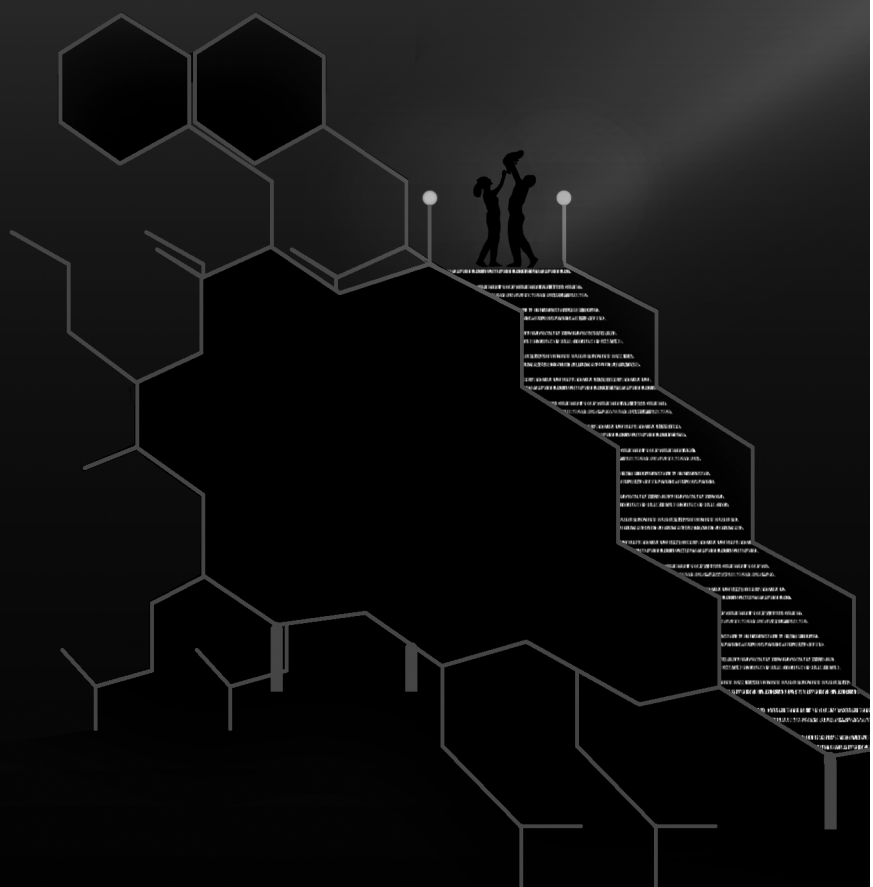
Perception of infant cues :the role of childhood experiences and oxytocin

Bhandari, R.

6

General Discussion



In the studies presented in this thesis we showed that childhood experiences of emotional maltreatment affect the processing of emotional and temperamental infant cues. Moreover, we found evidence for the involvement of the oxytonergic system in the association between early life emotional adversities and behavioral responses to infant stimuli. As described in Chapter 2, we found that emotional maltreatment (via endogenous oxytocin levels) was related to perceived positivity in happy infant faces. More emotional maltreatment experiences were associated with higher salivary oxytocin levels, which in turn were related to a more positive perception of the mood of happy infant faces. Furthermore, we found an association between experienced love withdrawal and perception of negativity in infant crying (Chapter 5). Fewer experiences of love withdrawal were associated with a less negative perception of infant crying, but this effect was most pronounced in individuals with high scores on temperamental orienting sensitivity. In Chapter 3 we presented a validation of the Baby Social Reward Task and we showed that experimentally manipulated infant mood information affected the perceived cuteness and the motivation to view these same infant faces with neutral expressions. Happy infants were rated as more cute, and participants expended more effort to view these infants after receiving the mood information, whereas they expended less effort to view sad infants. In Chapter 4 we reported our findings showing that intranasal oxytocin administration decreased the memory for infant mood information, making the happy and sad infants to be perceived more similar, however, this effect was present only for the group with more experiences of emotional maltreatment.

Childhood experiences and the oxytonergic system

Both early life stressful experiences and the oxytonergic system shape some common neural sites. For example, both of these have been shown to affect structural and functional properties of various brain regions such as amygdala (Inoue *et al*, 2010; Riem *et al*, 2011; Van Harmelen *et al*, 2012). In Chapter 5 we reported that participants with experiences of maternal disciplining strategy of love withdrawal rated infant crying as more negative. These results are in line with previous studies showing that experiencing childhood emotional maltreatment is associated with altered neural development, such as reduced prefrontal cortex volumes and enhanced amygdala and neural activation while viewing emotional faces (Huffmeijer *et al*, 2011; Van Harmelen *et al*, 2012; Van Harmelen *et al*, 2010b) as compared to typically developing individuals, which might possibly explain the behavioral differences seen in our studies. With regard to the contribution of oxytocin, in Chapter 2 we reported that higher oxytocin levels were associated with a more positive evaluation of the mood of a happy infant. These findings

corroborate studies showing that oxytocin is released in brain sites responsible for emotion processing, such as the nucleus accumbens, the amygdala, the septum and the bed nucleus of the stria terminalis, which all have high densities of oxytocin receptors (Gimpl and Fahrenholz, 2001). Moreover, these effects of oxytocin on emotion processing are thought to be brought about by decreased amygdala activation while viewing or listening to emotional stimuli such as facial cues or infant crying (Baumgartner *et al*, 2008; Kirsch *et al*, 2005; Riem *et al*, 2011). While experience of maltreatment has been associated with increased amygdala activity in response to emotional information, in individuals with higher oxytocin levels oxytocin might exert its anxiolytic effects and thereby decrease the over-arousal by dampening amygdala activity especially in maltreated individuals.

Next to these common sites of action, adverse childhood experiences have also been shown to directly influence the oxytonergic system. In Chapter 2 we report that early experiences of emotional maltreatment are associated with salivary oxytocin levels, similar to findings reported in previous studies (Heim *et al*, 2008; Pierrehumbert *et al*, 2010). However, the findings of various studies diverge, with some showing a negative relation between adverse experiences and activity of oxytonergic system (Heim *et al*, 2008) and others showing a positive relation (Pierrehumbert *et al*, 2010). We found higher salivary oxytocin levels associated with more self-reported maltreatment, which is in line with a recent study showing increased urinary oxytocin levels in young females with experiences of physical abuse (Seltzer *et al*, 2013). The implications of these observations have still to be elucidated. The effects of maltreatment and stressful life events are complex, affecting various neuro-hormonal systems, and they appear to be moderated by factors such as age and gender (Joels and Baram, 2009). Even within the oxytonergic system, the relation between exposure to stress and oxytocin levels is not yet well understood. Of the two most dominant theories about the interaction between oxytocin and stressful experiences, one theory suggests suppressive effects of oxytocin on the hypothalamic-pituitary-adrenal axis, with suppressed stress reactivity as a result, while the other suggests a greater release of oxytocin as part of stress reactivity (Pierrehumbert *et al*, 2010).

Early maltreatment may not only affect the secreted levels of the hormone, but might also bring about its effects by altering oxytocin receptor density (Francis *et al*, 2000), oxytocin receptor binding (Liberzon and Young, 1997) and/or epigenetic changes (Kumsta *et al*, 2013), a complexity which might be difficult to capture in studies with human subjects. In Chapter 2 we assessed the role of a single nucleotide polymorphism on the oxytocin receptor gene (*rs53576*) in moderating the relation between childhood emotional maltreatment and endogenous salivary oxytocin levels. We did not find a

significant moderating effect of the polymorphism, a finding consistent with a recent meta-analysis (Bakermans-Kranenburg and Van IJzendoorn, 2013). Although this polymorphism has been shown to moderate the effects of intranasal oxytocin administration on social preferences towards infants (Marsh *et al*, 2012) and has been associated with parenting and trust behaviors (Bakermans-Kranenburg and Van IJzendoorn, 2008; Rodrigues *et al*, 2009), the polymorphism is present in an intron of the oxytocin receptor gene and the functional significance of the polymorphism has yet to be demonstrated (Bakermans-Kranenburg *et al*, 2013). Well-designed studies with larger sample sizes and clearly defined ethnic groups are needed to study the effects of oxytocin receptor polymorphisms, as well as experimental work on the functional properties of oxytocin receptor polymorphisms in animals and humans.

The associations between emotional maltreatment and emotion processing, between oxytocin and emotion processing, and between emotional maltreatment and oxytocin have been replicated repeatedly (Marsh *et al*, 2010; Pollak *et al*, 2000; Seltzer *et al*, 2013). However, very few studies (mainly from our research group) have examined the combination of maltreatment and oxytocin in affecting neuro-behavioral outcomes (Huffmeijer *et al*, 2012; Riem *et al*, 2013; Riem *et al*, in press; Van IJzendoorn *et al*, 2011). For instance, individuals who experienced lower levels of love withdrawal by their mothers made more charitable donations when they receive oxytocin, whereas oxytocin administration does not affect donating behavior of their less fortunate peers who experienced high levels of love-withdrawal (Van IJzendoorn *et al*, 2011). While love withdrawal is an important component of emotional abuse and has an impact on the perception of infant cues (Chapter 5), we also studied the broader maltreatment construct with components of emotional abuse and neglect imparted by family members including parents and siblings (Chapter 2 and 4). In these studies we show that the experience of emotional maltreatment affects the development of the oxytonergic system, resulting in individual differences in the perception of infant temperament (Chapter 2). Moreover, the responsiveness of the oxytonergic system to externally administered oxytocin is affected by these negative experiences, resulting in impaired memory for infant temperamental cues only in maltreated individuals (Chapter 4).

Efficacy and reliability of oxytocin manipulation and assessment measures

We used intranasal administration to experimentally increase oxytocin levels and observed its effect on memory of infant temperament cues. We also measured endogenous salivary level to assess the association of oxytocin with mood recognition.

While these are currently the best available methods to experimentally increase oxytocin levels and collection of saliva constitutes a noninvasive method to measure physiological levels of oxytocin, there is some debate about the efficacy and reliability of these methods. In humans there is no experimental evidence yet showing that oxytocin can indeed cross the blood brain barrier after intranasal administration, or can reach relevant brain areas through other ways or means. It has been suggested however, that neuropeptides of similar size and structure as oxytocin (e.g., vasopressin) are indeed taken up in cerebrospinal fluid when administered intra-nasally and result in neurobiological and behavioral changes (Born *et al*, 2002). In a recent study we showed that salivary levels of oxytocin remained elevated for at least seven hours after the nasal spray administration (Van IJzendoorn *et al*, 2012). The study used different doses (16 and 24 IU) of oxytocin; these doses did not make a significant difference in salivary oxytocin levels (Van IJzendoorn *et al*, 2012), possibly due to the *saturation* by such high doses (Figure 1). Indeed, other studies using 16, 24 or even 40 IU have shown comparable effects in brain activity (Kirsch *et al*, 2005; Riem *et al*, 2011). One disadvantage of the nasal spray method is the inability to control the dosing amount. Absorption through the mucosal surface might be different among participants due to the specific anatomy of the nose, the structure of the nasal cavity and the environment in the nasal cavity, creating additional individual differences in the bioavailability of oxytocin in the brain (for a review see Guastella *et al*, 2013). More controlled administrations, taking into account any morphological differences might further improve the reliability of the effects on intranasal oxytocin administration in humans (Guastella *et al*, 2013).

Evidence that oxytocin can indeed reach the brain after intranasal administration (or alternatively, trigger a feed-forward reaction causing endogenous release of oxytocin) comes from a recent study conducted in rodents showing an increase in oxytocin levels in brain regions such as the amygdala and the hippocampus. Moreover, an increase in plasma levels of oxytocin after intranasal administration was short lived compared to brain levels (Neumann *et al*, 2013). However, direct experimental evidence showing that this phenomenon also translates to humans still awaits to be presented. Pieces of evidence so far suggest that, similar to animal studies, increased plasma levels of oxytocin after intranasal administration are short lived in humans as well, possibly also providing an indirect evidence for a disconnect between central and peripheral hormone levels (Gossen *et al*, 2012). The route taken by synthetic oxytocin from the nasal cavity to the brain is not known. Of several possible routes that an intranasally administered drug might take, a recent review suggest five most likely routes. These include, absorption and uptake by

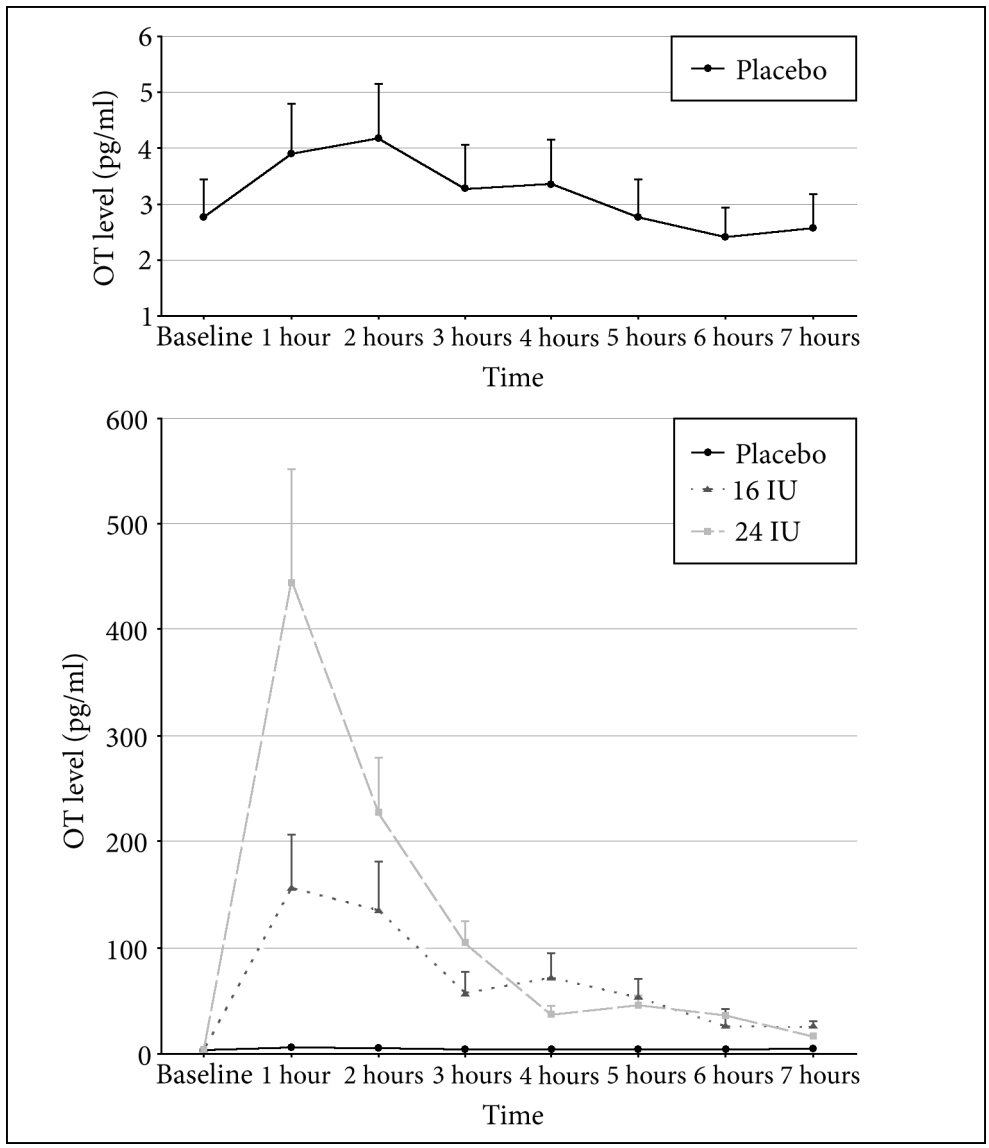


Figure 1. Salivary oxytocin levels over the day in placebo (A) and after administration of 16 IU or 24 IU oxytocin (B). *Administration of oxytocin or placebo through nasal spray directly after the baseline assessment; subsequent assessments every hour after administration of oxytocin or placebo (Van IJzendoorn et al, 2012).*

a) nasal vasculature into the systemic circulation, b) oral mucosa and gastroenterally, c) olfactory bulb pathways, d) trigeminal nerve pathways and e) the paravascular spaces that connect into the interstitial spaces of the brain parenchyma (for a detailed account on the topic see Guastella *et al*, 2013). Unfortunately, there has been no human research regarding the amount of oxytocin that actually reaches the brain, its half-life in the cerebrospinal fluid, and the brain area specific activity as might be assessed by receptor concentration and ligand - receptor binding. Salivary oxytocin levels are suggested to be coordinated with the central nervous system levels of oxytocin (Weisman *et al*, 2012). The study by Van IJzendoorn *et al* (2012) shows increased oxytocin levels in saliva after nasal spray with a gradual decrease until seven hours. Moreover, the stability of oxytocin levels in saliva without any drug administration supports the reliability of the measure. However, whether these measures actually correlate with cerebrospinal levels or not, and the degree of correlation between these two, cannot be implied with certainty. The invasive nature of the confirmatory tests has prevented this very basic but important knowledge required for the correct understanding and interpretation of the findings. At present, intranasal administration and salivary oxytocin levels are the best available, non-invasive tools in oxytocin research, the results should however be interpreted with caution.

Evolutionary significance of altered oxytonergic system with maltreatment experiences

Abusive and neglectful experiences have been related to interpersonal difficulties and problems in creating stable and secure attachments, both romantic and to one's offspring (Cyr *et al*, 2010; Hornor, 2012). Our findings might suggest that alterations in the oxytonergic system due to maltreatment experiences might be adaptive for some individuals, possibly by preparing them for more positive interactions with potential new attachment partners (as also argued by Seltzer *et al*, 2013). This argument might be supported by a study showing an increase in oxytocin concentration following physical contact with biologically unrelated children but not with related children (Bick and Dozier, 2010). It has been argued that this might be explained by the role of oxytocin in initiation (but not continuation) of maternal behaviors as also shown in rodent studies (Bick *et al*, 2010; Insel, 1997). In a similar vein we found that oxytocin was related to the perception of positivity in infant faces (Chapter 2) and that intranasal oxytocin decreased the perception gap between positive and negative infant temperamental cues, possibly to increase approach behavior towards infants with more negative temperaments, especially in the *at risk* maltreated group (Chapter 4).

Alternative mechanisms for modifying perception of infant cues

Infants' perceived cuteness, due to its rewarding nature, has also been associated with more sensitive parenting by their mothers (Langlois *et al*, 1995). This bias is inherently unfair and it is thus important to see whether perceptions of infant cuteness can be changed for the better. In Chapter 3 we show that experimental modulation of infant mood to create a more positive perception of temperament resulted in increased cuteness ratings and more effort to view them. For negatively perceived temperament, the cuteness ratings were not affected, but participants expended less effort to view these infants. In the human brain, reward processing is distinguished as having two components: liking and wanting (Kringelbach and Berridge, 2012). While rating the infants as cuter is a part of the liking response, expending energy to view the infant represents the wanting part of reward (Parsons *et al*, 2011). Some studies are now identifying different brain areas involved in the liking and wanting part of reward processing (Berridge and Kringelbach, 2013). Our results suggest that infant temperament has clear consequences for how adults perceive infant cues, with effects on both the liking and wanting components. Perception of infant cuteness is not based on physical facial features alone, and is modifiable through experience with that very infant.

Experimental tasks

The advantages of experimental manipulation over real life observational studies have been noted in literature, such as more controlled environmental conditions and the possibility of identifying causality. However, in highly controlled settings, the ecological validity of the stimulus is sometimes lost, and the generalizability of the findings to real life may be difficult. For validity of the experimental study, the researcher has to maintain the controlled environment while still allowing real life similarities to find their way (e.g., in real life, a crying sound is always accompanied by the presence of an infant). In this regard, the following two manipulations used in our studies deserve being mentioned.

Baby Social Reward Task (BSRT). The BSRT was used in Chapter 3 and 4 in order to manipulate the mood of infants to give the participants an idea of the temperament of the infant. Most of the experimental studies, both with adults and infants, use facial cues (Guastella *et al*, 2008; Marsh *et al*, 2010) or sounds (Out *et al*, 2010; Riem *et al*, 2011). While some studies have also used videos (Sitnikova *et al*, 2003), the controllability of these paradigms might be limited due to the complexity related to depth and movement. These attributes recruit various different brain areas (Jong *et al*, 1994)

and therefore might hamper the unequivocal interpretation of the data. Moreover, in brain imaging studies the results might be more complicated to interpret. In the BSRT, we coupled infant emotional facial cues with corresponding sounds in order to increase the ecological validity. We manipulated the mood of the infant, and by using more than one trial we aimed to create an infant with a specific temperament. Moreover, like in real life, the same infant showed both happy and sad moods. For example, an infant manipulated to be perceived as happy most of the time still cried in some trials. Similarly, an infant aimed to be perceived as difficult cried on most of the trials and showed happy mood in fewer trials. These manipulations were meant to make the task as more valid while still preserving a controlled environment as required for the experimental setting.

Infant Simulator. Most of the research on responses to cry sounds is done by using recorded and manipulated cry sounds of real infants, without the presence of an infant (Joosen *et al*, 2013). Moreover, in many studies with recorded cry sounds, participants cannot act to the crying by providing appropriate care. In Chapter 5, we used the infant simulator which is a *doll* resembling a real infant. Confronted with the infant *doll's* crying, participants have to figure out the reason for the cry and provide care such as feeding, changing the diaper, or burping. The participants were then asked to rate the perceived negativity of the cry. This whole setup mimics a natural caregiving event and allows us to capture caregivers' perception of infant cues similar to real life situation. Moreover, the variations in the caregiver's perception due to the frequency and pitch of crying can be controlled experimentally, which presents as an advantage over studies with real infants.

Limitations and future directions

We note some limitations of the studies presented in this thesis. The participants of all studies were adult females without offspring, and they had no daily experiences of caring for an infant. Research suggests heightened neuronal plasticity due to various hormonal and neurochemical processes during pregnancy, resulting in drastic changes in the maternal brain (for a review see Kinsley and Amory-Meyer, 2011). Oxytocin is one of the hormones which plays a major role during parturition. Moreover, mothers differ from females without children of their own in their responses to infant cues (Zeskind, 1980). Taken together this suggests that replicating our work in mothers would be helpful in understanding the significance of these neuronal and behavioral alterations. In a similar vein, mothers' responses to own versus unknown infants might differ too (Strathearn *et al*, 2008). The differences in maternal perception towards own versus genetically

unrelated infants might be of interest. Moreover, research has also reported gender differences both in oxytonergic system functioning and responses to infant cues (Parsons *et al*, 2011; Weisman *et al*, 2013). For example, gender has been shown to moderate the relations between oxytocin levels and anxiety ratings. Males with higher oxytocin levels score lower on trait anxiety but no such associations were seen for females (Weisman *et al*, 2013). Specifically in parenting behaviors, mothers' oxytonergic system (genes and hormones) was shown to be associated with children's social reciprocity towards peers but fathers' oxytonergic system was not associated with children's reciprocity (Feldman *et al*, 2013). The study of gender differences in oxytonergic system responses to infant cues therefore might shed more light on the different roles played by fathers and mothers in infant upbringing.

In the present studies, we used self-report measures of experienced maltreatment and maternal discipline strategies. Self-report measures might suffer from specific disadvantages such as biases due to current mood and personality of the respondents. Other biases such as social desirability tendencies might also result in biased information about the actual experiences of maltreatment. However, the questionnaires used in the present studies are reliable and well validated (Bernstein *et al*, 2003; Huffmeijer *et al*, 2011) and have been used in various studies to measure experienced maltreatment (Van Harmelen *et al*, 2012; Van Harmelen *et al*, 2010b). Future studies might however use other methods such as extensive interviews or eye witness reports to increase the accuracy of the reported experiences.

The present sample consisted of university students, with an under-representation of extreme cases of emotional abuse. Future studies may include the full range of maltreatment to clearly understand alterations in various neural and behavioral systems with extreme versus less extreme cases of abuse and neglect. Emotional maltreatment has been reported to co-occur with other forms of maltreatment. For example, a recent maltreatment prevalence study conducted in the Netherlands showed that of all children reported to be maltreated, only 55% of the children experienced one type of maltreatment, 30% experienced two different types, 13% experienced three types, and 2% experienced four or more types of maltreatment (Euser *et al*, in press). Another Dutch study assessing structural differences in brain's grey and white matter volumes in relation to experiences of emotional maltreatment reported that of the individuals suffering from childhood emotional abuse and neglect, 31% also reported physical abuse, and 29% also reported sexual abuse. In addition, 38% of all individuals reporting sexual abuse also reported physical abuse (Van Harmelen *et al*, 2010a). In the current sample, we did not

differentiate between individuals with experiences of emotional maltreatment and those having additional experiences of physical or sexual abuse. Our results might thus represent a combined effect of different types and frequency of maltreatment, and not reflect the effects of only emotional maltreatment.

Implications and Conclusions

In sum, we found that the perception of infant cues differs between individuals with fewer versus more experiences of emotional maltreatment (Chapter 5). These adverse experiences seem to change the activity and responsiveness of the oxytonergic system, such that higher levels of oxytocin are secreted to allow for a more positive evaluation of happy infant mood (Chapter 2). Intranasal administration decreases the negative perception of sad infant expressions and decreases the memory for negative infant cues in individuals who experienced emotional maltreatment during their childhood years (Chapter 4). Our results might suggest that developmental changes in the oxytonergic system might help maltreated individuals to be open to new, potentially positive relationship experiences and to facilitate new attachments. Moreover, we suggest that reward training might be helpful in changing individuals' perception of an infant for the better and to support parents to spend more energy to stimulate their child's development (Chapter 3). Overall, our findings might serve as a first step toward identifying cognitive and neurobiological mechanisms that might help to improve (future) parenting.

References

Bakermans-Kranenburg MJ, Van IJzendoorn MH (2008). Oxytocin receptor (OXTR) and serotonin transporter (5-HTT) genes associated with observed parenting. *Social Cognitive and Affective Neuroscience* **3**(2): 128-134.

Bakermans-Kranenburg MJ, Van IJzendoorn MH (2013). A sociability gene? Meta-analysis of oxytocin receptor genotype effects in humans. *Psychiatric genetics*.

Baumgartner T, Heinrichs M, Vonlanthen A, Fischbacher U, Fehr E (2008). Oxytocin shapes the neural circuitry of trust and trust adaptation in humans. *Neuron* **58**(4): 639-650.

Bernstein DP, Stein JA, Newcomb MD, Walker E, Pogge D, Ahluvalia T, *et al* (2003). Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse & Neglect* **27**(2): 169-190.

Berridge KC, Kringelbach ML (2013). Neuroscience of affect: Brain mechanisms of pleasure and displeasure. *Current Opinion in Neurobiology* **23**(3): 294-303.

Bick J, Dozier M (2010). Mothers' concentrations of oxytocin following close, physical interactions with biological and nonbiological children. *Developmental Psychobiology* **52**(1): 100-107.

Born J, Lange T, Kern W, McGregor GP, Bickel U, Fehm HL (2002). Sniffing neuropeptides: a transnasal approach to the human brain. *Nat Neurosci* **5**(6): 514-516.

Cyr C, Euser EM, Bakermans-Kranenburg MJ, Van IJzendoorn MH (2010). Attachment security and disorganization in maltreating and high-risk families: A series of meta-analyses. *Development and Psychopathology* **22**(01): 87-108.

Feldman R, Gordon I, Influs M, Gutbir T, Ebstein RP (2013). Parental oxytocin and early caregiving jointly shape children's oxytocin response and social reciprocity. *Neuropsychopharmacology* **38**(7): 1154-1162.

Francis DD, Champagne FC, Meaney MJ (2000). Variations in maternal behaviour are associated with differences in oxytocin receptor levels in the rat. *Journal of Neuroendocrinology* **12**(12): 1145-1148.

Gimpl G, Fahrenholz F (2001). The oxytocin receptor system: Structure, function, and regulation. *Physiological Reviews* **81**(2): 629-683.

Gossen A, Hahn A, Westphal L, Prinz S, Schultz RT, Gründer G, *et al* (2012). Oxytocin plasma concentrations after single intranasal oxytocin administration – A study in healthy men. *Neuropeptides* **46**(5): 211-215.

Guastella AJ, Hickie IB, McGuinness MM, Otis M, Woods EA, Disinger HM, *et al* (2013). Recommendations for the standardisation of oxytocin nasal administration and guidelines for its reporting in human research. *Psychoneuroendocrinology* **38**(5): 612-625.

Guastella AJ, Mitchell PB, Mathews F (2008). Oxytocin enhances the encoding of positive social memories in humans. *Biological Psychiatry* **64**(3): 256-258.

Heim C, Young LJ, Newport DJ, Mletzko T, Miller AH, Nemeroff CB (2008). Lower CSF oxytocin concentrations in women with a history of childhood abuse. *Mol Psychiatry* **14**(10): 954-958.

Hornor G (2012). Emotional Maltreatment. *Journal of Pediatric Health Care* **26**(6): 436-442.

Huffmeijer R, Alink LA, Tops M, Bakermans-Kranenburg M, Van IJzendoorn M (2012). Asymmetric frontal brain activity and parental rejection predict altruistic behavior: Moderation of oxytocin effects. *Cogn Affect Behav Neurosci* **12**(2): 382-392.

Huffmeijer R, Tops M, Alink LRA, Bakermans-Kranenburg MJ, Van IJzendoorn MH (2011). Love withdrawal is related to heightened processing of faces with emotional expressions and incongruent emotional feedback: Evidence from ERPs. *Biological Psychology* **86**(3): 307-313.

Inoue H, Yamasue H, Tochigi M, Abe O, Liu X, Kawamura Y, *et al* (2010). Association between the oxytocin receptor gene and amygdalar volume in healthy adults. *Biological Psychiatry* **68**(11): 1066-1072.

Insel TR (1997). A neurobiological basis of social attachment. *American Journal of Psychiatry* **154**(6): 726-735.

Joels M, Baram TZ (2009). The neuro-symphony of stress. *Nat Rev Neurosci* **10**(6): 459-466.

Jong BMd, Shipp S, Skidmore B, Frackowiak RSJ, Zeki S (1994). The cerebral activity related to the visual perception of forward motion in depth. *Brain* **117**(5): 1039-1054.

Joosen KJ, Mesman J, Bakermans-Kranenburg MJ, Pieper S, Zeskind PS, Van IJzendoorn MH (2013). Physiological reactivity to infant crying and observed maternal sensitivity. *Infancy* **18**(3): 414-431.

Kinsley CH, Amory-Meyer E (2011). Why the Maternal Brain? *Journal of Neuroendocrinology* **23**(11): 974-983.

Kirsch P, Esslinger C, Chen Q, Mier D, Lis S, Siddhanti S, *et al* (2005). Oxytocin modulates neural circuitry for social cognition and fear in humans. *The Journal of Neuroscience* **25**(49): 11489-11493.

Kringelbach ML, Berridge KC (2012). The joyful mind. *Scientific American* **307**(2): 40-45.

Kumsta R, Hummel E, Chen FS, Heinrichs M (2013). Epigenetic regulation of the oxytocin receptor gene: implications for behavioral neuroscience. *Frontiers in Neuroscience* **7**.

Langlois JH, Ritter JM, Casey RJ, Sawin DB (1995). Infant attractiveness predicts maternal behaviors and attitudes. *Developmental Psychology* **31**(3): 464-472.

Liberzon I, Young EA (1997). Effects of stress and glucocorticoids on CNS oxytocin receptor binding. *Psychoneuroendocrinology* **22**(6): 411-422.

Marsh A, Yu H, Pine D, Blair RJR (2010). Oxytocin improves specific recognition of positive facial expressions. *Psychopharmacology* **209**(3): 225-232.

Marsh A, Yu H, Pine D, Gorodetsky E, Goldman D, Blair RJR (2012). The influence of oxytocin administration on responses to infant faces and potential moderation by OXTR genotype. *Psychopharmacology* **224**(4): 469-476.

Neumann ID, Maloumby R, Beiderbeck DI, Lukas M, Landgraf R (2013). Increased brain and plasma oxytocin after nasal and peripheral administration in rats and mice. *Psychoneuroendocrinology* **38**(10): 1985-1993.

Out D, Pieper S, Bakermans-Kranenburg MJ, Van IJzendoorn MH (2010). Physiological reactivity to infant crying: A behavioral genetic study. *Genes, Brain and Behavior* **9**(8): 868-876.

Parsons CE, Young KS, Kumari N, Stein A, Kringelbach ML (2011). The motivational salience of infant faces is similar for men and women. *PLoS ONE* **6**(5): e20632.

Pierrehumbert B, Torrisi R, Laufer D, Halfon O, Ansermet F, Beck Popovic M (2010). Oxytocin response to an experimental psychosocial challenge in adults exposed to traumatic experiences during childhood or adolescence. *Neuroscience* **166**(1): 168-177.

Pollak SD, Cicchetti D, Hornung K, Reed A (2000). Recognizing emotion in faces: Developmental effects of child abuse and neglect. *Developmental Psychology* **36**(5): 679-688.

Riem MME, Bakermans-Kranenburg MJ, Huffmeijer R, Van IJzendoorn MH (2013). Does intranasal oxytocin promote prosocial behavior to an excluded fellow player? A randomized-controlled trial with Cyberball. *Psychoneuroendocrinology* **38**(8): 1418-1425.

Riem MME, Bakermans-Kranenburg MJ, Pieper S, Tops M, Boksem MAS, Vermeiren RRJM, *et al* (2011). Oxytocin Modulates Amygdala, Insula, and Inferior Frontal Gyrus Responses to Infant Crying: A Randomized Controlled Trial. *Biological Psychiatry* **70**(3): 291-297.

Riem MME, Van IJzendoorn MH, Tops M, Boksem MAS, Rombouts SARB, Bakermans-Kranenburg MJ (in press). Oxytocin effects on complex brain networks are moderated by experiences of maternal love withdrawal. *European Neuropsychopharmacology* **23**(10): 1288-1295.

Rodrigues SM, Saslow LR, Garcia N, John OP, Keltner D (2009). Oxytocin receptor genetic variation relates to empathy and stress reactivity in humans. *Proceedings of the National Academy of Sciences* **106**(50): 21437-21441.

Seltzer LJ, Ziegler T, Connolly MJ, Prososki AR, Pollak SD (2013). Stress-induced elevation of oxytocin in maltreated children: Evolution, neurodevelopment, and social behavior. *Child Development*.

Sitnikova T, Kuperberg G, Holcomb PJ (2003). Semantic integration in videos of real–world events: An electrophysiological investigation. *Psychophysiology* **40**(1): 160-164.

Strathearn L, Li J, Fonagy P, Montague PR (2008). What's in a smile? Maternal brain responses to infant facial cues. *Pediatrics* **122**(1): 40-51.

Van Harmelen A-L, de Jong PJ, Glashouwer KA, Spinhoven P, Penninx BWJH, Elzinga BM (2010a). Child abuse and negative explicit and automatic self-associations: The cognitive scars of emotional maltreatment. *Behaviour Research and Therapy* **48**(6): 486-494.

Van Harmelen A-L, Van Tol M-J, Demenescu LR, Van der Wee NJA, Veltman DJ, Aleman A, *et al* (2012). Enhanced amygdala reactivity to emotional faces in adults reporting childhood emotional maltreatment. *Social Cognitive and Affective Neuroscience*.

Van Harmelen A-L, Van Tol M-J, Van der Wee NJA, Veltman DJ, Aleman A, Spinhoven P, *et al* (2010b). Reduced medial prefrontal cortex volume in adults reporting childhood emotional maltreatment. *Biological Psychiatry* **68**(9): 832-

838.

Van IJzendoorn MH, Bhandari R, Van der Veen R, Grewen K, Bakermans-Kranenburg MJ (2012). Elevated salivary levels of oxytocin persist more than seven hours after intranasal administration. *Frontiers in Neuroscience* **6**.

Van IJzendoorn MH, Huffmeijer R, Alink LRA, Bakermans-Kranenburg MJ, Tops M (2011). The impact of oxytocin administration on charitable donating is moderated by experiences of parental love-withdrawal. *Frontiers in Psychology* **2**.

Weisman O, Zagoory-Sharon O, Feldman R (2012). Intranasal oxytocin administration is reflected in human saliva. *Psychoneuroendocrinology* **37**(9): 1582-1586.

Weisman O, Zagoory-Sharon O, Schneiderman I, Gordon I, Feldman R (2013). Plasma oxytocin distributions in a large cohort of women and men and their gender-specific associations with anxiety. *Psychoneuroendocrinology* **38**(5): 694-701.

Zeskind PS (1980). Adult responses to cries of low and high risk infants. *Infant Behavior and Development* **3**(0): 167-177.