened insula reactivity in women may underlie an affective empathic reaction (Fan et al., 2011) during these social situations and may be a female- or paradigm-specific neural finding; oxytocin administration in men did not affect empathy-related insula activity while subjects observed their romantic partners receiving physical pain (Singer et al., 2008), despite a behavioral finding that, in men, oxytocin can increase emotional empathy (i.e., arousal associated with emotional faces) to levels observed in untreated women (Hurlemann et al., 2010).

While the information one gets from initial contact with someone is highly influential for one’s social behavior and is influenced by oxytocin, our perception of others and underlying neural activity are greatly impacted by our previous affective experience of others. Using a

fear conditioning paradigm in men, Petrovic et al. (2008) investigated the influence of oxytocin on the affective ratings, and the underlying neural activity, associated with faces of direct and averted gaze (as a manipulation of social relevance) that were previously paired with a negative experience, i.e., neutral faces paired with shock, compared to faces not aversely conditioned. In agreement with the behavioral prosocial effects of oxytocin in humans, oxytocin reduced negative evaluations of faces associated with shock, a behavior accompanied by an oxytocin-induced attenuation of activity in the right amygdala, anterior cingulate and medial prefrontal cortex. When considering the eye gaze of the face stimuli, the activity in the right amygdala was found to be diminished by oxytocin only to aversely conditioned faces of high social relevance (direct gaze), which strongly activated amygdala under placebo (Petrovic et al., 2008). This suggests the effect of oxytocin on amygdala reactivity depends heavily on the social situation for which the amygdala is maximally engaged. Under oxytocin, a social fear-related activation of the right fusiform face area was also dampened for faces with direct gaze only, perhaps occurring as a consequence of attenuated amygdala activity (Vuilleumier et al., 2004).

Each of the aforementioned studies in this section has touched on the effects of oxytocin on neural activity related to some aspect of social emotion processing via observation, however, a great deal of human sociality relies heavily on information we obtain during interpersonal interactions. Using cleverly constructed paradigms that simulate real-life social exchanges, two recent studies have elucidated the influence of oxytocin on neural activity elicited by particular actions of others during social interactions. In the first of these studies, male subjects received either oxytocin or placebo prior to performing a trust game during fMRI to expose oxytocin influences on trust behavior and underlying neural activity (Baumgartner et al., 2008). Each round of the trust game entailed the subject (“investor”) choosing to transfer none, some, or all of his endowment of money to an anonymous partner (“trustee”). Any money transferred was tripled in value by the experimenter at which point the trustee could either choose to honor the trust of the investor by sending back a payoff equalizing the amount of money between the two partners, or he could violate the trust of the investor by keeping all the money. Under placebo, the realization of breached trust (via feedback received only after multiple rounds has been played) decreased trust behavior (i.e., decreased amount of money transferred to the trustee), whereas, in congruence with previous behavioral findings in men (Kosfeld et al., 2005), under oxytocin knowledge of trust violation did not lessen future trust behavior. This oxytocin-driven lack of trust behavior adaptation was accompanied by reduced activation in the bilateral amygdala and brainstem, in good agreement with the studies reviewed above and suggestive of decreased fear (LeDoux, 2000) and perception of untrustworthiness (Winston et al., 2002) when making a decision to trust someone, as well as a dampening of dorsal striatal activity, which may contribute to the diminished behavioral adaptation to relevant feedback (O'Doherty et al., 2004). In addition to shedding light on the neural circuitry modulated by oxytocin during trust interactions, this study serves as yet another example of the social-specificity of the influence of oxytocin on neural activity, as oxytocin had no impact on investing behavior or underlying neural activity when rounds were played with a computer, rather than human partner.

The second investigation of the effects on oxytocin on neural activity evoked during social interaction (Rilling et al., 2011) made use of the iterated Prisoner’s Dilemma game, which models reciprocal altruism by requiring both of two players to independently decide to cooperate or defect with monetary payment for both players being determined by the interaction of their respective choices. After intranasal administration of oxytocin or placebo, during fMRI, male subjects played multiple successive rounds of the game with putative human partners or a computer serving as a non-social control. While no significant behavioral effects of oxytocin compared to placebo were reported (a suspected statistical

power issue), activity in the left caudate nucleus and left amygdala was augmented by oxytocin compared to placebo in response to reciprocated cooperation, specifically when interacting with putative human partners. In response to unreciprocated cooperation (i.e., subject cooperates, partner defects), oxytocin enhanced activity in the ventral prefrontal cortex. Furthermore, in concordance with a previous oxytocin pharmacological fMRI study (Kirsch et al., 2005), oxytocin decreased amygdala connectivity with brainstem, as well as increased amygdala functional connectivity with inferior temporal cortex and anterior insula. While the lack of an effect of oxytocin on social interactive behavior renders the oxytocin-induced neural modulations difficult to interpret, the findings are nonetheless important in that they implicate activity in particular neural structures and circuits as susceptible to modification by oxytocin during specific social exchanges.

Overall, in recent years, oxytocin pharmacological studies have greatly advanced our knowledge of the brain regions in which social cognition-related activity is perturbed by oxytocin. Despite the relative surge in such investigations, however, inconsistent findings exist, and a plethora of human social cognitive processes remain uninvestigated. We look to future studies to build on those currently published and hopefully be successful in determining the specificity of results related to particular paradigms or gender, as well as continue to expand beyond social emotion perception (where to-date the majority of studies have focused) to more complex or subtle aspects of human social behavior.

Imaging Genetics Studies: Effects of Oxytocin Receptor Genetic Variations

To assess chronic effects of variation in the oxytocin system on neural circuitry related to human social cognition, research has just begun to investigate the influence of genetic variations in the oxytocin receptor gene on brain structure and function using imaging genetics techniques. Imaging genetics first requires selection of genetic variations of interest, usually based on known functional consequences at a cellular level or clinical/behavioral associations. In the case of the oxytocin receptor gene imaging genetics studies, single nucleotide polymorphisms (SNPs) of interest were determined primarily by their associations with autism, a disorder plagued by social dysfunction, yet importantly investigated in healthy subjects. Two oxytocin receptor gene SNPs have been highlighted in these studies – rs2254298 and rs53576 – both associated, somewhat inconsistently, with autism in Caucasian and/or Asian samples (Jacob et al., 2007; Lerer et al., 2008; Liu et al., 2010; Wu et al., 2005), but of unknown functionality. For rs2254298, directionality of association appears to strongly depend on ethnicity with the A allele associated with autism in the Asian population (Liu et al., 2010; Wu et al., 2005) and the G allele in Caucasians (Jacob et al., 2007; Lerer et al., 2008).

The majority of oxytocin imaging genetics studies to date have focused on neural structural consequences of the oxytocin receptor gene SNP, rs2254298. Using manual tracing techniques on high-resolution MRIs, bilateral amygdala volume has been linked with rs2254298 genotype in healthy individuals, irrespective of ethnicity. Specifically, A allele load predicted larger amygdala volume (AA > AG > GG) in Japanese (Inoue et al., 2010), as well as in Caucasians where G/G homozygotes had smaller bilateral amygdala volumes than carriers of the A allele (Furman et al., 2011). Furthermore, an investigation of three SNP haplotypes revealed that two haplotypes, both containing the G allele of rs2254298, were associated with diminished amygdala volume (Inoue et al., 2010). Interestingly, these associations between amygdala volume and rs2254298 genotype could not be replicated when using voxel based morphology (VBM) techniques, rather than manual tracing, in either Caucasians (Furman et al., 2011; Tost et al., 2011) or Japanese (Yamasue et al., 2011). Rather, using VBM, it was revealed that rs2254298 G/G Caucasians possessed smaller posterior brainstem gray matter volume and greater gray matter volume in a region of the dorsomedial anterior cingulate cortex than A/G participants (Furman et al., 2011). An

effect in the same direction was found in a Japanese sample, where A allele load was associated with less gray matter volume in dorsomedial anterior cingulate cortex (Yamasue et al., 2011). The aforementioned associations between rs2254298 genotype and brain structure do not, as of yet, appear to be sexually-dimorphic in nature; however, correlations between rs2254298 genotype and hypothalamus gray matter volume have been shown to be influenced by gender, in a way perhaps dependent on ethnicity. In male Caucasian subjects, G/G homozygotes had greater hypothalamus gray matter volume compared to A allele carriers, whereas rs2254298 genotype did not significantly impact hypothalamus volume in females (Tost et al., 2011). Alternatively, in a Japanese sample, an rs2254298 A allele effect on hypothalamus gray matter volume was only significant in female subjects (Yamasue et al., 2011).

In addition to rs2254298, the oxytocin receptor gene SNP rs53576 has been subjected to structural imaging genetics investigations. While rs53576 genotype has not been associated with autism in a Caucasian sample (Jacob et al., 2007), the A allele of rs53576 has been associated with decreased prosocial behavior and temperament (Rodrigues et al., 2009; Tost et al., 2010) as well as associated with autism in a Chinese sample (Wu et al., 2005). Although rs53576 genotype did not correlate with amygdala volume (as assessed with manual tracking) in Japanese subjects (Inoue et al., 2010), Tost et al. (2010) demonstrated an A allele load increase in right amygdala gray matter volume, as well as decrease in hypothalamus gray matter volume in Caucasian men measured with VBM. It remains unclear at this time if the differential findings between these structural imaging genetics studies involving rs53576 genotype are driven by subject ethnicity/gender or methodology differences, stressing how imperative it is for future studies to carefully consider methodology and subject demographics.

While the neural functional consequences, if any, of regional brain volume are currently unknown, Tost and colleagues have demonstrated neural functional effects of both rs2554298 and rs53576 genotype during an implicit social emotion processing task (Hariri et al., 2002) – of note, the same task used by Kirsch et al (2005) to investigate the acute effects of oxytocin administration, reviewed in the previous section – in two investigations on healthy Caucasian subjects (Tost et al., 2010; Tost et al., 2011). The rs2254298 A carriers showed a significant decrease in medial anterior cingulate cortex deactivation elicited when processing negative social emotional face stimuli (Tost et al., 2011), in the same area other studies revealed an rs2254298 A allele decrease in gray matter volume (Furman et al., 2011; Yamasue et al., 2011). While rs2254298 genotype was not associated with amygdala reactivity, this anterior cingulate cortical region has been associated with amygdala mediated fear regulation (Hariri et al., 2003) and has been established as part of a regulatory negative feedback loop with the amygdala (Stein et al., 2007). On the other hand, rs53576 genotype was shown to impact amygdala reactivity directly; A allele load predicted a significant decrease in amygdala reactivity to negative facial emotion processing (Tost et al., 2010), perhaps underlying the A allele-mediated decrease in empathic temperament (Rodrigues et al., 2009; Tost et al., 2010).

The interpretation of the aforementioned oxytocin receptor gene imaging genetics studies are limited by the lack of known functional consequences of the SNPs at a cellular level. As genetics advances shed light on the functionality of these SNPs, and the link between regional brain volume and neuronal activity is clarified, the implications of these imaging genetics studies will be realized more fully. Furthermore, to date relatively few oxytocin imaging genetics investigations exist. We have much to learn as these research endeavors continue, while making use of other genetic variations in oxytocin system genes and using paradigms that assess other social cognitive processes in functional imaging genetics.

Vasopressin

Pharmacological fMRI Studies: Effects of Intranasal Vasopressin Administration

To date, pharmacological fMRI studies investigating the effects of vasopressin on neural activity related to social cognition are far outnumbered by those of oxytocin; yet a few studies, using double-blind, placebo-controlled procedures, have demonstrated distinct neural activation patterns related to intranasal administration of vasopressin in men (Rilling et al., 2011; Zink et al., 2011; Zink et al., 2010). Despite the marked structural similarity between vasopressin and oxytocin – differing in only two amino acids – administration of vasopressin modulates activity in discrete brain regions, and perhaps particularly striking is a lack of direct vasopressin influence on amygdala reactivity, at least at this time. The first of these vasopressin pharmacological fMRI investigations made use of a face matching task (Hariri et al., 2002) well-validated to probe the basic social cognitive process of social emotion encoding by requiring subjects to match faces of negative affect or geometric shapes as a control condition. Intranasal administration of 40 IU of vasopressin abolished the decrease of medial prefrontal cortex activity, particularly in the subgenual cingulate, elicited during exposure to fearful and angry facial expression under placebo (Zink et al., 2010), as opposed to modulating amygdala reactivity as had been the case following oxytocin administration using a version of the same experimental paradigm (Kirsch et al., 2005). Furthermore, vasopressin altered the connectivity between subgenual and supragenual cingulate in that the positive influence of subgenual cingulate on supragenual cingulate under placebo was negative under vasopressin. While no neural influence of vasopressin was found directly in amygdala, a validated model of medial prefrontal cortex–amygdala connectivity, i.e., amygdala to subgenual cingulate to supragenual cingulate to amygdala, previously established as a regulatory negative feedback loop (Pezawas et al., 2005; Stein et al., 2007) was shown to be altered by vasopressin, particularly at the level of subgenual cingulate activity and effective connectivity, perhaps shedding light on the neural mechanism by which vasopressin increases social stress responses (Ebstein et al., 2009) and promotes aggressive behavioral responses to social stimuli (Thompson et al., 2004).

Vasopressin has also been shown to promote social recognition in both animals (Caldwell et al., 2008) and men (Guastella et al., 2010), begging the question as to how vasopressin modulates social familiarity-related neural activity in humans. In rodents, the lateral septum, a brain region connected to the olfactory system, has been critically implicated in the actions of vasopressin to influence social recognition (Bielsky et al., 2005), but given that humans rely primarily on auditory and visual information for social recognition, cortical areas with access to multimodal auditory/visual information are perhaps more likely to underlie the influence of vasopressin on social familiarity in humans. In a vasopressin pharmacological fMRI study designed to investigate precisely that, Zink et al. (2011) employed a matching paradigm that again, similar to the previous study (Zink et al., 2010), entailed implicit processing of emotional stimuli, but now with an added component related to stimuli familiarity. Male participants matched familiar (previous exposure) and unfamiliar (first exposure) faces expressing negative affect or negative scene orientations as a non-social control condition. A 40 IU administration of vasopressin modulated social recognition-related left TPJ activity – a brain region highly implicated in social cognitive processes (Van Overwalle, 2009), including the processing of social background context and familiarity (Gobbini and Haxby, 2007; Saxe and Wexler, 2005) – as assessed with the interaction of sociality and familiarity of presented stimuli. Specifically, during exposure to socially unfamiliar stimuli, vasopressin abolished the left TPJ activation evoked by social unfamiliarity under placebo to a level comparable to that elicited by social familiar stimuli under placebo (Zink et al., 2011). These findings suggest that under vasopressin, stimuli are more readily transferred to a familiar categorization, as represented in TPJ reactivity.

In addition to social emotion perception and social recognition, social interindividual interaction constitutes a prominent component of human sociality, and therefore, elucidating the impact of vasopressin administration on neural activity elicited by particular social exchanges is a valuable research endeavor. As was done with oxytocin pharmacological fMRI, Rilling et al. (2011) assessed the impact of vasopressin on reciprocated and unreciprocated cooperation using the iterated Prisoner's Dilemma game, a paradigm modeling reciprocal altruism by requiring both of two players to independently decide to cooperate or defect with monetary outcome determined by the interaction of their respective choices. It was found that in response to reciprocated cooperation, intranasal administration of 20 IU of vasopressin in men augmented activation in amygdala output pathways (Davis and Whalen, 2001) and regions characterized as part of vasopressin circuitry implicated in social cognitive processes (Goodson and Thompson, 2010), including the bed nucleus of the stria terminalis, lateral septum, and stria terminalis. Similar to the effects of oxytocin in the same paradigm, vasopressin increased medial prefrontal cortex reactivity to unreciprocated cooperation. Vasopressin also modulated right amygdala connectivity in a similar way as oxytocin, but in a more widespread fashion; specially, vasopressin decreased amygdala connectivity with brainstem while increasing amygdala connectivity with anterior insula, subgenual anterior cingulate cortex, and inferior temporal cortex. As with the corresponding investigation with oxytocin (Rilling et al., 2011), the lack of an effect of vasopressin on relevant social interaction behavior leaves the exact implications of these activation patterns uncertain, yet nonetheless valuable for understanding the neural circuitry impacted by vasopressin during social exchange.

It is only in very recent years that research has focused on the effects of vasopressin on neural signals underlying social cognitive processes, and as such, to date, our knowledge of the subject remains elementary. It should be noted that vasopressin pharmacological fMRI studies in females have yet to be published, which will be important given the likelihood of sexual-dimorphism. Because amygdala effects, among others, differed in the Rilling et al., (2011) study using half the dose of intranasal vasopressin as those of Zink and coworkers, dose effects should also be studied. Moreover, future studies are required to shed light on the effects of vasopressin on neural circuitry that encodes various as-of-yet investigated elements of human sociality, both simple and complex, before our knowledge in this area is complete.

Imaging Genetics Studies: Effects of Vasopressin Receptor Genetic Variations

While several studies of the influence of the human vasopressin receptor gene, AVPR1A, on social behavior exist (Ebstein et al., 2010; Ebstein et al., 2009; Rilling et al., 2011), to date, only one vasopressin imaging genetics study has been carried out to investigate the impact of two microsatellite repeat polymorphisms in the promotor region of AVPR1A, RS1 and RS3, on amygdala reactivity during implicit processing of social negative emotion (Meyer-Lindenberg et al., 2009). RS1, a $(GATA)_n$ repeat, has 9 different alleles in the population of which the 312 bp allele has been shown to be overtransmitted in a subset of autistic probands (with preserved language) and the 320 bp allele undertransmitted (Wassink et al., 2004). RS3, a $(CT)_4$-TT-$(CT)_8$-$(GT)_n$ repeat, has 16 different alleles in the population of which the 334 bp and 340 alleles has been associated with overtransmission in autism (Kim et al., 2002). These particular autism-associated RS1 and RS3 alleles (excluding the RS3 340 allele due low prevalence in the sample) were investigated in an imaging genetics procedure in which participants were subjected to the face matching paradigm described in the previous section (Hariri et al., 2002), exposing them faces displaying fear and anger expressions to assess amygdala responses evoked by threatening facial stimuli according to RS1 and RS3 genotype (Meyer-Lindenberg et al., 2009). Exposure to social negative emotion elicited the highest left amygdala activation in carriers of the RS3 334 bp risk allele

compared to all other alleles. Interestingly, the RS1 320 bp allele previously shown to be overtransmitted in autism (Wassink et al., 2004) was associated with the least activation of left amygdala relative to all other alleles, including the RS1 312 bp allele associated with undertransmission in autism. Moreover, for RS1 a comparison between long and short alleles revealed that greater evoked amygdala activity was associated with the short alleles, whereas for RS3, the long alleles were associated with greater amygdala reactivity to fearful/angry facial expressions.

Although studies have begun to elucidate the cellular functionality of these polymorphisms (Knafo et al., 2008), data remain too limited to definitively define the impact of RS1 and RS3 genotype on AVPR1A expression and function, which limits the exact interpretation of the observed genotype-dependent amygdala activation patterns. Nonetheless, this first vasopressin system imaging genetics investigation does implicate the amygdala as a neural correlate of the impact of vasopressin transmission on human social behavior in a genetic-specific manner. Future imaging genetics investigations associating human vasopressin-related genetic variations with regional neural gray matter volume and brain activity assessed with different social cognitive paradigms will surely point to other brain areas as targets of vasopressin's influence on human social cognition as well.

Neuroimaging of Oxytocin and Vasopressin in Psychiatric Disorders

Accumulating evidence suggests a role of oxytocin and/or vasopressin in a host of neuropsychiatric disorders, particularly those with aspects of social dysfunction, including autism spectrum disorder, social anxiety disorder, obsessive-compulsive disorder, depression, schizophrenia, and attachment disorders (Heinrichs et al., 2009; McCarthy and Altemus, 1997). Up to this point, the oxytocin and vasopressin pharmacological fMRI and imaging genetics studies highlighted in this review have been investigated in healthy men and women. Probing the acute and chronic impact of oxytocin and vasopressin on social cognition neural circuitry in those with mental disorders is relatively underrepresented in the literature, limited to two studies of the influence of oxytocin administration on social emotion-related brain activity in generalized social anxiety disorder (Labuschagne et al., 2010) and depression (Pincus et al., 2010).

Relative to age- and gender-matched control subjects, unmedicated men with generalized social anxiety disorder (GSAD) show bilateral amygdala hyperactivity during exposure to fearful face stimuli, but not happy faces (Labuschagne et al., 2010). Interestingly, this hyperactivation was normalized following the intranasal administration of 24 IU of oxytocin; in GSAD, oxytocin, compared to placebo, significantly attenuated the heightened amygdala response elicited by social fear stimuli to a level similar to that evoked in healthy individuals (Labuschagne et al., 2010). Although a single dose of oxytocin had no effect on mood or anxiety, these findings hint at the possibility that prolonged treatment with oxytocin could potentially improve symptoms of GSAD via normalization of amygdala reactivity to threat-related social cues.

The effect of intranasal administration of oxytocin on brain activity has also been investigated in those with depression. While neural reactivity in unmedicated clinically depressed women during social affective attribution (i.e., attributing affective states of others from their eyes) was not significantly different than matched healthy individuals, intranasally administered oxytocin (40 IU) differentially modulated particular neural circuitry in depressed and healthy subjects (Pincus et al., 2010). Oxytocin, relative to placebo, uniquely increased activation in the right amygdala and caudate nucleus in healthy women, whereas in those with depression, oxytocin uniquely augmented right middle frontal gyrus and right insula activity when identifying emotional states of others. This study of this

relatively small sample size (n ≈ 8) requires replicated in a larger sample, as well as in men, but nonetheless indicates that the effects of oxytocin on social cognition-related brain circuitry can be distinctly impacted by one's mental health.

These investigations in GSAD and depressed samples demonstrate that, whether acting on neural systems differentially activated by social cognitive processes in those with a psychiatric disorder or acting on unique brain regions depending on diagnosis, oxytocin's neural impact is not universal, but rather can be mental health-specific. Of course, many psychiatric disorders remain to be examined, and to date, the effects of vasopressin administration on social-related brain activation patterns have not be studied in any clinical psychiatric populations. Moreover, oxytocin/vasopressin imaging genetic studies capturing chronic effects have only been performed on healthy individuals (although we should be reminded that each of the oxytocin and vasopressin system genes subjected to imaging genetics investigations were selected because of their association with autism). Together these limitations leave many unanswered questions related to the impact of these neuropeptides in mental illness.

Conclusions and Future Directions

As intricate as human social behavior is, the influence of oxytocin and vasopressin on the neural circuitry underlying social cognitive processes is also undeniably complex. While in the last several years oxytocin and vasopressin pharmacological fMRI and imaging genetics research has produced multiple promising findings, they are often diverse and disparate, limiting their generalizability and conclusiveness. Oxytocin and vasopressin effects on social-related neural responses are strongly influenced by experimental paradigm, gender, genetics, and mental health. It will be imperative for future studies to carefully consider these factors, and combinations of factors, to more concisely define the modulatory role of oxytocin and vasopressin on the neural underpinnings of complex human sociality.

As it currently stands, the investigations reviewed here have only just begun to touch on certain aspects of human social cognition, largely related to social emotion processing and recognition. A handful of studies have introduced aspects of social interaction into paradigms, but our knowledge of the effects of oxytocin and vasopressin on brain activity surrounding human social behavior is limited by the elements of sociality that have been tapped in neuroimaging studies. The expansion of models of particular social constructs implemented in future studies will reveal a more complete picture regarding the ways in which oxytocin and vasopressin influence the underlying neural correlates. Based on relevant animal literature, particular emphasis should perhaps be placed on social cognitive processes related to social anxiety, interaction with attachment partners, and non-competitive social interactions.

Interpretations of the findings presented in this review are also restricted by our current knowledge, or lack thereof, of oxytocin/vasopressin molecular and cellular mechanisms in humans. Our incomplete knowledge of oxytocin and vasopressin receptor localization throughout the human brain leaves much to be desired. It remains unproven that oxytocin and vasopressin are acting directly on receptors in the brain regions implicated in the aforementioned studies or rather are acting indirectly. Furthermore, the oxytocin and vasopressin receptor genetic variations investigated in imaging genetics paradigms to date are of unknown molecular functionality, thereby rendering the results of those investigations difficult to fully appreciate. These issues will undoubtedly be remedied as the molecular mechanisms by which oxytocin and vasopressin act in the human brain are elucidated and advances in human genetics continue. For now oxytocin and vasopressin pharmacological fMRI and imaging genetics studies remain completely separated. It will becomes essential,

however, for future research endeavors to probe the interaction between neuropeptide administration and related genetics in order to completely realize the capability of oxytocin and vasopressin to modulate neuronal systems related to human social cognitive processes and behavior.

Overall, making use of innovative technology in neuroimaging and genetics, we have only just begun to uncover the acute and chronic effects of oxytocin and vasopressin on human brain function, particularly pertaining to the complex construct of human social cognition. We rely on future investigations to unify the somewhat noisy current findings and provide us with the biological basis of the effects of these fascinating neuropeptides on human sociality. Nevertheless, what is clear, even at this stage, is that the prosocial neuropeptides, given intranasally, powerfully modulate key circuits for social cognition involved in psychiatric disorders. These pharmaco-fMRI data, together with the emerging evidence of common genetic variants affecting the same or strongly overlapping circuits, provide researchers with a ‘translational toolkit’ to begin to develop improved causal molecular therapies for a highly relevant treatment domain in psychiatry, social dysfunction. In this sense, progress in understanding oxytocin and vasopressin in human brain has the potential to be a proof of principle of leveraging basic science and animal data to translational promise through a thorough investigation of human neural mechanisms.

HIGHLIGHTS

- Human oxytocin and vasopressin pharmacological fMRI studies reveal acute effects on social cognition neural circuitry.
- Human oxytocin and vasopressin imaging genetics studies reveal chronic effects on brain structure and function.
- Implications for mental disorders characterized by social dysfunction are discussed.

Acknowledgments

C.F.Z. acknowledges support from the Intramural Research Program of the National Institute of Mental Health during the preparation of this manuscript. A.M.-L. acknowledges grant support from the Deutsche Forschungsgemeinschaft (DFG; SFB 636), Bundesministerium für Bildung und Forschung (BMBF; NGFN-MooDs, Bernstein-Programme), European Union (NEWMEDS, OPTIMIZE and EU-GEI) and National Alliance for Research on Schizophrenia and Depression (NARSAD; Distinguished Investigator Award) during the preparation of this manuscript.

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Table 1

Oxytocin and Vasopressin Neuroimaging Studies in Healthy Volunteers

OXYTOCIN

Pharmacological fMRI: Intranasal Oxytocin Administration

Author (Year)	N*	Sex	Dose	Social Cognitive Process	Effect of Oxytocin on Brain Activity
Baumgartner et al. (2008)	49_{btw}	M	24 IU	*Interactive Trust:* deciding whether to trust partner after trust had been breached	↓ L/R amygdala ↓ L brainstem ↓ L/R caudate
Domes et al.(2007)	13_{win}	M	24 IU	*Implicit Facial Emotion Processing:* identifying gender of fearful, angry, and happy faces	↓ R amygdala (all emotions) ↓ L/R temporal pole (fear and happy) ↓ L Temporoparietal junction (fear and happy)
Domes et al.(2010)	16_{win}	F	24 IU	*Explicit Facial Emotion Processing:* rating arousal of fearful, angry, and happy faces	↑ L amygdala (fear only) ↑ R brainstem (fear only) ↑ L temporal pole (fear and happy) ↑ L superior temporal gyrus (fear and happy) ↑ L/R fusiform gyrus (fear and happy) ↑ L insula (fear and happy) ↑ L/R prefrontal cortex (angry only)
Gamer et al. (2010)	46_{btw}	M	24 IU	*Explicit Facial Emotion Processing:* classifying emotion of fearful and happy faces initial attention focus to mouth redirecting social attention to eyes *Connectivity*	↓ L anterior amygdala (fear only) ↑ L anterior amygdala (happy only) ↑ L/R superior colliculus ↑ R posterior amygdala ↑ posterior amygdala—superior colliculus
Kirsch et al. (2005)	15_{win}	M	27 IU	*Implicit Facial Emotion Processing:* matching fearful and angry faces *Connectivity*	↓ L amygdala ↓ amygdala—brainstem
Petrovic et al.(2008)	27_{btw}	M	32 IU	*Aversely Conditioned Face Processing:* rating likeability of neutral faces (direct and indirect gaze) that were previously paired with negative experience	↓ R amygdala (direct gaze only) ↓ R anterior cingulate ↓ R medial prefrontal cortex ↓ R fusiform area (direct gaze only)
Riem et al. (2011)	42_{btw}	F	24	*Auditory Exposure to Crying Infant*	↓ R amygdala ↑ L/R insula
Rilling et al. (2011)	60_{btw}	M	24 IU	*Altruistic Interaction:* reciprocated cooperation unreciprocated cooperation *Connectivity*	↑ L amygdala ↑ L caudate ↑ L ventral prefrontal cortex ↓ amygdala—brainstem ↑ amygdala—insula ↑ amygdala—inferior temporal cortex
Singer et al. (2008)	20_{win}	M	32 IU	*Empathy for Pain:* Observing Pain Inflicted on Partner	No significant activations

Imaging Genetics: Oxytocin Receptor Genetic Variations

Author (Year)	N	Sex	Ethnicity	SNP	Method and Measure	Effect of Genetic Variation
Furman et al. (2011)	51	F	Caucasian	rs2254298 (A>G)	Manual Tracing: regional brain volume Voxel Based Morphology: regional gray matter volume	↑ L/R amygdala ↑ L posterior brainstem ↓ L dorsomedial anterior cingulate cortex
Inoue et al. (2010)	208	M/F	Japanese	rs2254298 (A>G) rs53576 (A>G)	Manual Tracing: regional brain volume Manual Tracing: regional brain volume	↑ L/R amygdala no effect on amygdala volume
Tost et al. (2010)	212 228	M/F	Caucasian	rs53576 (A>G)	Voxel Based Morphology: regional gray matter volume Functional MRI: negative facial emotion processing	↑ R amygdala (male only) ↓ R hypothalamus (male only) ↓ L amygdala activity

Imaging Genetics: Oxytocin Receptor Genetic Variations

Author (Year)	N	Sex	Ethnicity	SNP	Method and Measure	Effect of Genetic Variation
Tost et al. (2011)	212 228	M/F	Caucasian	rs2254298 (A>G)	Voxel Based Morphology: regional gray matter volume Functional MRI: negative facial emotion processing	↓ R hypothalamus (male only) ↓ medial anterior cingulated cortex deactivation
Yamasue et al. (2011)	206	M/F	Japanese	rs2254298 (A>G)	Voxel Based Morphology: regional gray matter volume	↓ R dorsomedial anterior cingulate cortex ↓ R hypothalamus (female only)

VASOPRESSIN

Pharmacological fMRI: Intranasal Vasopressin Administration

Author (Year)	N	Sex	Dose	Social Cognitive Process	Effect of Neuropeptide
Rilling et al. (2011)	59_{btw}	M	20 IU	*Altruistic Interaction:* reciprocated cooperation unreciprocated cooperation *Connectivity*	↑ L bed nucleus of the stria terminalis ↑ L insula ↑ L stria terminalis ↑ L ventral prefrontal cortex ↓ amygdala—brainstem ↑ amygdala—insula ↑ amygdala—subgenual cingulate cortex ↑ amygdala—inferior temporal cortex
Zink et al. (2010)	20_{win}	M	40 IU	*Implicit Facial Emotion Processing:* matching fearful and angry faces *Connectivity*	↑ subgenual cingulate (abolished decrease) ↓ subgenual cingulate—supragenual cingulate
Zink et al. (2011)	20_{win}	M	40 IU	Social Recognition: matching familiar and unfamiliar fearful and angry faces	↓ L temporoparietal junction (unfamiliar only)

Imaging Genetics: Vasopressin Receptor Genetic Variations

Author (Year)	N	Sex	Ethnicity	SNP	Method and Measure	Effect of Genetic Variation
Meyer-Lindenberg et al. (2010)	121	M/F	Caucasian	RS1 320 bp RS3 334 bp	Functional MRI: negative facial emotion processing	↓ L amygdala activity ↑ L amygdala activity

*btw = between subject design, win = within subject design; IU = international unit; L = left, R = right.