Developmental Perspectives on Oxytocin and Vasopressin

Elizabeth AD Hammock^{*,1}

¹Vanderbilt Kennedy Center and Department of Pediatrics, Vanderbilt University, Nashville, TN, USA

The related neuropeptides oxytocin and vasopressin are involved in species-typical behavior, including social recognition behavior, maternal behavior, social bonding, communication, and aggression. A wealth of evidence from animal models demonstrates significant modulation of adult social behavior by both of these neuropeptides and their receptors. Over the last decade, there has been a flood of studies in humans also implicating a role for these neuropeptides in human social behavior. Despite popular assumptions that oxytocin is a molecule of social bonding in the infant brain, less mechanistic research emphasis has been placed on the potential role of these neuropeptides in the developmental emergence of the neural substrates of behavior. This review summarizes what is known and assumed about the developmental influence of these neuropeptides and outlines the important unanswered questions and testable hypotheses. There is tremendous translational need to understand the functions of these neuropeptides in mammalian experience-dependent development of the social brain. The activity of oxytocin and vasopressin during development should inform our understanding of individual, sex, and species differences in social behavior later in life.

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INTRODUCTION

After a century of study, two tiny nine-amino-acid peptide hormones continue to capture the attention and fuel the scientific curiosity of diverse fields from biology to sociology. Numerous disciplines have contributed to the copious studies indicating a role for oxytocin and vasopressin systems in adult social behavior (for detailed reviews, see Carter *et al*, 2008; Donaldson and Young, 2008; Insel, 2010; Gordon *et al*, 2011; Kavaliers and Choleris, 2011; Meyer-Lindenberg *et al*, 2011; Young *et al*, 2011; Albers, 2012; Bosch and Neumann, 2012; Ebstein *et al*, 2012; Wacker and Ludwig, 2012; Zink and Meyer-Lindenberg, 2012; Goodson, 2013). We know that manipulating these systems in adulthood alters brain and behavior, so why should we consider oxytocin and vasopressin in the developmental emergence of brain and behavior? Given the prevalence of developmental disorders and the contribution of early life experience to lasting outcomes, it is important to uncover the underlying mechanisms of experience-dependent development. What are the effector molecules of the early life social environment that lead to species-typical developmental

trajectories for social behavior, such as preference for social contact with a conspecific, which requires developmental entrainment (Denenberg *et al*, 1964)? As a result of their prominent roles in adult social behavior, brain oxytocin and vasopressin systems appear as low hanging fruit in the garden of potential effector molecules underlying the developmental mechanisms of social behavior. Their experience-dependent activity during developmental sensitive periods likely contributes to individual, sex, and species differences in social behavior later in life.

There is a long history of studying oxytocin and vasopressin in social behavior in adult animals, which set the stage for exploring oxytocin and vasopressin in brain and social behavior development. Peter Klopfer (Klopfer and Klopfer, 1968; Klopfer, 1971) first proposed a role for oxytocin in the brain to modulate adult social behavior, specifically the transition to maternal behavior in goats. Testing that hypothesis, Pedersen and Prange (1979) showed in rats that, in an estrogen-dependent manner, oxytocin acting in the brain facilitated the transition to maternal behavior (pup grouping, licking, crouching, nest building, and pup retrieval). This was followed by a hypothesis that oxytocin acting in the brain in adults may facilitate the development of sociosexual bonds between adult partners (Witt *et al*, 1990). This was tested in prairie voles—a rodent species with the neural capacity to form a selective social bond in adulthood with another adult (eg, monogamy). Central injection of oxytocin facilitated the

*Correspondence: Dr EAD Hammock, Department of Pediatrics, Vanderbilt University, 2215 Garland Avenue, 7415 MRBIV, Nashville, TN 37232, USA, Tel: +1 404 275 3523, Fax: +1 615 343 5845, E-mail: Liz.hammock@gmail.com

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TABLE 1 Review Highlights

Oxytocin and vasopressin have significant roles in adult species-typical social behavior.
More direct research on oxytocin and vasopressin function in experience-dependent development is needed.
Vasopressin and oxytocin are available to the developing brain: vasopressin emerges before oxytocin and reaches higher levels in males than females.
Vasopressin receptors (V1aR) and oxytocin receptors (OXTR) show dynamic developmental profiles. Their distribution patterns in the brain depend on age and species, with quantitative levels modulated by gonadal hormones and experience.
Vasopressin and oxytocin both influence a primordial social behavior (neonatal familiar orienting bias), but in opposite directions. Oxytocin promotes, while vasopressin inhibits neonatal orienting bias.
Parental engagement activates the oxytocin system in the infant.
Vasopressin and oxytocin activity in the neonate impact behavior into adulthood, indicating a role for activity-dependent development.
Both oxytocin and vasopressin activity during development have long-term impacts on the brain.
If oxytocin and vasopressin mediate developmental experience, then genetic variation in system components should interact with the developmental environment to contribute to individual, sex, and species differences in social behavior.
Oxytocin (and perhaps other neuroendocrine hormones) may have a key role in experience-dependent programming of sensory systems during development for species-typical social expertise in adulthood.
The pre-clinical data suggest that clinical effectiveness of oxytocin and vasopressin during development will be strongly influenced by environmental factors.

formation of a selective partner preference in the laboratory partner preference test. Vasopressin and oxytocin are evolutionary paralogs, so it is not surprising that vasopressin was subsequently tested in the prairie vole and also observed to facilitate selective partner preference behavior (Winslow *et al*, 1993), especially as vasopressin was already appreciated for its central role in flank marking in hamsters, which is a species-typical olfactory social communication behavior (Ferris *et al*, 1984). There is now an abundance of evidence that both oxytocin and vasopressin contribute to adult species-typical social behavior, including effects on human social behavior. As such examples of species-typical social behavior are influenced by both genetics (Lim *et al*, 2004; Hammock and Young, 2005) and early life experience (Denenberg *et al*, 1964; Pedersen and Boccia, 2002), a full understanding of the mechanisms of social behavior must include uncovering the genetic and neural circuit mechanisms of experience-dependent development.

The main tools used to investigate oxytocin and vasopressin systems in social behavior are pharmacological, genetic (viral vectors, transgenic and knock-out mice), biomarker, and gene association studies. Although pharmacological manipulation of neuropeptide systems in adult and developing animals can yield clues about how receptor activation changes behavior, knockout and gene association studies can tell us only if there is an association between gene and behavior: congenital knockout and gene association studies fail to distinguish between genetic contributions to developmental processes ('organizational' effects) and genetic contribution to adult function of the gene product itself ('activational' effects). Thus, the role of these systems in development must be directly probed and addressed separately from activational effects in adulthood. Pharmacological activation of receptors during development as well as temporally regulated genetic manipulation during development can both be used to answer developmental questions. So far, the neurobiological research on oxytocin, vasopressin, and development falls into two non-mutually exclusive categories: one asks if developmental

events affect adult levels of oxytocin and vasopressin system function (eg, reviewed in Bales and Perkeybile, 2012; Veenema, 2012) and the other asks if oxytocin and vasopressin activity during sensitive periods shapes brain and behavior development (reviewed here and Bales and Perkeybile, 2012). Both kinds of questions are informative and lead to a greater understanding of the roles of oxytocin and vasopressin in the experience-dependent development of social behavior.

In the remainder of this review, I discuss brain oxytocin and vasopressin systems as mediators of experience-dependent development. First, I discuss the neuroanatomy of these systems during development. Then, I describe the effects of oxytocin and vasopressin on infant behavior and on adult behavior after neonatal manipulation of these systems. Next, I discuss data demonstrating short- and long-term effects of oxytocin and vasopressin on brain development. Then, I describe data that support a gene by environment development model of oxytocin and vasopressin systems. The main ideas and key points in this review are summarized in Table 1. I conclude the review with a synthesis of current findings and future directions. This review should arm the reader with a fresh perspective on the roles of oxytocin and vasopressin in species-typical experience-dependent development and provide a theoretical framework for the interpretation of surprising clinical and gene association studies in humans.

Dynamic Developmental Profiles: When and Where are the Factors Present in Development?

Neuropeptide distribution in the brain. Oxytocin and vasopressin are produced in and available to the developing brain, including the developing human brain (reviewed in Swaab, 1995). In all species examined, vasopressin mRNA and protein emerge before oxytocin mRNA and protein, and in greater quantities (Choy and Watkins, 1979; Buijs *et al*, 1980; Burford and Robinson, 1982; Wolf *et al*, 1984; Van Der Sluis *et al*, 1986; Altstein and Gainer, 1988; Iqbal and

Jacobson, 1995a,b). In humans, vasopressin has been detected as early as 11 weeks gestation and oxytocin as early as 14 weeks, and both peptides appear to have adult-like levels of immunoreactive cell number in the paraventricular nucleus (PVN) by 26 weeks gestation (Goudsmit *et al*, 1992), although the volume of the PVN is still immature (Rinne *et al*, 1962). In rats and mice, based on *in situ* hybridization studies, immunohistochemistry, and quantitative immunoassay, vasopressin has consistently been detected prenatally, while oxytocin is sometimes detected prenatally, and sometimes not detected until the first or second postnatal day (Sinding *et al*, 1980a; Wolf *et al*, 1984; Whitnall *et al*, 1985; Reppert and Uhl, 1987; Altstein and Gainer, 1988; Yamashita *et al*, 1988a,b; Laurent *et al*, 1989; Bloch *et al*, 1990; Hyodo *et al*, 1992; Jing *et al*, 1998; Lipari *et al*, 2001). Both vasopressin- and oxytocin-producing cells continue to develop postnatally (Krisch, 1980; Sinding *et al*, 1980a; Wolf *et al*, 1984; Van Tol *et al*, 1986; Almazan *et al*, 1989). Oxytocin and vasopressin are both produced in the PVN and the supraoptic nucleus (SON) of the hypothalamus, while only vasopressin is produced in the suprachiasmatic nucleus, which emerges slightly later with a day–night rhythm of vasopressin content by E21 in rats (Reppert and Uhl, 1987). The rat extrahypothalamic vasopressin system (vasopressin-producing cells in the bed nucleus of the stria terminalis and the medial amygdala) is established early postnatally and is sexually dimorphic with much greater vasopressin production in males (De Vries *et al*, 1981; Szot and Dorsa, 1993; Rood *et al*, 2013). Sex differences in extrahypothalamic vasopressin production, which emerge by postnatal day 12 in rats, are testosterone dependent, leading to more immunoreactive fibers in the lateral septum and habenula (De Vries *et al*, 1981). Compared with fibers in adult rats, fibers in the adult mouse appear to be even more widespread (Rood and De Vries, 2011), although a complete developmental profile in mice has not yet been performed for vasopressin immunoreactivity. Sex differences are apparent in adult mice too (Rood *et al*, 2013). Vasopressin development has been studied in golden hamsters (Delville *et al*, 1994b), and while male hamsters produce more vasopressin than female hamsters, the sex differences in hamsters are evident in the hypothalamus, and not the extrahypothalamic areas (Delville *et al*, 1994a). A transient vasopressin immunoreactivity in the cortex in the first postnatal week of golden hamsters has also been reported (Delville *et al*, 1994b). Vasopressin neurons are also detected in the locus coeruleus of rats (Caffe and Van Leeuwen, 1983) and have also been detected in the adult rat olfactory bulb (Tobin *et al*, 2010), but the development of this population is unknown. The genes encoding oxytocin and vasopressin each include a neurophysin, which serves as a carrier protein. The detection of the neurophysin component precedes the fetal detection of either vasopressin or oxytocin (Silverman, 1975; Choy and Watkins, 1979; Sinding *et al*, 1980a,b). The developmental significance of this earlier onset of neurophysin expression is unknown, although one early study indicated that neurophysin II (vasopressin's carrier protein) enhances proliferation of

non-neuronal hypothalamic cells *in vitro* (Worley and Pickering, 1984).

In rat, primary fetal brain cultures from the hypothalamus, vasopressin mRNA and peptide can be detected, but oxytocin cannot (Di Scala-Guenot *et al*, 1990a,b) without stimulation by potassium or thyroid hormone (Madarasz *et al*, 1992). This difference is consistent with *in vivo* results that vasopressin emerges earlier than oxytocin and is also consistent with the hypothesis that developmental oxytocin is activity dependent (Zheng *et al*, 2014). However, oxytocin mRNA levels in primary cultures derived from postnatal rat brains did not appear to be affected by lack of serum in the culture media or the presence of tetrodotoxin (Wray *et al*, 1991). In summary, vasopressin and oxytocin are produced in and available to the developing brain, vasopressin production precedes oxytocin production, and oxytocin production may be activity dependent.

Vasopressin and oxytocin receptors in the brain. Although the peptides are available early in development, their receptors have a more dynamic developmental time course of availability. Receptors for oxytocin and vasopressin are the oxytocin receptor (OXTR), vasopressin 1a (V1aR), 1b (V1bR) and V2 (V2R) receptors. OXTR and V1aR are abundant in the developing and adult brain and are typically assumed to be the main brain receptors in the adult, with V1bR expression limited to the pituitary and V2R receptor in the kidney. The presence of V1bR (Hernando *et al*, 2001) and V2R (Kato *et al*, 1995; Vargas *et al*, 2009) in the brain during development has not been ruled out, and this could be an important research avenue for V1bR in particular (Wersinger *et al*, 2002, 2004, 2008; Caldwell *et al*, 2008; Stevenson and Caldwell, 2012; Zai *et al*, 2012). OXTR and V1aR mRNA and ligand-binding capacity have both been detected prenatally in rats, but their interesting transient developmental patterns appear postnatally, with an adult-like pattern around the time of typical weaning, and further maturing in quantity into adulthood (Lukas *et al*, 2010). Some, but not all adult sex differences in OXTR expression are influenced by developmental exposure to testosterone (Tribollet *et al*, 1990; Uhl-Bronner *et al*, 2005; Dumais *et al*, 2013) and are actively regulated in adulthood (Bale and Dorsa, 1995a,b; Bale *et al*, 1995a,b). There do not appear to be gonadal steroid-dependent sex differences in brain V1aR expression, as determined by tritiated vasopressin ligand binding (Tribollet *et al*, 1990).

In voles, rats, and mice, the binding profiles for OXTR (Shapiro and Insel, 1989; Snijdwint *et al*, 1989; Tribollet *et al*, 1989, 1991a, 1992; Wang and Young, 1997; Hammock and Levitt, 2013) and V1aR (Snijdwint *et al*, 1989; Tribollet *et al*, 1991a,b; Wang *et al*, 1997; Wang and Young, 1997; Hammock and Levitt, 2012) have been mapped during postnatal development. Receptor mRNA has also been measured in development (Yoshimura *et al*, 1996; Chen *et al*, 2000) in rats. Each species studied to date has a specific transient map of receptor ligand binding. In rodents, there is a transient peak of ligand binding in some

brain areas in the first week for V1aR and in the second week in some brain areas for OXTR. The brain regions that display these transient appearances of receptors are not conserved across rodent species. For example, in separate experiments using the same radioactive ligand, pre-weanling rats have peak OXTR specifically in the cingulate neocortex (Shapiro and Insel, 1989; Tribollet *et al*, 1989), while mice have a peak in OXTR throughout the entire neocortex (Hammock and Levitt, 2013). Readers are referred to the primary literature for more details of their species of interest. This suggests that experience-dependent oxytocin and vasopressin activity during these time points may help to shape activity-dependent development in a species-specific manner, in which species differences in genetics influence the brain distribution of receptors.

Species differences and human relevance. Species specificity of receptor distribution patterns in the adult brain is a common theme in the oxytocin/vasopressin family of receptors. There are numerous examples of species-specific distribution of binding sites for these receptors—in primates, rodents and even non-mammals such as birds and fishes. This diversity of receptor locations affects behavior. For example, the monogamous prairie vole has an abundance of V1aR in the ventral pallidum, while the closely related non-monogamous meadow vole does not (Young, 1999; Lim and Young, 2006). Adding V1aR by viral vector gene transfer to the ventral pallidum of the meadow vole confers the males with the ability to form a partner preference (Lim *et al*, 2004), which is a laboratory test of the pair bonding component of monogamous social behavior. Receptor locations in adulthood and throughout development have significant implications for the underlying mechanisms of the influence of oxytocin and vasopressin on social behavior. Importantly, these receptor densities vary by species, sex, age, and to a lesser extent, by individual, providing a putative neurobiological mechanism for individual, sex, and species differences in experience-dependent developmental trajectories.

Are there transient profiles of OXTR and V1aR in human brain development? Yes. Data from the Allen Brain Atlas indicate that V1aR mRNA expression is high in the human neocortex during the second trimester (Kang *et al*, 2011). In mice, the V1aR transient peak occurs around P7, and includes intense transient ligand binding in the hippocampus and neocortex that is not present in the adult mouse (Hammock and Levitt, 2012). The translation of neurodevelopmental events occurring at this time suggests that this time is similar to the second trimester in human brain development (Clancy *et al*, 2007). Human OXTR expression seems to be high at birth and for the first 3 years in the neocortex, with prolonged expression in the medial prefrontal cortex (Kang *et al*, 2011). The peak of OXTR ligand binding in the neocortex (see Figure 4b) in mice around P14 (Hammock and Levitt, 2013) translates to perinatal human neurodevelopmental events (Clancy *et al*, 2007). This consistent and direct neurodevelopmental

translation of peak expression for both AVPR1A and OXTR suggests that mice will be very valuable models of the activity-dependent effects of oxytocin and vasopressin on neocortical development. The functional significance of the robust transient peak of OXTR in the neocortex of mice has recently been demonstrated by Zheng *et al* (2014), and will be discussed in much further detail below.

Behavioral Influence During Development

Oxytocin and vasopressin both have a role in adult behavior. Their role in neonatal behavior is less well established, but deserves careful consideration, as this may significantly contribute to species-typical trajectories of experience-dependent development. Social expertise in adulthood is initiated by experience during development (eg, Denenberg *et al*, 1964), so alterations in infant activity that bring the infant in contact with social stimuli will positively contribute to the development of social expertise, while behavior that removes them from social contexts may negatively impact the development of species-typical social behavior.

Vasopressin influences early social behavior and blocks early familiarity preference. Several lines of evidence indicate both long-term and short-term behavioral effects of neonatal vasopressin exposure. A single study of enhanced vasopressin exposure during the neonatal period in prairie voles resulted in heightened aggression in adult voles, while exposure to an antagonist reduced aggression, with no effects on exploration in the elevated plus maze and partner preference behavior (Stribley and Carter, 1999). A few studies in the neonatal period in rats also indicate a role for vasopressin in social behavior. Neonatal mice and rats emit ultrasonic vocalizations when separated from their mother, perhaps in a reflex pattern that may elicit her attention. Large doses (100 ng) of vasopressin given intracerebroventricularly to neonatal rats (Winslow and Insel, 1993) reduced ultrasonic vocalizations but also core body temperature, and while vasopressin reduced the latency for righting in an inclined surface assay indicating potential regulation of sensory-motor integration, it also reduced motor activity in general. Consistent with a motor inhibiting effect of central injections of large doses of vasopressin, the vasopressin-deficient Brattleboro rat neonate is hyperactive and social contact fails to elicit a typical quiescence response in this mutant line (Schank, 2009). Further, Brattleboro neonates show disturbances in early odor orienting (Nelson and Panksepp, 1998) and dysregulation of the HPA axis in response to maternal separation as neonates (Fodor and Zelena, 2014). Flank marking (a social communication behavior) in hamsters emerges around P19–P22 and is tied to a robust increase in vasopressin in the hypothalamus (Ferris *et al*, 1996). Together, these data strongly suggest an early role for vasopressin in the modulation of species-typical social behavior.

Early orienting to specific odor cues is a significant contributor to mammalian species-typical social behavior

Figure 1. Vasopressin blocks and oxytocin promotes primordial social orienting behaviors in neonatal rodents. Early orienting to social cues increases exposure to social stimuli required for the development of species-specific social behavior expertise. (a) Vasopressin acting at the V1aR eliminates preferences for maternally associated odors in neonatal female mice on postnatal day 8. Copied with permission from Hammock *et al* (2013). Copyright Elsevier. *Significant difference. (b) Oxytocin antagonism eliminates preferences for maternally associated odors in rats on postnatal day 15. Copied with permission from Kojima and Alberts (2011a). Copyright Elsevier. *Significant huddling preference, †Significant difference in huddling preference.

developmental trajectories (Denenberg *et al*, 1964; Brunjes and Alberts, 1979; Rosenblatt, 1983; Balogh and Porter, 1986). Not unlike visual or auditory imprinting in many birds (Hess, 1959), olfactory imprinting in rodents helps to orient to the initial food source (the mother) and allows the infant to begin to build a neural representation of the social world through classical conditioning of innately social odor sources (eg, the mom, the littermates, species-typical food odors, and species-typical nest materials) with other stimuli (Rosenblatt, 1983; Hammock and Levitt, 2006; Hammock *et al*, 2013). Therefore, it is important to understand the neural mechanisms that underlie these important early orienting processes as they are at the foundation of building a social brain. We have explored the role of vasopressin in early olfactory learning in neonatal mice. Vasopressin, acting through the brain V1a receptor, acts as a barrier to the display of olfactory preferences in neonatal female mice

(Figure 1a; Hammock *et al*, 2013). In these experiments, a novel odor was presented for 1 h to C57BL/6J mouse litters on postnatal day 8, in the home cage with the mother. After odor exposure, the mom and odor source were removed from the cage. Two hours later, the neonates were individually tested for an odor preference for the trained odor vs a novel odor. Wild-type females showed a preference for the odor when that odor had been presented with the mom in the home cage, but failed to show a preference if the odor was presented without the mom in the cage. V1aR knock-out females showed a strong preference for the odor after training with the mom and also showed a strong preference for the odor when trained without the mom. This suggested that the absence of V1aR signaling was permissive for exposure alone (or the odor plus littermates) to generate strong olfactory preferences and indicated that activation of V1aR may inhibit the expression of early olfactory preferences. To test for a blocking effect for vasopressin on the expression of maternally paired odors, we next trained neonates as before, and just before testing gave them a central (intracerebroventricular) injection of vasopressin and demonstrated that vasopressin blocked the expression of a trained odor preference, at a low dose that did not affect motor activity. Further, vasopressin failed to block olfactory preferences in V1aR knock-out females, indicating that this receptor was required for the preference-blocking effects of vasopressin. Surprisingly, the wild-type and V1aR knock-out male mouse neonates were poor performers in this task and showed no evidence of olfactory preferences in any condition. A similar role for vasopressin activation of V1aR to reduce familiarity preference was also observed for rats at postnatal day 17 (Sigling *et al*, 2009) and postnatal day 33 (Veenema *et al*, 2012). Although the most straightforward interpretation of these data indicate a blocking effect by vasopressin on familiarity bias, it may also be possible that vasopressin acting at the V1aR imposes more stringent conditioning expectations, such that a neonate will not condition to a novel odor without an appropriate social context. Regardless of the interpretation, these data demonstrate a role for vasopressin at V1aR in very early sensory-dependent development of the social brain.

Oxytocin influences early separation distress vocalizations and social contact behavior in neonates. Neonates of some species vocalize, which may elicit parental care when needed. Both oxytocin knock-out (Winslow *et al*, 2000) and OXTR knock-out mice (Takayanagi *et al*, 2005) show low rates of isolation-induced vocalizations, but instead of increasing ultrasonic vocalizations, oxytocin delivered to the brains of neonatal rats actually inhibits isolation-induced vocalizations (Insel and Winslow, 1991). Oxytocin application in decerebrate rat neonates reduced vocalizations in response to electrical stimulation of the whiskers, a pain-inducing stimulus (Mazzuca *et al*, 2011). CD38 has been identified as a potent releaser of oxytocin in the hypothalamus (Jin *et al*, 2007), and these mice have altered

social behavior in the neonatal period (Higashida *et al*, 2010), including a reduction in isolation-induced ultrasonic vocalizations (Liu *et al*, 2008). Therefore, as presence of oxytocin, total lack of oxytocin, or poor oxytocin secretion, all result in reduced separation or stress-induced vocalizations, the role of oxytocin in ultrasonic vocalizations in neonatal rodents is unclear. In addition to vocalizing, and learning social odors (described above), neonatal rodents in a litter also modulate their huddle size based on ambient temperature and activity levels. Tighter more compact huddling by a litter of rats was observed after brain injections of oxytocin at postnatal day 10, but not earlier at postnatal day 7 (Alberts, 2007), indicating a role for oxytocin in a very early social behavior. A similar increase in tighter rat pup huddling after oxytocin treatment compared with antagonist treatment was also observed on postnatal day 14 (Kojima and Alberts, 2011a). Oxytocin also induces oral/suckling behaviors and grooming, especially during somatosensory vibrissae stimulation (Nelson and Alberts, 1997). As described earlier, rodent neonates learn to prefer a novel odor if that odor is paired with their mother. An oxytocin antagonist injected into the brain of 14-day-old rats just before pairing a novel odor with the mother resulted in the elimination of preference for that paired odor when tested the next day (Figure 1b). In contrast, rats injected with saline or oxytocin both demonstrated strong odor preferences for the odor that had been paired with the mother (Nelson and Panksepp, 1996; Kojima and Alberts, 2011a). The oxytocin antagonist may block the formation of these olfactory preferences by interfering with huddling and pup-mother contact during the odor exposure period, which is positively correlated with the strength of the olfactory preference (Kojima and Alberts, 2009, 2011b). In short, oxytocin activity in the neonate may enhance the required proximity to social cues that permit social learning.

Oxytocin in the infant is associated with parental engagement. Although there are several studies in rodents that demonstrate long-term effects of the quality of maternal care on the adult levels of oxytocin and vasopressin function (eg, Francis *et al*, 2000, 2002; Champagne *et al*, 2001; Pedersen and Boccia, 2002), there are fewer studies that measure an effect of parental care on oxytocin or vasopressin systems during development. In non-human primates, mother-reared monkeys show increased CSF oxytocin levels measured at 18, 24, and 36 months compared with nursery-reared infants, which displayed maladapted social and self-regulatory behaviors (Winslow *et al*, 2003). In neonatal rats, OXTR levels were lower in the dorsal hippocampus during postnatal development after repeated maternal separations (Noonan *et al*, 1994). Mogi *et al* (2011) report that oxytocin content is lower in the cingulate cortex of rats at postnatal day 14 when separated from their mother. Oxytocin responds to maternal separation and skin-to-skin contact in pre-weanling rats (Kojima *et al*, 2012). Oxytocin concentrations were sampled from

pre-weanling rat hypothalamus and blood at several time points during a separation and reunion paradigm with a foster mother, which in previous studies elicits a huddling preference in the pups. In the hypothalamus, 1 h of separation from a maternal figure resulted in increased oxytocin concentrations in the hypothalamus. Prolonged isolation for another 2 h induced further increases in oxytocin concentration in the hypothalamus, while 2-h treatment with a foster mother reduced oxytocin concentrations in the hypothalamus. In contrast, in serum a 1-h separation increased oxytocin concentrations as it did in the hypothalamus, but serum concentrations were decreased after a further 2-h period of isolation from a maternal figure. Perhaps the initial loss of contact with the mother results in an increased production of oxytocin in the hypothalamus and release into the periphery to organize the infant behavior to solicit social contact, but that further isolation results in conservation of activity of the oxytocin system. During the interaction with the foster mother, skin-to-skin contact was recorded, and there was a significant positive correlation between duration of contact and hypothalamic oxytocin concentrations (Figure 2a), but no relationship between skin-to-skin contact and peripheral oxytocin concentrations. At baseline, central hypothalamic and peripheral serum oxytocin concentrations were not correlated. However, after 1 h of separation, the infant's central and peripheral oxytocin were positively correlated. The group that received contact with a foster mother maintained a correlation between peripheral and central oxytocin concentrations, but the group that remained isolated from a maternal figure for 3 h lost their initial isolation-induced central and peripheral correlation, and the oxytocin concentrations in the hypothalamus and the blood were no longer correlated. These results indicate a relationship between nurturing contact and oxytocin in the neonate, but the relationship is dynamic, and will require very careful further study to understand fully the relationship between nurturing social contact and the activity of the oxytocin system within the brain and periphery. Nelson and Panksepp (1996) argued that '...gradual elevation and inhibition of oxytocinergic activity may be a critical aspect of the natural dynamics of social interaction in young rats, and it is possible that a patterned release of oxytocin in the presence of a social stimulus may be necessary to form conditioned odor preferences'. This important consideration still must be carefully addressed. Oxytocin may be released at social transitions rather than being continuously released during social contact.

Single injections of oxytocin just after birth has long-term sex-specific effects on behavior in prairie voles. As oxytocin is used frequently to induce labor, Bales and Carter (2003) attempted to determine the long-term behavioral effects, if any, of a single perinatal application of oxytocin. Early postnatal manipulations of prairie voles with oxytocin or an oxytocin antagonist have sexually dimorphic effects on later behavior, with males seemingly

Figure 2. Social contact is associated with oxytocin system activity in rodent and human infants. (a) In neonatal rats, the duration of skin-to-skin contact with a surrogate mother after a period of isolation was positively correlated with the concentration of oxytocin in the hypothalamus. Copied with permission from Kojima *et al* (2012). Copyright Wiley. (b, c) In 4- to 8-month-old human infants, intranasal oxytocin delivery to their fathers resulted in a very robust increase in infant salivary oxytocin (b) and a significant increase in social gaze and object manipulation in the infants (c), perhaps mediated by enhanced social contact induced by oxytocin in the father (c). Copied with permission from Weisman *et al* (2012). Copyright Elsevier. * $P < 0.05$, *** $P < 0.001$.

more affected by such perinatal treatments (reviewed in Carter *et al*, 2009). A single postnatal injection of oxytocin in male prairie voles increased the probability of partner preference and reduced anxiety-like behavior in adulthood (Bales and Carter, 2003), and a neonatal dose of OXTR antagonist reduced alloparental behavior in adult male prairie voles, without affecting partner preference behavior (Bales *et al*, 2004). The same perinatal dose in females did not affect partner preference behavior in adulthood, although higher doses did affect partner preference behavior, but in a non-linear manner (Bales *et al*, 2007b; Carter *et al*, 2009).

Chronic oxytocin during postnatal development alters later social behavior. As oxytocin has been considered as a potential therapeutic agent for autism and schizophrenia, Bales *et al* (2013) tested the effects of chronic exposure to exogenous oxytocin in the postnatal brain. Daily intranasal delivery of oxytocin to prairie voles during the juvenile period interferes with species-typical partner preference behavior in adulthood in males, but not females (Bales *et al*, 2013). Four groups of male and female prairie vole weanlings underwent chronic exposure to either one of three doses of oxytocin or a saline control. The doses were chosen such that the medium dose approximates doses being used in clinical trials on children. Importantly, social

behavior was measured in the acute phase of drug delivery as well as in the long term. Immediately after drug delivery, male juveniles receiving intranasal oxytocin showed increases in social behavior (contact time) with a familiar cage mate and decreased time spent autogrooming at low, medium, and high doses of oxytocin. Juvenile females failed to show a change in social contact time immediately after intranasal oxytocin delivery. As adults, males that received low and medium doses of oxytocin as juveniles were, without a change in total social contact time, less likely to form a partner preference that is an important species-typical social behavior for prairie voles. On the surface, this appears as if chronic exogenous oxytocin exposure has a negative outcome (ie, reduction in the probability of an important species-typical behavior), however, prairie voles can adapt their mating strategy from monogamy to non-monogamy to adjust to various selection pressures, thus non-monogamy is not necessarily a pathological trait, but potentially an adaptive trait (argued in Young, 2013). Pedersen and Boccia (2002) delivered oxytocin subcutaneously to female rat pups on postnatal days 2–10 and observed that females treated with oxytocin grew up to show higher levels of maternal attention to pups (pup licking) than saline-treated females. Further, adults who as pups were given daily injections of an OXTR antagonist showed lower levels of pup licking compared with saline-

treated females. These data highlight important timing (acute *vs* chronic and developing *vs* mature), dose, and sex effects on social behavior outcomes after exogenous manipulation of oxytocin. A recent study in adult male mice also revealed a counterintuitive reduction in social investigation after chronic intranasal oxytocin (Huang *et al*, 2014). Combined, these data indicate caution and careful study design for future chronic use of oxytocin in clinical populations. If oxytocin facilitates environmental encoding or social learning, then the context in which oxytocin is applied deserves special attention. To be successful clinically, it will probably be important for oxytocin to be given along with behavioral and/or environmental intervention. Chronic oxytocin treatment in the absence of an ethologically appropriate social setting may actually degrade the value of oxytocin as a social signal.

In human infants, there is evidence that the infant's oxytocin system responds to social engagement with the parent (Figures 2b and c; Feldman *et al*, 2010; Weisman *et al*, 2012). Thirty-five healthy fathers were given either placebo or oxytocin intranasally, and 45 min later interacted with their 4- to 8-month-old infants. The fathers that were given oxytocin showed enhanced social engagement with their infant, and those infants showed markedly increased levels of oxytocin in their saliva. This very interesting result needs replication and is consistent with the hypothesis that nurturing parental engagement activates the human infant oxytocin system.

Oxytocin and Vasopressin Impact Brain Development

Given that vasopressin and oxytocin appear to influence neonatal behavior and that there are brain areas with a developmental transience of oxytocin and vasopressin receptor expression, what is the experimental evidence that either receptor has a role in brain development? The Brattleboro rat exhibits a natural mutation rendering them vasopressin knock-outs. Boer *et al* (1982a, b) published some very early studies demonstrating the non-subtle changes in brain development observed in these rats, which included changes in the cerebellum (Boer, 1985) and noradrenergic content (Boer *et al*, 1995). Those early studies gave the first clues that neuropeptide signaling may regulate brain development.

Hormonal imprinting confers long-term changes. Perinatal manipulations of the levels of oxytocin and vasopressin or steroid hormones can alter the long-term programming of oxytocin and vasopressin systems and impact other neurotransmitter systems. This programming phenomenon was first described in rats (Swaab and Boer, 1983; Boer, 1993; Boer *et al*, 1994) and named 'hormonal imprinting' by Csaba (1986). Reviewed in Bales and Perkeybile (2012), single doses of oxytocin given to newborn prairie vole pups have long-term sex-specific consequences on PVN oxytocin and on other systems such as V1aR and estrogen receptor alpha (Yamamoto *et al*, 2004, 2006; Kramer *et al*, 2006; Bales

et al, 2007a; Pournajafi-Nazarloo *et al*, 2007). For example, as adults, prairie voles treated with a single dose of oxytocin or an OXTR antagonist given intraperitoneally on postnatal day 1 had altered levels of V1aR in various brain regions in a sex-dependent manner (Bales *et al*, 2007a), although surprisingly, no treatment effects on OXTR or the dopamine D2 receptor were observed. Chronic intraperitoneal postnatal treatments in rats also altered estrogen receptor alpha (Perry *et al*, 2009). Although intraperitoneal delivery of oxytocin or oxytocin antagonists may not be an ideal way to investigate central effects, it does result in differential c-fos activation of neonatal prairie vole brains (Cushing *et al*, 2003), indicating that peripheral injection of oxytocin does affect the brain. Subcutaneous injections of oxytocin within 24 h of birth also has long-term brain and behavioral consequences in mandarin voles (Jia *et al*, 2008a, b). A single perinatal injection of oxytocin impacts serotonin and dopamine metabolism in the hypothalamus and striatum in adult rats (Hashemi *et al*, 2013). This potent capacity for a single exposure of oxytocin in the peripartum period has raised concerns about the potential consequences of routine use of oxytocin in labor and delivery (Swaab and Boer, 1983; Carter, 2003; Hashemi *et al*, 2013).

Oxytocin is neuroprotective and analgesic during labor and delivery. Despite concerns about exogenous application of oxytocin in the peripartum period, it appears as though oxytocin released during birth acts within the neonatal brain to dampen excitatory neurotransmission, thus serving as a putative neuroprotective factor. In adult tissues, GABA is hyperpolarizing and inhibitory because of the low concentration of chloride ions inside the cell relative to higher concentrations outside the cell. During development, however, GABA is excitatory and depolarizing because of high intracellular chloride concentration. Acting in a manner that may alleviate the stress of the birth process and its potential excitatory neurotoxicity, at the time of birth, oxytocin temporarily shifts the chloride concentrations in neurons such that GABA becomes hyperpolarizing and inhibitory (Tyzio *et al*, 2006; Khazipov *et al*, 2008). Most recently, Tyzio *et al* (2014) observed that the transient hyperpolarization induced by oxytocin at birth is absent in two rodent models of autism: the sodium valproate model and a fragile X genetic model. The authors were able to rescue this deficit by pretreating the mothers before delivery with bumetanide that targets the chloride pump required to alter the gradient of chloride ions. In addition to modulating GABA signals in the forebrain and protecting against potential excitotoxicity, oxytocin also reduces the depolarizing actions of GABA on nociceptive neurons during birth giving it a powerful analgesic property (Mazzuca *et al*, 2011). These potential neuroprotective and analgesic effects of endogenous oxytocin at birth must be reconciled with the data described above demonstrating long-term 'hormonal imprinting' by exogenous oxytocin. Is the dose or exact timing of exposure to large quantities of oxytocin key to the distinction of neuroprotective *vs* potentially harmful

perinatal exposure to oxytocin? Do the effects vary by brain region or system?

Developmental vasopressin and oxytocin have long-term effects on cortical plasticity. As we observed transient V1aR in the mouse neocortex, we questioned whether V1aR knock-out mice would have a measurably atypical neocortex as adults. We focused on parvalbumin interneurons because of their role in experience-dependent plasticity (Hensch, 2005) and their relationship with schizophrenia (Lewis *et al*, 2005) and mouse models of autism (Gogolla *et al*, 2009). We observed that adult V1aR knock-out mice had greater numbers of parvalbumin immunoreactive cells than their wild-type littermates (Hammock and Levitt, 2012). This indicates that transient V1aR signaling during postnatal development affects neocortical developmental outcomes. The mechanisms and the behavioral contributions of these excess interneurons remains to be elucidated.

There is also indirect evidence that developmental exposure to oxytocin leaves a long-term mark on the function of the neocortex. An intriguing and orphan result from the earliest data from the oxytocin knock-out mouse (Ferguson *et al*, 2001) suggests an important organizational role for oxytocin in neocortical neurocircuitry: after introduction to a social stimulus, the primary somatosensory neocortex of adult oxytocin knock-out mice shows exceptionally robust c-Fos immunoreactivity compared with similarly exposed wild-type mice (see panel c in Figure 4). This has remained unexplained because in the adult, when the c-Fos study was performed, there are relatively few oxytocin (or vasopressin) receptors. This suggests that oxytocin may promote the experience-dependent development of the neocortex (see below): the absence of developmental oxytocin signaling through transient neocortical OXTR may lead to atypical or labored processing of multisensory information in the adult neocortex (Figure 4).

Oxytocin modulates signal:noise processing. Neocortical OXTRs appear poised to facilitate signal to noise processing for multi-sensory signals. Oxytocin enhances signal:noise processing in the neocortex and the hippocampus, although through different mechanisms. Oxytocin applied to acute slices made from 3- to 4-week-old mouse medial prefrontal cortex (Ninan, 2011) caused a reduction in post-synaptic excitatory currents (EPSCs) in layer V pyramidal cells at baseline (a reduction in noise), but an increase in glutamate transmission when a 5 Hz stimulus was applied to inputs from layer II/III neurons. The stimulus-evoked long-term potentiation induced by oxytocin required an NMDA receptor-dependent mechanism. More recently, Owen *et al* (2013) showed the same phenomenon of oxytocin enhancing signal:noise processing in the adult mouse hippocampus, although they determined that the effect was through oxytocin modulation of fast spiking GABAergic interneurons, rather than modulation of NMDA currents.

Oxytocin has recently been shown to enhance neocortical experience-dependent plasticity during postnatal mouse

development (Figure 3; Zheng *et al*, 2014). After unisensory deprivation by either whisker trimming from birth, or rearing in total darkness, at postnatal day 14, layer II/III pyramidal neurons in auditory, somatosensory, and visual primary sensory neocortex showed reduced spontaneous firing rates and reduced excitatory synaptic transmission. The prefrontal cortex was not affected under these conditions. To identify potential mediators of this cross-modal plasticity in primary sensory neocortex, Zheng *et al* screened for potential transcript changes between control and sensory deprived mice. Although transcriptomic analysis of the neocortical areas failed to reveal a consistent pattern, transcriptomic analysis of combined hypothalamus and thalamus mRNAs revealed that oxytocin mRNA was consistently downregulated after both kinds of sensory deprivation (whisker trimming and dark rearing). These results were confirmed with qPCR and immunohistochemical analysis clearly demonstrating reduced oxytocin levels in the PVN after developmental sensory deprivation. Sensory deprivation reduced the firing of oxytocinergic cells in the PVN, and resulted in lower detectable oxytocin peptide in S1 and V1 neocortex. This oxytocin detected in the neocortex comes from the hypothalamus and most likely reaches the neocortex through the CSF, and less likely through blood or direct projections: sensory deprivation did not change plasma levels, no direct projections from PVN to S1 neocortex were detected, and injecting an oxytocin sequestering antibody into the ventricles reduced the frequency of miniature excitatory post-synaptic currents (mEPSCs) in the neocortex in non-deprived animals. Oxytocin knock-out mice showed reduced mEPSC frequency like the sensory deprived mice, and exogenous oxytocin in the neocortex increased mEPSC frequency of layer II/III pyramidal cells and rescued the effects of sensory deprivation on cross-modal plasticity. This effect was mediated through OXTR as the OXTR antagonists OTA and atosiban, and siRNA against OXTR, each prevented the ability of exogenous oxytocin to increase mEPSC frequency in layer II/III neurons. In a final experiment, environmental enrichment during postnatal development increased oxytocin mRNA in the PVN and oxytocin protein in S1 and V1 cortex, increased mEPSC frequency in S1 and V1 cortex, and finally, rescued the mEPSC frequency of whisker deprived and dark reared pups to control levels reared in standard housing. Together, these data indicate that sensory experience drives oxytocin activity in the PVN of the hypothalamus, leading to enhanced oxytocin availability at neocortical receptor sites to modulate cross-modal neocortical developmental plasticity. The identification of this novel action of oxytocin in experience-dependent neocortical developmental plasticity is a profound and potentially transformative result.

Gene by Environment Interactions

The data described above point to an organizational role for oxytocin and vasopressin where their early activity during

Figure 3. Oxytocin in the neocortex modulates experience-dependent multisensory plasticity. (a) Representative miniature post-synaptic current (mEPSC) recordings for conditions as indicated from the primary somatosensory cortex (S1), primary visual cortex (V1), and primary auditory cortex (Au1). (b) Whisker-deprivation (WD) significantly reduced mEPSC frequencies in S1. (c) WD significantly reduced mEPSC frequencies in V1. (d) WD significantly reduced mEPSC frequencies in Au1. (e) Illustration of the location of the paraventricular (PVN) and supraoptic (SON) nuclei, both in the mouse hypothalamus, in a coronal brain slice. (f) Representative images of oxytocin-positive neurons in the PVN and SON of P14 mice, conditions as indicated; scale bar = 200 μ m. (g) WD reduced the number of oxytocin-positive neurons in the PVN, but not SON. (h) WD significantly reduced oxytocin peptide level in S1 and V1, but not blood plasma. (i) Oxytocin knockout mice showed reduced mEPSC frequencies in S1. (j) Oxytocin injection increased mEPSC frequencies and rescued the effects of whisker-deprivation in S1. (k) Environmental enrichment (EE) significantly increased oxytocin peptide level in S1 and V1. (l) EE increased mEPSC frequencies and rescued the effects of whisker deprivation in S1. Figure and Figure legend courtesy of Dr Xiang Yu (Zheng *et al*, 2014), copyright Nature Publishing Group. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

developmental sensitive periods may developmentally program later social behavior. Emerging evidence suggests a critical interaction of early environment and oxytocin function in humans. For example, adult women retrospectively reporting childhood abuse have decreased oxytocin in CSF (Heim *et al*, 2009). Both men (Meinlschmidt and Heim, 2007) and women (Riem *et al*, 2013) show altered responses to intranasal oxytocin after a childhood with significant disruptions in the parent-child relationship. Further, peripheral (urine) oxytocin levels were lower after a social encounter in children with early life histories in institutional settings compared with children who were reared in typical home settings (Wisner Fries *et al*, 2005). These data in humans suggest that careful attention to experiences in childhood may help disentangle the true

nature of the influence of oxytocin and vasopressin system genetics in developing and adult behavior. Two main research areas support this assumption: oxytocin system differences during development may alter the methylation of the OXTR gene leading to developmentally programmed levels of adult OXTR function, and recent gene association studies indicate significant gene $\times$ environment interactions. The emerging picture points to experience-dependent organizational effects of oxytocin and vasopressin systems during mammalian development of brain and behavior.

Methylation of OXTR with experience. Methylation of DNA contributes to tissue-specific and dynamic or stimulus-evoked regulation of gene expression. Methylation of the mouse *Oxtr* gene is associated with brain region-specific

Figure 4. Hypothesis in which development shines light on the ‘Dark Matter of Social Neuroscience’, or the unclarified neural mechanisms between social sensory inputs and social behavior outputs (Insel, 2010). (a) During developmental sensitive periods, parental nurturing (Kojima *et al*, 2012; Weisman *et al*, 2012) and/or sensory inputs (Zheng *et al*, 2014) drive the activity of the PVN resulting in increased release of oxytocin. This oxytocin can regulate multi-sensory plasticity in the neocortex. (b) OXTRs are transiently available during experience-dependent developmental sensitive periods (Hammock and Levitt, 2013). Arrows point to layer II/III of neocortex, which has a high density at postnatal day 14, but not postnatal day 21 or later ages. Perhaps this entrains the developing brain to attend to relevant stimuli, which acquire social definitions because of their proximity in time and space to the nurturing caregiver. After such a developmental trajectory, an adult brain is tuned to ascribe social, affect-modulating properties to multisensory information. (c) For example, wild-type mice are tuned to social stimuli and can rapidly resolve sensory input to determine if a mouse is familiar or novel. In contrast, oxytocin knock-out mice are unable to resolve this social sensory information, despite very active neural processing in primary sensory cortex as measured by c-Fos immunoreactivity after a social encounter (Ferguson *et al*, 2001), c-Fos images courtesy of Dr Larry Young, copyright The Society for Neuroscience; hatched box at P21 in ‘b’ indicates cortical barrel fields measured in young adult (>P50) mice in panel (c). Thus, developmentally transient experience-dependent neocortical oxytocin signals may allow social support (ie, maternal contact) to fine tune the function of the entire neocortex during a developmental sensitive period for social contact. This layer II/III positioning makes OXTR a promising modulator of multi-sensory integration across modalities by changing the window of opportunity in which separate neural signals could be bound into one unified percept. Developmental modulation in this way by other classic neuroendocrine modulators (eg, CRF, vasopressin) during various sensitive periods may have a significant role in the species-typical development of the brain.

expression levels of *Oxtr* mRNA (Mamrut *et al*, 2013; Harony-Nicolas *et al*, 2014) and is dynamically regulated in the uterine myometrium and mammary tissue at parturition and lactation (Mamrut *et al*, 2013) and in the brain after drug exposure in adulthood (Aguilar-Valles *et al*, 2013). There is significant associative evidence that methylation of the human *OXTR* gene may also contribute to developmental and dynamic regulation of *OXTR* gene expression (reviewed in Kumsta *et al*, 2013). Methylation of the third intron of the human *OXTR* was associated with repressive binding proteins from non-expressing peripheral blood leukocytes, while relative hypomethylation of this region was associated with myometrium from non-pregnant and term pregnancy (Mizumoto *et al*, 1997). Kim *et al* (2013) assessed some methyl sites in the 5' UTR of the *OXTR* in term, pre-term labored and term unlabored amnion. Methylation of the human *OXTR* gene predominantly at a site called MT2 contributes to tissue-specific repression of *OXTR* mRNA expression, *in vitro* (Kusui *et al*, 2001) and is associated with *OXTR* mRNA repression in human brain (Gregory *et al*, 2009).

Gregory *et al* (2009) showed increased methylation in the MT2 region of *OXTR* in blood cells in 20 individuals with autism compared with 20 matched controls. Further, a similar pattern of methylation was observed in DNA from

temporal cortex from 10 individuals with autism compared with matched controls, and the increased methylation was associated with reduced *OXTR* expression in temporal cortex. In addition to an association between methylation and *OXTR* expression levels, *OXTR* methylation has also been associated with brain activity during an fMRI task. *OXTR* methylation at site –934 in whole blood has been associated with increased fMRI BOLD signal in the left superior temporal gyrus/supramarginal gyrus and right dorsal anterior cingulate cortex during a task that involved perception of ‘animacy’ and the ability to attribute mental states to geometric shapes (Jack *et al*, 2012).

The methylation status of the *OXTR* gene has also been explored in conduct disorder (Dadds *et al*, 2014), a developmental antecedent to psychopathic traits in adulthood. Significantly higher methylation status of *OXTR* was observed in older children aged 9–16 years with comorbid callous-unemotional traits compared with the same age individuals with low callous-unemotional traits. No methylation differences related to callous-unemotional traits were observed in younger children aged 3–8 years. Further, the older children with high levels of callous-unemotional traits also had lower peripheral levels of oxytocin in plasma.

In addition to methylation, *Oxtr* is also regulated by estrogen receptors, and methylation of that gene. Licking

and grooming of rodent pups is a strong signal of high-quality care with long-term positive developmental effects (Francis *et al*, 1999). Adult rodents who received low levels of licking and grooming in the neonatal period have reduced OXTR levels in the medial preoptic area (MPOA) and show low levels of licking and grooming to their own offspring (Champagne *et al*, 2001). Estrogen receptor alpha regulates the levels of OXTR in the MPOA (Young *et al*, 1998), and is itself methylated and repressed after an early history of low levels of licking and grooming (Champagne *et al*, 2003, 2006). The low levels of ER alpha in the MPOA of these offspring make them less responsive to the effects of estrogen and less able to increase the necessary complement of OXTR in the MPOA to facilitate high levels of maternal licking grooming. This represents a neural mechanism of the transgenerational effects of low levels of maternal-infant interaction, with a sensitive period between postnatal days 6 and 10 in rats (Pena *et al*, 2013). This developmental time window in rodents translates to the perinatal period in human neonates (Clancy *et al*, 2007). These effects are not immutable, however, a socially enriched peri-adolescent environment can rescue the low levels of OXTR in the MPOA in individual rats who did not have much licking and grooming as neonates as well as promote the transmission of high levels of licking and grooming to the next generation (Champagne and Meaney, 2007).

Interaction between OXTR genotype and early social experience. OXTR genotype interacts with early adversity to increase risk for depression and social anxiety in female adolescents (Thompson *et al*, 2011), and depression in a population of college students (Mcquaid *et al*, 2013). Intranasal oxytocin has 'prosocial' effects in women who had more nurturing childhoods, suggesting important individual differences in the activity of the OXT system during experience-dependent refinement of neural circuits.

Recently, Feldman *et al* (2013) tracked first time parents and their infants from 1 month to 3 years of age and measured the relationship between parental oxytocin-related genes, maternal care, and infant salivary oxytocin. They report that infant salivary oxytocin at 3 years is related to maternal care and maternal oxytocin genotypes. In a separate study (Apter-Levy *et al*, 2013), maternal depression was linked with overall lower oxytocin measures in saliva among mothers, fathers, and their 6-year-old children. Further, variation in the OXTR rs2254298 (GG genotype) was more prevalent in the depressed mothers and significantly predicted the low oxytocin concentrations in the saliva. Children of depressed mothers were more likely to have a behavioral disorder such as anxiety or conduct disorder and had lower empathy and social engagement scores. These findings underscore the importance of gene by environment interaction models in gene association studies for genes that may be involved in experience-dependent developmental plasticity.

Future Research Directions

What are the unanswered questions? The available evidence is consistent with the hypothesis that oxytocin and vasopressin contribute to experience-dependent development. There are numerous unanswered questions about the specific mechanisms of this special developmental plasticity. At this stage, we could potentially distill our working models of oxytocin and vasopressin in to very simple approach/avoid models: does oxytocin increase the ability to orient/make social contact in the neonatal period, and increase the encoding of the environment? Does vasopressin decrease the ability to orient/make social contact in the neonatal period and decrease encoding of the environment? Through this lens, oxytocin may facilitate the internalization of stimuli in the environment (both nurturing/appropriate and toxic/inappropriate environments), while vasopressin may block the internalization of the external social environment. These predictions must be vetted with direct experiments in which environment is precisely controlled.

Oxytocin and vasopressin can act at synapses as classical neurotransmitters through synaptic release, and also as hormones, by bolus release and diffusion through the extracellular space after dendritic release or by perfusion through direct release into the CSF (reviewed in Landgraf and Neumann, 2004; Neumann, 2007; Stoop, 2012). We do not yet know if in infancy oxytocin and vasopressin have more of a hormonal role (bathing the tissue through CSF and extracellular space) or by modulation of synapses from direct projections of oxytocin and vasopressin cells. Also, we do not know if constant contact or perhaps transitions between social contexts are more potent releasers of oxytocin and vasopressin. In infants, we do not know if the amplitude, frequency, or both of oxytocin and vasopressin release convey environmental signals. The rhythm of secretion of hypothalamic hormones is physiologically significant in adults (reviewed in Gan and Quinton, 2010). Oxytocin is released with parturition, lactation, and chronic dehydration in the adult. This oxytocin results in a reduction in glia around oxytocin cells in the SON and PVN, which places oxytocin neurons in close juxtaposition with each other (Theodosis *et al*, 1986). This contributes to the pulsatility of release, which is a critical aspect of the efficacy of oxytocin in milk ejection, for example. Oxytocin measured in blood in 1-day-old human infants points to pulsatile release (Marchini and Stock, 1996). The pattern of release and the mechanisms that contribute to pattern generation are important future research targets.

Oxytocin and vasopressin systems interact in adult animals (reviewed in Neumann and Landgraf, 2012). As described above, the available data suggest that in very young animals, oxytocin may facilitate social orienting, while vasopressin may inhibit social orienting. These opposing actions are reminiscent of the opposing aspects of oxytocin and vasopressin function on emotional behavior in adult animals. However, in contrast to opposing actions on social orienting in neonates, oxytocin and vasopressin

often, but not always, regulate social behavior in the same direction in adults. The significance of potential developmental interaction of oxytocin and vasopressin tone remains to be fully explored.

What are the behavioral or perceptual implications of oxytocin modulating early postnatal excitatory activity in the neocortex? Is this a potential mechanism of neocortical hypoactivity or delayed maturation observed by EEG in Romanian orphans after extreme social and sensory neglect (Marshall *et al*, 2004) or children at psychosocial risk for cognitive disability (Otero *et al*, 2003)? Does more oxytocin activation of the neocortex in the context of a rich social and sensory environment improve early perceptual skills? Newer gene association studies have identified sensory processing relationships with *OXTR* genotype in adults, including decoding speech in a noisy environment (Tops *et al*, 2011), sensitivity to infant cues (Bakermans-Kranenburg and Van Ijzendoorn, 2008), and facial emotion processing (O'connell *et al*, 2012; Melchers *et al*, 2013). As described above, perception of 'animacy' was also recently associated with *OXTR* methylation status (Jack *et al*, 2012). These gene association data cannot differentiate between an organizing role for *OXTR* genotype in the developing sensory neocortex (Figures 3 and 4), or an activational role in adult sensory cortex. In light of the model of oxytocin-dependent neocortical development, we would predict an organizational role for the individual differences in *OXTR* genetics. For example, we would predict that infant T carriers of the rs2268498 SNP and GG carriers of the rs53576 single-nucleotide polymorphism would have more robust sensory encoding in layers II/III of neocortex during a postnatal developmental sensitive period. In combination with an enriched social-sensory developmental environment, this enhanced developmental expression of neocortical *OXTR* should lead to enhanced social expertise in adulthood because of more facile neural computation of sensory input as adults (Figure 4). Atypical neocortical multisensory processing is a proposed etiological factor in autism, indicating that this mechanism may help explain some of the gene association studies implicating *OXTR* in autism (Wu *et al*, 2005; Jacob *et al*, 2007; Israel *et al*, 2008; Lerer *et al*, 2008; Liu *et al*, 2010; Campbell *et al*, 2011), and also that it may be difficult to detect the effect of *OXTR* alleles on autism risk (Tansey *et al*, 2010) without controlling for social and sensory environment in early life. As sensory systems are exceptionally tractable experimental targets in human neuroscience research, exploring the interaction between oxytocin and neocortical function should be a highly informative research area in the near term. For example, some individuals with autism show atypical multisensory integration in psychophysical tasks like the flash-beep illusion (Foss-Feig *et al*, 2010; Stevenson *et al*, 2014), which involves combining visual and auditory cues into a single percept. Will intranasal delivery of oxytocin narrow the window of sensory integration in these individuals, but perhaps only at younger ages when neocortical *OXTR* levels are highest? Perhaps oxytocin

permits developmental 'binding' of sensory information into a single unified perceptual whole.

What general direction is the field heading? In the next 10 years, we should have a clearer picture of how oxytocin and vasopressin relate to social support in development, and the risks and/or benefits of early exogenous exposure to these neuropeptides. The work of Zheng *et al*, although serendipitous in their discovery of a novel role for oxytocin in the neocortex, will open some exciting doors in helping to unravel mysteries in oxytocin and vasopressin contributions to development. We do not yet know how sensory experience, like whisker deprivation or total darkness, could directly reduce the production and release of oxytocin in the hypothalamus. An alternative explanation is that maternal factors rather than sensory deprivation *per se* mediate the enhanced oxytocin seen very early: it is possible that sensory deprived pups elicit lower maternal contact than intact pups. Further, an enriched environment may induce more maternal contact and thus more oxytocin activity, as a deprived environment disturbs maternal care in mice (Rice *et al*, 2008). Maternal care was not directly measured and although the effects of whisker deprivation were obtained in litters with whisker-deprived and intact control littermates, suggesting that maternal care toward the litter may not have a role, it is possible that dams show differential provisioning of care (eg, Cavigelli *et al*, 2010) to injured *vs* intact neonates. A lack of change in maternal care toward deprived pups will be needed to confirm this very exciting hypothesis that sensory inputs directly modulate oxytocin release from the PVN during experience-dependent development.

Social neuroscience has grown markedly in the past decade, and foundational research in behavioral neuroendocrinology, neuroethology, and sensory neuroscience have led the way to uncover brain mechanisms of social stimulus perception and social behavior action (Insel, 2010). The 'dark matter of social neuroscience' (Insel, 2010) is the gray area between perception and action, and is represented in a question like 'how does the adult brain identify a stimulus as 'social' so that it may act upon it?' This is both a mechanistic and a developmental question (Denenberg *et al*, 1964; Rosenblatt, 1983): early unconditioned stimuli in the environment such as maternal odor become paired with multisensory stimuli, which then acquire reinforcing properties. To many, it may come as a shock to see an effect of whisker trimming or dark rearing on a 'social neuropeptide' system like oxytocin—why does a non-social intervention like whisker trimming or total darkness reduce oxytocin content? Given the rather robust effects on oxytocin in these studies, why aren't there obvious effects of intranasal oxytocin on vision or somatosensation in the human studies? I would argue that the effects of oxytocin on the neocortex are limited to early development and that they are part of the neural mechanism of mammalian social imprinting. The ability of experience to yield high levels of oxytocin in the neocortex appears time delimited: neocortical oxytocin levels were high at P7 and P14, but reached low adult levels by

typical weaning age of P21, and further, robust receptor availability in the neocortex is limited to the pre-weaning period. These results are from developing animals—animals that are still acquiring their experience-dependent definitions of what is and what is not social. Ethologically, for altricial and helpless infants, everything in infancy is social: smells, touches, temperatures—there is nowhere the infant can go or exist on their own outside of a social context. Developmental comparisons of neuroendocrine systems in precocial *vs* altricial species should be particularly informative. In mice, this developmental period is when they are learning what it means to be a mouse (Denenberg *et al*, 1964). If any kind of sensory input at this age can drive oxytocin function, then it is going to be refined and entrained to be a very easy neural computation and perhaps a releaser of oxytocin later in life—the smell of the mother, the feel of her fur, her body temperature, her posture, the way she grooms herself and others, etc—these are the multisensory subtleties that mice should process quickly after such developmental experience is encoded in the brain. The recent exciting findings by Zheng *et al* provide a potential neurodevelopmental substrate to marry neuroendocrinological and sensory neuroscience approaches through an integration of hypothalamic and neocortical function around sensory experience. These findings shed light on ‘the dark matter of social neuroscience’ (Insel, 2010), by demonstrating oxytocin effects on sensory processing capacity in the developing neocortex (Figure 4).

What will the next big trends or discoveries be and what techniques will need to be developed or implemented to address these questions? Rapid progress continues in all areas of social neuroscience at many levels of analysis. Well designed and precisely controlled behavioral, pharmacological, and optogenetic studies in developing animals will help to further our mechanistic understanding of oxytocin and vasopressin in experience-dependent developmental plasticity. Intranasal drug delivery and gene association studies in humans that take special care to include early life history variables (eg, childhood maltreatment, maternal depression) will be an interesting and likely productive research effort (Tabak, 2013). Ongoing clinical trials will do well to include life history variables, environmental context, and consider the potential contribution of individual differences in the genetics of these signaling pathways. As a result of the limitations of human research, we could use better biomarkers and a clear picture of the distribution of OXTR and V1aR in human tissue via the development of selective PET ligands (Smith *et al*, 2012), and endophenotype approaches to gene–brain–behavior relationships (Haas *et al*, 2013).

Clinical Implications

The clinical implications of the developmental roles for oxytocin and vasopressin are weighty. As oxytocin and vasopressin systems contribute to different aspects of brain physiology in different species thus having a role in species-

typical social behaviors (Goodson, 2013), it is important to sample from a wide variety of animal systems to get a broad picture of both the potential and limitations of these systems in humans. The ability to translate appropriately across species and developmental time points becomes imperative as the enthusiasm grows for intranasal oxytocin and vasopressin therapies in various developmental disabilities and mental illness (Guastella *et al*, 2009, 2010; Andari *et al*, 2010; Feifel *et al*, 2010; Goldman *et al*, 2011; Pedersen *et al*, 2011; Simeon *et al*, 2011; Hall *et al*, 2012). In addition to gathering data from a wide variety of species, it will be important to understand the behavioral context in which oxytocin and vasopressin function. For example, if, in addition to enhancing social orienting, oxytocin facilitates developmental encoding of the environment, then oxytocin given to a child while in a toxic environment could potentially exacerbate the negative effects of that toxic environment.

Summary

Oxytocin and vasopressin contribute to the brain basis of social behavior. They influence brain and behavior development, yet more mechanistic research is needed in the area of the developmental contributions of these two neuropeptides.

CONCLUSIONS

The past decade has seen a robust and enthusiastic translation of neuropeptide research in animal models into human social behavior. As we move into the next era, we should see rapid gains in our understanding of the mechanisms of the roles of oxytocin and vasopressin in the experience-dependent development of the social brain. This is an exciting time.

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