Toward a neuroscience of parenting : adult attachment and oxytocin affect neural and behavioral responses to infant attachment signals

Hendricx - Riem, M.M.E.

Author: Hendricx-Riem, Madelon
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1 Introduction

As infants are fully dependent on their parents, correct perception and interpretation of infant signals is crucial for infant survival. It is therefore not surprising that specific brain circuits and neuroendocrine processes have evolved to perceive infant signals correctly and to respond adequately. However, parents vary in their ability to respond to their infants in a sensitive way and several factors may be involved in parental sensitive responsiveness. One important factor influencing parenting behavior is the neuropeptide oxytocin. Of all the hormones involved in parenting and other social behaviors, oxytocin has received the most interest, as evidenced by the high number of scientific studies over the past decade (Bos, Panksepp, Bluthé, & Honk, 2012; Van IJzendoorn & Bakermans-Kranenburg, 2012). Many studies suggest that oxytocin is related to sensitive parenting (Bakermans-Kranenburg & Van IJzendoorn, 2008; Feldman, Gordon, Schneiderman, Weisman, & Zagoory-Sharon, 2010; Feldman, Weller, Zagoory-Sharon, & Levine, 2007), although the exact mechanism underlying this positive association is not entirely clear yet. Another factor that influences parenting behavior is adult state of mind with respect to attachment (Van IJzendoorn, 1995). In the current dissertation, the role of oxytocin and adult attachment in parenting is examined with a series of functional magnetic resonance imaging experiments.

Oxytocin: a neuroendocrine basis of social affiliation

The neuropeptide oxytocin is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus and is released from the posterior pituitary into the bloodstream, for example in response to sexual stimulation, uterine dilatation, and nursing (Insel, 2010). It is crucially involved in the initiation of maternal care, attachment formation and several other forms of social behavior in rodents (Carter, 1998). The popularity of oxytocin, which is often labeled 'the love hormone', has increased exponentially the past decade, and so has the number of scientific studies investigating oxytocin's role in social cognition and behavior (Van IJzendoorn & Bakermans-Kranenburg, 2012). Correlational studies have shown that endogenous oxytocin is positively related to social behaviors, including human trustworthiness (Zak, Kurzban, & Matzner, 2005) and generosity in an ultimatum game (Barraza & Zak, 2009). Other studies found that intranasal administration of oxytocin stimulates a range of social behaviors (Graustella & MacLeod, 2012). It enhances trust (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005), empathy (Bartz et al., 2010), emotion understanding (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007), cooperative behaviors (Rilling et al., 2012), and the familiarity of faces (Rimmele, Hediger, Heinrichs, & Klaver, 2009).

Recent research suggests that oxytocin also plays a role in parenting behaviors (Galbally, Lewis, Van IJzendoorn, & Permezel, 2011). Bakermans-Kranenburg and

Van IJzendoorn (2008) found that mothers with the presumably more efficient variant (GG) of the oxytonergic system gene (OXTR) showed higher levels of sensitive responsiveness, defined as the ability to accurately perceive children's signals and to respond in an adequate and prompt way (Ainsworth, Blehar, Waters, & Wall, 1978). In addition, Feldman, Weller, Zagoory-Sharon, and Levine (2007) showed that oxytocin levels across pregnancy and the postpartum period predict maternal behavior and the emotional bond with the infant. Moreover, oxytocin levels in fathers have been found to increase after stimulatory contact with their infant (Feldman et al., 2010), indicating that oxytocin is not only important for maternal behavior but also for fathering. However, these studies were correlational and do not provide evidence for a causal role of oxytocin in human parenting. The study by Naber, Van IJzendoorn, Deschamps, Van Engeland, and Bakermans-Kranenburg (2010) was one of the first experiments to investigate the role of oxytocin in parenting. Naber et al. found that intranasal oxytocin administration leads to more responsive interactions of fathers with their child during play, thus providing experimental evidence for a causal role of oxytocin in elevating the level of paternal responsiveness.

Although many studies show that oxytocin plays an important role in parenting, it is not yet clear *how* oxytocin influences parenting behaviors. One way in which oxytocin might influence parenting behaviors is by affecting the perception of infant signals. Infant crying is one of the most salient attachment signals. It enhances infant survival by eliciting parental proximity and care and by conveying information on the health condition of the child (Bowlby, 1969/82; Soltis, 2004). It has been described as a graded signal that changes as a function of the level of distress of the infant (Gustafson, Wood, & Green, 2000). For example, infants who are in pain cry at higher fundamental frequencies than infants who are hungry (Soltis, 2004). Parents are sensitive to the acoustics of crying and use this information in combination with contextual clues to select an adequate caregiving response. On the other hand, crying also elicits negative emotions such as aversion and anger (Dix, 1991; Dix, Gershoff, Meunier, & Miller, 2004) and excessive infant crying can even trigger child abuse and neglect (Soltis, 2004). In the Netherlands, six months after the infant's birth nearly 6% of the parents report that they have shaken, smothered, or slapped their infant in order to stop the crying (Reijneveld, Van der Wal, Brugman, Sing, & Verloove-Vanhorick, 2004). Because excessive infant crying has been found to be one of the major triggers of child abuse and neglect, examining the mechanisms that are involved in reactions of adults to infant crying is crucial. Individual differences in oxytocin levels may explain why some parents remain sensitive whereas other parents lack the empathic ability to abstain from harsh or even abusive responses their infant's crying.

Oxytocin might also influence parenting behaviors by affecting the perception and processing of happy infant signals such as infant laughter. Laughter is suggested to be the outcome of a long evolutionary history (Van Hooff, 1972), and its production as well as perception might be hardwired in human beings (Owren & Bachorowski, 2003). Infant smiling and laughing are basic attachment behaviors that create closer proximity to a caregiver, thereby enhancing infant survival (Bowlby, 1969/82; Sroufe & Waters, 1976). Infant laughter is a uniquely rewarding experience for parents and it activates neural reward centers in the parental brain (Kringelbach et al., 2008; Strathearn, Li, Fonagy, & Montague, 2008). However, not all parents may perceive their laughing or smiling infant as a reward. Mothers with a postpartum depression are less responsive to their infants, show less positive affect and are less accurate in identifying happy infant stimuli (Arteche et al., 2011; Reck et al., 2004), possibly because of the malfunctioning of reward centers in the brain (Moses-Kolko et al., 2011). Low oxytocin levels may be involved in the reduced rewarding value of infant stimuli in depressed mothers, as oxytocin may link social cues, such as infant laughter, with dopaminergic brain regions involved in reward processing (Strathearn, Fonagy, Amico, & Montague, 2009).

Some neuro-imaging studies suggest that oxytocin might sensitize caregivers to infant crying and laughter by modulating neural circuits related to the perception of infant signals. For example, mothers who experienced childbirth by vaginal delivery showed a unique pattern of neural responses to their own infant's crying sounds as compared to mothers who had a cesarean section delivery (Swain et al., 2008). The difference in brain responses to crying between mothers who gave birth through vaginal delivery and cesarean section may be explained by the increase in oxytocin release that occurs after vaginal delivery but not after cesarean section. Furthermore, Bos, Hermans, Montoya, Ramsey, and Van Honk (2010) found that testosterone administration increased activation in the thalamocingulate region, insula, and the cerebellum in response to crying, possibly by influencing the oxytocin system. However, the exact influence of oxytocin on neural responding to infant signals is still unknown. In Chapter 2 and 3, we try to shed more light on this topic by investigating the effects of intranasal oxytocin administration on neural responses to infant crying and laughter, measured with functional Magnetic Resonance Imaging (fMRI). These chapters aim to provide more insight into the mechanism underlying the positive effects of oxytocin on parenting.

Adult attachment: predictor of responses to infant crying

Adult attachment has been shown to be another important factor influencing sensitive responsiveness to infant crying. Adult attachment reflects the current state of mind with respect to attachment and refers to the mental representation of past and present attachment experiences. The Adult Attachment Interview (AAI) is considered the "gold standard" for the measurement of adult attachment (George, Kaplan, & Main, 1985; Hesse, 2008; Main & Goldwyn, 1984). It is an hour-long interview in which participants are asked about their childhood attachment experiences with their parents and how they think they were affected by these experiences (Hesse, 2008; Main & Goldwyn, 1984). Coding of the AAI yield three major attachment classifications: Secure-Autonomous, Insecure-Dismissing, and Insecure-Preoccupied. Individuals who are classified as secure-autonomous value attachment relationships, describe their attachment experiences (whether positive or negative) coherently, and consider them influential in their personality development. Adults classified as insecure-dismissing, however, are uncomfortable with the topic of the interview. They idealize their childhood experiences or tend to minimize the importance of attachment in their own lives. Adults with a preoccupied classification show active anger towards attachment figures and tend to emphasize the influence of their attachment experiences.

Research has shown that adult attachment influences parental responding to infant crying. Secure parents are suggested to be able to respond adequately to their crying infants since they are free of distorted perceptions of their infants' needs (Ainsworth et al., 1978). Insecure parents, on the other hand, are less accurate at identifying infant emotions and tend to make negative, internal attributions to the nature of the crying (e.g., the child is spoiled or has a difficult temperament) (Leerkes & Siepak, 2006). In addition, an fMRI study showed that insecure mothers show increased activation in a brain region associated with feelings of unfairness and disgust while looking at pictures of their own infant's sad face, whereas secure mothers showed activation of reward areas (Strathearn et al., 2009). Thus, insecure parents seem to perceive attachment-related information in a defensive and negatively biased manner. This kind of information processing contributes to insensitive parental caregiving, which can in turn result in insecure infant attachment (Dykas & Cassidy, 2011). It is therefore of great importance to understand the mechanism underlying the negative perception of infant signals in individuals with insecure attachment representations. Chapter 4 sheds more light on this mechanism by focusing on neural, emotional and behavioral responding to infant crying in adults with different attachment representations.

Oxytocin: context and person matter

Many studies on the beneficial effects of oxytocin on social cognition and behavior have been published over the past ten years (for review see Graustella & Macleod, 2012; Van IJzendoorn & Bakermans-Kranenburg, 2012). However, recent research indicates that the effects of oxytocin are more nuanced than previously thought (Bartz, Zaki, Bolger, & Ochsner, 2011). Contextual factors and individual differences seem to moderate the effects of oxytocin on social cognition. For example, the trust-enhancing effects of oxytocin disappear when partners are unknown or believed to be unreliable (Declerck, Boone, & Kiyonari, 2010; Mikolajczak et al., 2010). In a series of experimental studies De Dreu et al. (2010) showed that oxytocin can even have negative effects on social behavior. Intranasal oxytocin enhanced in-group altruism, but at the same time increased defensive reactions toward out-group members, indicating that oxytocin may drive a 'tend and defend' response. Social context may thus be crucial in shaping the effects of oxytocin on social cognition. It is currently unknown whether and how context may modulate the effects of oxytocin on parental behaviors. Chapter 5 addresses this issue by focusing on the effects of contextual factors on the influence of oxytocin on neural responding to infant crying.

In addition to contextual factors, individual differences may also be involved in shaping the effects of oxytocin on social behaviors. For example, Bakermans-Kranenburg, Van IJzendoorn, Riem, Tops, and Alink (2012) found that intranasal oxytocin decreased the use of excessive handgrip force in response to infant crying, but only in individuals who did not experience harsh discipline. Similarly, Van

IJzendoorn, Huffmeijer, Alink, Bakermans-Kranenburg, and Tops (2011) found that intranasal oxytocin administration enhanced donating to a charity, but only in individuals who had experienced low levels of love withdrawal, a parental strategy that involves withholding love and affection when a child misbehaves or fails at a task. These findings indicate that unfavorable caregiving experiences moderate the beneficial effects of oxytocin. In Chapter 6 we investigate the effects of intranasal oxytocin on prosocial helping behavior toward an excluded person during a virtual ball-tossing game called Cyberball (Williams & Jarvis, 2006), taking into account experiences of maternal love withdrawal as a potential moderator. Cyberball has been used in many studies to examine the effects of being excluded (Crowley, Wu, Molfese, & Mayes, 2010; Gonsalkorale & Williams, 2007; Harmon-Jones, Peterson, & Harris, 2009; Zadro, Williams, & Richardson, 2004). So far, few studies investigated the way individuals respond when they observe someone else being excluded.

An important research tool that can be used to study the influence of individual differences on the effects of oxytocin is resting state fMRI. The brain consumes about 20% of the body's energy during rest, partly because of spontaneous neuronal activity (Fox & Raichle, 2007). This resting-state energy consumption is very high when compared with task-related increases in neuronal metabolism (<5%), suggesting that intrinsic activity is far more important than evoked activity in terms of overall brain function (Raichle, 2009). Although spontaneous neuronal activity consumes a high amount of the brain's energy, these spontaneous fluctuations have been viewed as noise for many years. This view changed when studies found that spontaneous blood oxygenation level dependent (BOLD) fluctuations are not random noise, but specifically organized in the resting human brain (Biswal et al., 2010). Smith et al. (2009) found that regions that are functionally related tend to be highly correlated in their spontaneous BOLD activity during rest. The degree of correlation has been shown to predict behavioral outcomes (Vincent et al., 2006) and is related to clinical conditions (Greicius, 2008), such as dementia (Hafkemeijer, van der Grond, & Rombouts, 2011), depression (Veer et al., 2010), schizophrenia (Zhou et al., 2007) and autism (Cherkassky, Kana, Keller, & Just, 2006).

Interestingly, it has been shown that drugs produce specific and detectable changes in these resting state networks (Khalili-Mahani et al., 2012; Tanabe et al., 2011). This indicates that resting state fMRI could be useful for "finger-printing" different pharmacological agents within the same individual's brain (Khalili-Mahani et al., 2012) as well as for studying differential pharmacological effects (e.g., effects of oxytocin administration) in individuals with different backgrounds. Little research has been conducted on the effects of pharmacological treatments on brain function and connectivity. Moreover, it is unknown how unfavorable caregiving experiences influence the effects of intranasal oxytocin on resting state at the neural level. This is investigated in Chapter 7, which focuses on the effects of intranasal oxytocin administration on functional brain connectivity during rest, taking into account experiences of maternal love withdrawal as a potential moderator. Examining the effects of oxytocin on brain connectivity during rest is especially interesting because it provides more insight into the influence of oxytocin on the baseline state of the brain, in the absence of stimuli or any social context.

Focus and outline of the present thesis
The general aim of the current thesis is to gain more insight into the associations between oxytocin, adult attachment and parenting behaviors, and into the role of context and family background in shaping oxytocin effects. The thesis presents a series of functional magnetic resonance imaging studies that shed more light on the effects of intranasal oxytocin administration on brain activation and connectivity. The studies presented in Chapter 2, 3, 4, and 7 are based on a sample of female twin pairs (aged 22-49 years) without children of their own. The studies presented in Chapter 5 and 6 are based on a different sample of women (aged 18-27 years), again without children of their own. Women without children of their own were selected for participation in these studies in order to reduce hormonal influences associated with differences in parental experience and between men and women, because of the lack of studies investigating oxytocin effects in women (Bos et al., 2012), and because it is especially maternal behavior that affects child developmental outcomes (Cabrera, Fagan, Wight, & Schadler, 2011).

Figure 1 presents a graphic representation of the topics of the current dissertation. In the first part of the thesis we aim to clarify the mechanism underlying the positive association between oxytocin and parenting. More specifically, we examine the effects of intranasal oxytocin administration on

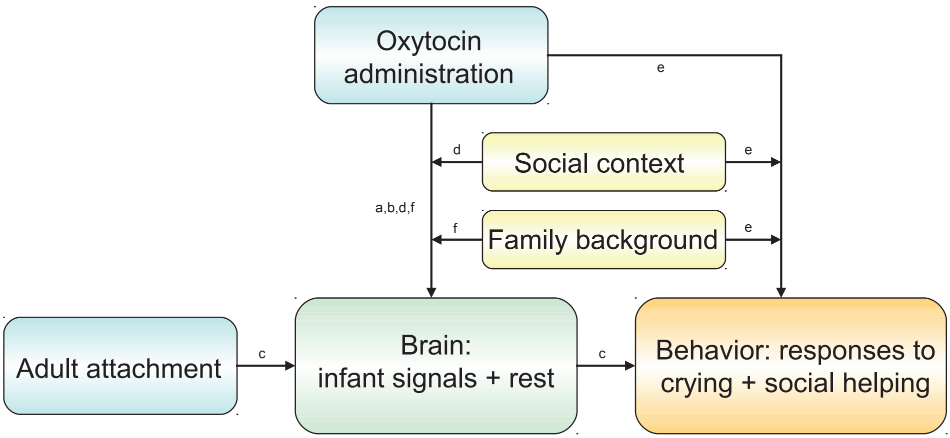

Figure 1. Graphic representation of the topics of the current dissertation. In Chapter 2 and 3 we examine the influence of oxytocin on brain responses to infant crying (a) and laughter (b). In Chapter 4, a study about the influence of adult attachment representation on neural, emotional and behavioral responding to infant crying is presented (c). Chapter 5 focuses on the influence of social context on the effects of oxytocin on brain responses to infant crying (d). In Chapter 6 and 7 we examine oxytocin effects on social helping behavior to an excluded known person with a sad or neutral facial expression (e) and on brain connectivity during rest (f), taking into account family background as a potential moderating factor.

neural responses to infant crying (Chapter 2, a in Figure 1) and laughter (Chapter 3, b in Figure 1) with a randomized controlled trial with female twin pairs. Chapter 4 addresses the influence of adult attachment, measured with the Adult Attachment Interview, on neural, emotional and behavioral responses to infant crying (c in Figure 1). In Chapter 5, 6 and 7 we aim to gain more insight into the influence of contextual factors and individual differences on the effects of oxytocin on parenting and social behavior. Chapter 5 focuses on the influence of intranasally administered oxytocin on the perception of infant crying in systematically varied contexts (d in Figure 1). We examine differential effects of oxytocin on neural responding to crying that was indicated as coming from a sick infant and crying coming from a bored infant. Chapter 6 presents a randomized-controlled trial which investigates the effects of oxytocin administration on prosocial behavior during Cyberball (e in Figure 1). Effects of intranasal oxytocin administration on prosocial helping behavior toward an excluded known person with a neutral or a sad facial expression were examined, taking into account experiences of love withdrawal as a potential moderator. Chapter 7 focuses on the influence of harsh caregiving experiences on the effects of intranasal oxytocin at the neural level (f in Figure 1). Resting state fMRI was used to explore the effects of oxytocin on functional brain connectivity in a 'task-free' setting, again taking into account experiences of love withdrawal as a potential moderator. In the concluding chapter, the findings of the studies are discussed and implications for future research are presented. Lastly, the appendix presents a study in which we investigated the role of oxytocin in parenting from a different point of view, namely by examining the influence of OXTR genotype as well as depressive symptoms on heart rate responses to infant crying.