Oxytocin, adversity and attachment contribute to the interactive behavior of mothers with and without mental illness

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Abstract

A large body of literature has explored the variables contributing to individual differences in the quality of maternal behavior. Psychosocial factors, including history of adversity, attachment insecurity, and mental health problems, have been linked to poorer maternal care. In recent years, there has been increasing interest in identifying the neurobiological substrates of maternal behavior. The neuropeptide oxytocin (OT) has been shown to promote maternal behavior, and varies with a history of adversity, attachment insecurity, and mental health problems. Thus, OT may represent a biological mechanism underlying the relationship between these psychosocial characteristics and maternal interactive behavior.

The present thesis is designed to address two primary goals: (1) Study 1 and 3 examined psychosocial factors associated with individual differences in circulating concentrations of OT; (2) Study 2 explored the moderating role of mental health in the relationship between OT levels and maternal interactive behaviors.

OT has been linked to adult attachment but studies have yielded inconsistent results, leaving it unclear why OT would be inversely associated with attachment insecurity in some adults but not others. History of adversity may help to shed light on these divergent findings, as it has been associated with both attachment insecurity and lower concentrations of OT. To determine whether adversity moderates the relationship between OT and attachment, Study 1 examined the association between OT and attachment in a clinical sample of pregnant women who had endured high rates of adversity throughout life. We found lower OT concentrations in insecurely than securely attached women, and in those who experienced stressful life events in the last 12 months. Study 3 compared the relationship between OT and attachment insecurity in childbearing women with and without a background of early adversity. Results showed that early

adversity moderated the association between OT and attachment insecurity; OT levels were inversely associated with attachment avoidance, but only in those with a history of early adversity. These studies underline the need to consider the role of adversity in order to obtain a more complete understanding of the relationship between OT levels and adult attachment.

Study 2 was designed to investigate the moderating role of mental health in the relationship between OT levels and maternal interactive behaviors. Because OT exerts anti-stress and anxiolytic effects, it may be particularly beneficial to the interactive behaviors of mothers with mental health problems. We hypothesized that mental health would moderate the association between OT levels and interactive behaviors. To test this hypothesis, Study 2 compared the association between OT concentrations and interactive behavior in mothers with versus without mental health problems. Higher levels of OT were associated with less intrusive interactive behavior in the overall sample. Consistent with our hypothesis, OT was also associated with less depressive (tense, self-focused, lethargic) interactive behaviors, but only in mothers with mood, anxiety or adjustment disorders. These results suggest that higher levels of OT may buffer the effects of their mental health problems on their interactive behaviors, and these anti-stress and anxiolytic effects of OT could be less necessary or apparent in mothers without such problems.

Overall, the results of the current thesis highlight the importance of examining the relationships among multiple psychosocial variables in order to better account for individual differences in circulating concentrations of OT, as well as the importance of considering both biological and psychosocial variables in an effort to more fully comprehend individual differences in the quality of maternal behavior.

Résumé

De nombreuses publications ont exploré les facteurs contribuant aux différences individuelles de qualité de comportement maternel. Les facteurs psychosociaux, tels que les antécédents d'adversité, l'attachement de type insécurisant, et les problèmes de santé mentale, sont liés à des soins maternels de plus faible qualité. Récemment, les chercheurs s'intéressent aux origines neurobiologiques du comportement maternel. La neuropeptide ocytocine est liée à de meilleurs comportements maternels, et peut varier avec des antécédents d'adversité, l'attachement de type insécurisant, et des problèmes de santé mentale. L'ocytocine pourrait ainsi être un mécanisme biologique expliquant le lien entre ces facteurs psychosociaux et les comportements maternels.

Cette thèse vise à atteindre deux objectifs: (1) Les études 1 et 3 examinent les facteurs psychosociaux associés aux différences individuelles de taux d'ocytocine endogène; (2) L'étude 2 explore le rôle modérateur de la santé mentale dans le lien entre l'ocytocine et le comportement maternel.

Certaines études ont lié l'ocytocine à l'attachement adulte, mais les trouvailles sont contradictoires. Les raisons pour lesquelles l'ocytocine serait inversement liée à l'attachement insécurisant chez certains adultes mais pas d'autres restent ambigües. Des antécédents d'adversité pourraient élucider ces trouvailles, car ils sont liés à l'attachement de type insécurisant et à de plus faibles taux d'ocytocine. Afin de déterminer si les antécédents d'adversité ont un rôle modérateur dans le lien entre l'ocytocine et l'attachement, l'étude 1 examine l'association entre l'ocytocine et l'attachement chez des femmes enceintes ayant vécu des taux élevés d'adversité. Les résultats indiquent que les taux d'ocytocine étaient plus bas chez les femmes ayant un attachement de type insécurisant et chez les femmes ayant vécu des

évènements stressants dans les 12 derniers mois. L'étude 3 compare le lien entre l'ocytocine et l'attachement de type insécurisant chez les femmes avec ou sans antécédents d'adversité. L'adversité en enfance jouait un rôle modérateur dans le lien entre l'ocytocine et l'attachement de type insécurisant; les taux d'ocytocine étaient inversement liés à un style d'attachement de type évitant, mais seulement chez les femmes ayant des antécédents d'adversité en enfance. Ces études confirment le besoin de considérer l'adversité dans le lien entre les taux d'ocytocine et l'attachement adulte.

L'étude 2 visait à examiner le rôle modérateur de la santé mentale dans le lien entre l'ocytocine et les comportements maternels. L'ocytocine a des effets antistress et anxiolytiques, et pourrait d'autant plus bénéficier les comportements interactifs des mères ayant des problèmes de santé mentale. Nous avons émis l'hypothèse que la santé mentale modérerait le lien entre l'ocytocine et les comportements interactifs. Afin de tester cette hypothèse, l'étude a comparé le lien entre l'ocytocine et les comportements interactifs chez des mères avec ou sans problèmes de santé mentale. Chez toutes les femmes, des taux d'ocytocine plus élevés étaient associés à des comportements maternels moins envahissants. Confirmant notre hypothèse, l'ocytocine était aussi liée à des comportements interactifs moins dépressifs, mais seulement chez les mères ayant des troubles d'humeur, d'anxiété ou d'ajustement. Ces résultats suggèrent que l'ocytocine pourrait atténuer les effets des problèmes de santé mentale sur les comportements interactifs. Cependant, les effets antistress et anxiolytiques de l'ocytocine pourraient être moins nécessaires ou évidents chez les mères sans ces problèmes.

Globalement, les résultats de cette thèse soulignent l'importance de considérer les facteurs psychosociaux dans les différences individuelles d'ocytocine endogène, ainsi que

l’importance de considérer les facteurs biologiques et psychosociaux pour mieux comprendre les différences de qualité de comportements maternels.

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I would like to thank all of the participants who made this research possible. I am also grateful to the granting agencies that supported this research: The original longitudinal study of mothers from pregnancy to postpartum was funded by the Canadian Institutes of Health Research # GTA-91755, and Dr. Nancy Feeley was supported by a Research Scholar Award

from the Fonds de Recherché du Québec - Santé (FRQ-S). The follow-up study of mothers and their children at about 2.5 years postpartum was funded by the Canadian Institutes of Health Research MOP-123354.

Study 1 was published in the journal of Attachment & Human Development, and Study 2 was published in the Infant Mental Health Journal; I am grateful for the feedback of the reviewers and of the journal editors Dr. Howard Steele (Study 1) and Dr. Paul Spicer (Study 2).

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Dedication

I dedicate this thesis to my father, Michael Samuel, whose unconditional love has given me the confidence to pursue my goals and whose intrinsic love of learning represents my greatest source of inspiration, and to my husband, Erick Provost, whose endless love, support, and kindness makes everything good in my life both possible and meaningful.

Preface & Contribution of Authors

Study 1 and Study 2 were based on a subset of data from a larger longitudinal study of childbearing women from pregnancy to approximately 2 months postpartum. This larger study was designed by Drs. Phyllis Zelkowitz, Ian Gold, Nancy Feeley, Barbara Hayton, C. Sue Carter, Togas Tulandi, and Haim A. Abenhaim. Participants were recruited and scheduled by Silvia Petrella and Erin Yong Ping under the coordination of Marie-Eve Carrier. Assessments were conducted by research assistants including Erin Yong Ping and Madeleine Tait. Dr. Barbara Hayton and her medical residents conducted diagnostic interviews with mothers from the clinical sample at the Institute of Community and Family Psychiatry of the Jewish General Hospital. Mother-infant interactions were coded by Madeleine Tait, Anna MacKinnon, Beth Crutchley, Evan Newton and Dr. Phyllis Zelkowitz.

Study 3 was based on a subset of data from a larger follow-up study of participants from the original longitudinal study at about 2.5 years postpartum. The larger follow-up study was designed by Drs. Phyllis Zelkowitz, Ian Gold, Jennifer Bartz, Nancy Feeley, Barbara Hayton, Lawrence Joseph, Ellen Moss, and Gustavo Turecki. I scheduled participants along with numerous other lab members including Silvia Petrella, Anna MacKinnon, Leonora Gangadeen-King, and Helena Barr. I tested participants along with many other lab members including Anna MacKinnon, Leonora Gangadeen-King, Madeleine Tait, Helena Barr, Rachel Idelson, Lisa Yang, Vivian Gu, Mariam Naguib, Suzy Read, and Mikaela Dimick.

In Study 1-3, blood samples were assayed by Hossein Nazarloo. Stephanie Robins played an integral role in coordinating the numerous staff members involved in this research project, and contributed a great deal to my knowledge of biological processes. Blood draws were

performed by a number of nurses including Danielle Landry, Cecilia Finoli, Florence Baux, Marine Namin, Anne Schweitzer, Pauline Chan, Sandra Kirk and the staff of Soins Direct.

I was the primary author of the three papers that comprise the present doctoral dissertation. I reviewed the literature and formulated the research questions. I also conducted statistical analyses with the help of Pavel Levin and Dr. Rhonda Amsel. Stephanie Robins created the Figures for Study 1 using Prism. Co-authors made numerous suggestions and revisions on drafts. Dr. Sue Carter contributed significantly to the description of OT measurement in the Methods sections, and added a paragraph about vasopressin to the Limitations section of Study 3. Moreover, the journal reviewers and editors provided helpful suggestions for revisions of Study 1 and 2. Finally, my supervisor Dr. Phyllis Zelkowitz read multiple drafts of each paper and imparted extremely helpful feedback.

All three studies in the present thesis are original contributions to the scientific literature. A more detailed explanation of these contributions can be found in each manuscript, as well as in the General Discussion section of this thesis. Briefly, research suggests that higher levels of prenatal OT in women with high rates of cumulative psychosocial adversity (CPA) were associated with more optimal maternal behaviors (Zelkowitz et al., 2014), which are known to predict important child outcomes (de Wolff & Van Ijzendoorn, 1997; Dexter, Wong, Stacks, Beeghly, & Barnett, 2013; Laucht, Esser, & Schmidt, 2002; Mäntymaa, Puura, Luoma, Salmelin, & Tamminen, 2004; Wang & Dix, 2013). Thus, it is important to determine which pregnant women with high levels of CPA may be more likely to have higher or lower levels of OT. Past studies have investigated the link between endogenous OT and either attachment security (Eapen et al., 2014; Marazziti et al., 2006; Pierrehumbert, Torrisi, Ansermet, Borghini, & Halfon, 2012) or stressful life events (Taylor et al., 2006; Turner, Altemus, Enos, Cooper, & McGuinness,

1999). However, insecure attachment has been linked with adversity (Bifulco et al., 2006), making it important to investigate the independent contributions of each factor to endogenous OT levels within the same model. Moreover, previous studies of circulating OT and attachment security have focused on adults without mental health problems. However, individual differences including mental health problems moderate the effects of OT (Bartz, Simeon, et al., 2011; Bartz, Zaki, Bolger, & Ochsner, 2011; Cardoso, Kingdon, & Ellenbogen, 2014; Olff et al., 2013; Simeon et al., 2011), leaving it unclear whether the association between OT and attachment security would extend to individuals with mental health problems. Thus, Study 1 was the first to my knowledge to examine the contributions of both attachment security and recent stressful life events to levels of plasma OT in pregnant women who reported high rates of CPA and who had been diagnosed with mood, anxiety or adjustment disorders. The results of Study 1 bring us closer to recognizing which pregnant women with high rates of CPA may be expected to have higher or lower levels of plasma OT.

Previous investigations have detected positive relationships between maternal circulating OT concentrations and interactive behaviors with their infants (Atzil, Hendler, & Feldman, 2011; Feldman, Gordon, Schneiderman, Weisman, & Zagoory-Sharon, 2010; Feldman, Gordon, & Zagoory-Sharon, 2011; Feldman, Weller, Zagoory-Sharon, & Levine, 2007; Feldman et al., 2012; Gordon, Zagoory-Sharon, Leckman, & Feldman, 2010a, 2010b; Levine, Zagoory-Sharon, Feldman, & Weller, 2007). Mothers with mental health problems exhibit poorer caregiving behaviors with their children (Lovejoy, Graczyk, O'Hare, & Neuman, 2000; Nicol-Harper, Harvey, & Stein, 2007; Whaley, Pinto, & Sigman, 1999; Zelkowitz, Papageorgiou, Bardin, & Wang, 2009), and some research indicates that they may have lower concentrations of OT (Anderberg & Uvnas-Moberg, 2000; D. S. Carson et al., 2014; Eapen et al., 2014; Garfield et

al., 2015; Gordon et al., 2008; Ozsoy, Esel, & Kula, 2009; Scantamburlo et al., 2007; Skrundz, Bolten, Nast, Hellhammer, & Meinlschmidt, 2011; Stuebe, Grewen, & Meltzer-Brody, 2013; Weisman, Zagoory-Sharon, Schneiderman, Gordon, & Feldman, 2013; Yuen et al., 2014), which is thought to have antidepressant and anxiolytic effects (Arletti & Bertollni, 1987; de Oliveira, Zuardi, Graeff, Queiroz, & Crippa, 2012; Feifel, Macdonald, McKinney, Heisserer, & Serrano, 2011; Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Nowakowska, Kus, Bobkiewicz-Kozlowska, & Hertmanowska, 2002). However, most studies of endogenous OT and maternal behavior during the postpartum period have focused on community samples of healthy mothers without mental health problems. Thus, Study 2 was the first to my knowledge to compare the relationship between plasma OT and interactive behavior in mothers with and without mood, anxiety or adjustment disorders during the postpartum period. Results showed that maternal mental health moderated the association between plasma OT levels and depressive interactive behavior.

Finally, previous studies have found positive (Buchheim et al., 2009; De Dreu, 2012; Feldman et al., 2011; Pierrehumbert et al., 2012), negative or discrepant associations (Eapen et al., 2014; Marazziti et al., 2006; Weisman et al., 2013) between OT and attachment security. Study 3 compared the relationship between OT and attachment insecurity in childbearing women with and without a background of early life stress (ELS), which is thought to have an enduring effect on the OT system (Bakermans-Kranenburg & van IJzendoorn, 2013; Fries, Ziegler, Kurian, Jacoris, & Pollak, 2005; Heim et al., 2009; Riem, Bakermans-Kranenburg, Huffmeijer, & van IJzendoorn, 2013; Riem, van IJzendoorn, et al., 2013). Study 3 was the first to my knowledge to find that ELS moderated the association between OT concentrations and attachment avoidance. By specifying that OT levels were only associated with attachment

avoidance in those with a history of ELS, Study 3 may help to shed light upon the conflicting results reported in the literature to date. The results also underline the need to consider both ELS and attachment insecurity in order to better account for individual differences in circulating levels of plasma OT.

General Introduction

In mother-infant interactions, the mother is faced with the challenge of responding to her nonverbal infant (Barrett & Fleming, 2011). Sensitive maternal interactive behavior is complicated and involves responding to child cues consistently and promptly, with behaviour that is appropriate, warm, and accepting with little to no intrusiveness, withdrawal or hostility (Barrett & Fleming, 2011). To accomplish this, a mother needs to be motivated to bond with her baby (Barrett & Fleming, 2011). She also needs to be emotionally equipped to balance the demands of mothering with other stresses inherent in daily life (Barrett & Fleming, 2011). She has to accurately perceive her infant's signals, tapping social-cognitive skills such as her ability to empathize, recognize emotions, and interpret social cues (Barrett & Fleming, 2011). She should also view interactions with her infant as rewarding rather than aversive, reinforcing her desire to communicate sensitively with her infant (Barrett & Fleming, 2011). As such, sensitive maternal behavior involves diverse processes including motivation, emotion, social cognition, and reward, all of which vary greatly across mothers (Barrett & Fleming, 2011).

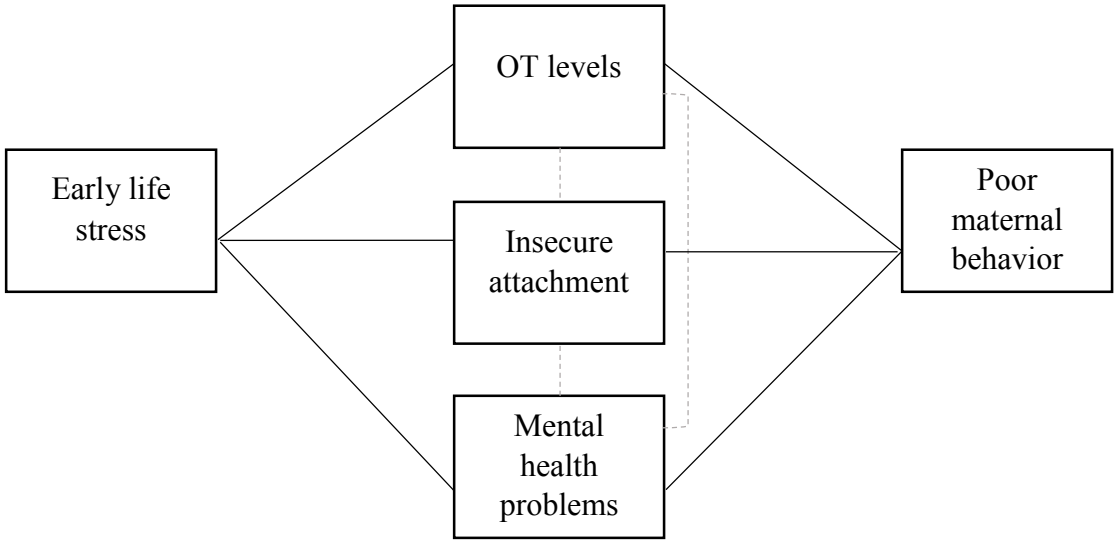
Research has explored how numerous psychosocial factors may contribute to individual differences in the quality of maternal behavior, including the mother's demographic characteristics and the nature of early caregiving that she experienced. A subset of these factors, namely history of adversity, insecure attachment, and mental health problems, are linked in multiple ways. First, individuals with a history of adversity may be more likely to be insecurely attached, both of which are associated with mental health problems. Second, mothers with these psychosocial characteristics exhibit poorer interactive behavior with their infants. Third, some studies indicate that individuals with these psychosocial characteristics have lower concentrations of oxytocin (OT), a neuropeptide which has been found to promote maternal

behavior in animal and human studies. Indeed, a mounting body of research indicates that OT may promote emotional well-being and reduce stress by interacting with the hypothalamic pituitary adrenal (HPA) axis, and that OT may promote bonding by increasing activation in brain regions that regulate reward, affiliation, and empathy. As such, OT has a role to play in many of the processes involved in sensitive maternal behavior, including emotion, reward, motivation, and social cognition. For these reasons, OT has been the focus of considerable research attention in the effort to identify the neurobiological substrates of maternal behavior.

Studies relating OT to adversity, attachment, and mental health problems suggest that OT may be a biological mechanism underlying the relationships between these psychosocial factors and maternal behavior. Some insight into the nature of these relationships can be derived from reports that individuals exposed to adversity during childhood or adolescence (e.g. harsh parenting) are less sensitive to exogenous OT and have lower concentrations of OT during adulthood, prompting researchers to propose that early adversity may have a long-lasting effect upon the OT system through epigenetic mechanisms such as OT receptor (OTR) gene methylation (e.g. Bakermans-Kranenburg & van IJzendoorn, 2013). In addition to predicting lower concentrations of OT, early adversity has been linked with insecure attachment and mental health problems in adults, both of which are associated with lower concentrations of OT in some studies. Together, these strands of evidence form the basis of the following model of maternal behavior:

Maternal exposure to early adversity may have an enduring effect upon the OT system, bringing about lower concentrations of circulating OT in adulthood. Early adversity may also predict adult attachment insecurity and mental health problems such as depression and anxiety, both of which have been linked to OT concentrations in some human studies. Because this

neuropeptide has been linked with affiliative motivation and social-cognitive skills, it may have a role to play in adult attachment insecurity. In addition, in light of studies suggesting that OT has anti-stress, anxiolytic and antidepressant effects, it may have a role to play in mental health problems in adulthood. Together, lower concentrations of OT, attachment insecurity, and mental health problems may contribute to poorer maternal behavior.



The following literature review examines the evidence base for this model by reviewing the physiology and functions of OT, with particular attention to its roles in processes relevant to maternal behavior, including motivation, emotion, social cognition, and reward (see Barrett & Fleming, 2011). Studies linking early adversity to maternal behavior are reviewed next, and the potential impact of early adversity upon the OT system is outlined. Studies linking insecure attachment and mental health problems with maternal behavior are described next, highlighting the potential role of OT in each of these psychosocial factors. Finally, studies linking lower concentrations of OT to poorer maternal behavior are summarized.

Physiology of OT

OT is composed of nine amino acids (a ring composed of six amino acids and a tail composed of three amino acids), distinct from vasopressin in only two amino acids (Carter, 1998). Mainly synthesized in the magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus, OT is then secreted from the posterior pituitary into the bloodstream (Carter, 1998; Lee, Macbeth, Pagani, & Young, 2009). OT is also produced in multiple other sites throughout the body, including the heart, uterus, testis, placenta, corpus luteum, and amnion (D. S. Carson, Guastella, Taylor, & McGregor, 2013).

OT only has one receptor (OTR; Lee et al., 2009). This G protein–coupled receptor is made up of 389 amino acids, and it is expressed in organs including the kidney, uterus, ovary, and heart (D. S. Carson et al., 2013). In humans, staining revealed that the OTR is present in tissue from multiple brain sites, including the uncus, ventrolateral septal nucleus, basolateral amygdala, central amygdala, solitary nucleus, medial preoptic area, ventromedial nucleus, and tuberomamillary nucleus (Boccia, Petrusz, Suzuki, Marson, & Pedersen, 2013). OT that is secreted by the supraoptic and paraventricular nuclei of the hypothalamus binds to OTRs on these hypothalamic magnocellular neurons, inducing more OT secretion in a positive feedback cycle (D. S. Carson et al., 2013).

Estrogen has been found to augment OT gene promoters in both animals and humans (Lee et al., 2009). Some animal studies have found greater concentrations of OT in females than males (e.g. Kramer, Cushing, Carter, Wu, & Ottinger, 2004), though certain human studies have not detected sex differences in basal concentrations of plasma OT (e.g. Hoge, Pollack, Kaufman, Zak, & Simon, 2008; Taylor, Saphire-Bernstein, & Seeman, 2010).

OT, based on the ancient Greek terminology for "quick birth", has long been known to ease delivery and lactation (D. S. Carson et al., 2013; Lee et al., 2009). OT secretion from the posterior pituitary induces contractions during delivery (Carter, 1998). In labor, contractions of the uterus promote OT secretion from the hypothalamus, and OT binds to receptors in the hypothalamus and the myometrium, which in turn elicit more uterine contractions and OT secretion (D. S. Carson et al., 2013). In addition, OT promotes the contraction of myoepithelial tissue giving rise to milk ejection in lactation (Carter, 1998). In both labor and breastfeeding, OT neurons in the supraoptic nucleus of the hypothalamus are rearranged to promote inter-neuron communication as well as OT secretion into the periphery (D. S. Carson et al., 2013).

OT and Processes Related to Maternal Behavior

OT has been shown to be involved in some of the processes important to maternal behavior, including social cognition, reward, motivation and emotion (for a review, see Rilling & Young, 2014).

OT enhances social-cognitive abilities that may contribute to more sensitive maternal behavior. For instance, exogenous OT was found to augment emotion recognition (Lischke et al., 2012), and the ability to "mind read" using social stimuli from the ocular area (Domes, Heinrichs, Michel, Berger, & Herpertz, 2007). Others have found that OT can increase functional connectivity among brain regions associated with emotion, touch, and interpreting another's mental state (Riem, van IJzendoorn, et al., 2013). By helping mothers accurately interpret infant cues and emotions, OT may promote their ability to respond appropriately, which is a critical component of sensitive parenting. Studies showing that OT enhances brain activation in areas linked to bonding and empathy (Riem et al., 2011) point to another way that OT may promote

maternal behavior. In addition, it has been suggested that OT may enhance social-cognitive skills by increasing both the desire to affiliate and the focus on social stimuli in individuals whose skill deficits stem primarily from their reduced concern with the social environment (Bartz, Zaki, et al., 2011).

Experimental evidence indicates that OT may make infant-related stimuli less aversive and/or more rewarding. In women exposed to infant cries (Riem et al., 2011) or infant laughter (Riem et al., 2012), OT administration was found to lower activation of the amygdala, a region related to the processing of unpleasant emotions such as fear (also see Kirsch et al., 2005). In addition, OT administration augmented functional connectivity of the amygdala with brain areas important for emotion regulation in women listening to infant laughter (Riem et al., 2012). Via interactions with the dopaminergic system, maternal OT may also enhance the feeling of reward that parents derive from their children (Carter, 1998; Liu & Wang, 2003; Pedersen, 1997; Shahrokh, Zhang, Diorio, Gratton, & Meaney, 2010; Strathearn, Fonagy, Amico, & Montague, 2009); this positive reinforcement may in turn motivate parents to interact with their children more frequently and sensitively.

OT may also promote maternal behavior via its impact on maternal stress, anxiety or depressed mood, all of which have been linked to impaired interactive behaviors. OT may exert these effects on mental health in part via its interactions with the HPA axis. When healthy adults are faced with a stressor, the HPA axis responds as follows: corticotropin-releasing factor (CRF) is released by neurons in the paraventricular nucleus of the hypothalamus, prompting adrenocorticotropin hormone (ACTH) to be secreted from the anterior pituitary (Heim, Plotsky, & Nemeroff, 2004). This leads glucocorticoids including cortisol to be secreted from the adrenal cortex, and these glucocorticoids provide negative feedback to the HPA axis until homeostasis is

established (Heim et al., 2004). However, research indicates that CRF may be secreted excessively among individuals with depression and some anxiety disorders (Heim & Nemeroff, 1999). Indeed, Heim and Nemeroff (1999) stated that "increased HPA-axis activity in major depression is one of the most robust findings in the history of biological psychiatry". Studies of childbearing women also provide evidence for dysregulation of the HPA axis in depression; for instance, increasing ACTH levels triggered an increase in cortisol levels in non-depressed, but not in depressed, postpartum women (Jolley, Elmore, Barnard, & Carr, 2007). Interestingly, OT is released in times of stress, and can dampen HPA axis activation (Carter, 1998; Neumann, 2002). In addition, OT offsets the CRF effects following stress (Heim et al., 2004), and decreases ACTH and cortisol (Cardoso, Ellenbogen, Orlando, Bacon, & Joober, 2013; Ditzen et al., 2009; Heinrichs et al., 2003; Legros, 2001; K. J. Parker, Buckmaster, Schatzberg, & Lyons, 2005). OT was also found to decrease amygdala activation (Kirsch et al., 2005). In these ways, OT may exert anti-stress, anxiolytic and antidepressant effects.

Animal studies offer evidence for the antidepressant properties of OT. For instance, male mice injected with OT displayed less depressive behavior in behavioral despair and learned helplessness tasks; indeed, these effects were comparable to those of the antidepressant imipramine (Arletti & Bertollni, 1987). OT administration also reduced depressive behavior, operationalized as immobility, in male rats during a forced swimming test (Nowakowska et al., 2002).

Moreover, experimental studies in humans have demonstrated the anxiolytic effects of OT. Relative to placebo, OT administration decreased anxiety ratings in males preceding public speaking, indicating that OT reduced anticipatory anxiety (de Oliveira et al., 2012). In another sample of men, OT administration reduced anxiety during a stressful procedure (Heinrichs et al.,

2003). In adults being treated for Generalized Anxiety Disorder, OT administration over 3 weeks reduced anxiety levels in men but not in women (Feifel et al., 2011). In sum, these stress-reducing, antidepressant and anxiolytic properties of OT may ameliorate maternal mental health, which may impact the quality of maternal interactive behavior.

In the next section, I consider the role of OT in the relationships between psychosocial factors and maternal behavior, that is, whether OT could be a biological mechanism underlying the relationships between maternal behavior and history of adversity, insecure attachment, and mental health problems. History of adversity, as it relates to both maternal behavior and OT, is reviewed first.

History of Adversity

The literature suggests that mothers with a history of adversity, such as childhood abuse or neglect, score lower on measures of bonding and positive interactive behaviors. For example, after statistically adjusting for depression, mothers who endured abuse or neglect early in life were found to report more difficulty bonding to their infants than did a comparison group of mothers without this background (Muzik et al., 2013). These mothers also exhibited poorer caregiving behaviors with their 6-month-olds on a composite scale related to sensitivity, warmth, flexibility and engagement (Muzik et al., 2013). Mothers who endured incest during childhood also had lower scores on all scales of the Parenting Skills Inventory, including communication skills, than did a comparison group of mothers without this history (Cohen, 1995). The degree of sexual abuse endured by mothers was negatively related to their involvement with their infants; for instance, mothers who endured more extreme sexual abuse were more disengaged from their infants and exhibited more flat affect (Lyons-Ruth & Block, 1996). Relative to a comparison

group of mothers without a background of child abuse, those who had been sexually abused by an older relative by age 14 were less child-focused, and made fewer understanding or affirming comments with their 5- to 10-year-old children (Burkett, 1991).

Moreover, mothers reporting a history of adversity have been found to exhibit more negative interactive behaviors. For example, mothers who endured sexual or physical abuse exhibited more intrusiveness with their infants than did mothers without this background (Moehler, Biringen, & Poustka, 2007). Similarly, the degree of physical abuse endured by mothers was positively related to the hostility-intrusiveness that they exhibited with their infants (Lyons-Ruth & Block, 1996). Mothers who had been sexually abused by an older relative by age 14 made more blaming or belittling comments during interactions with their 5- to 10-year-old children than did a comparison group of mothers without a history of child abuse (Burkett, 1991). Mothers who were sexually abused in childhood used more violence during conflict with their children (Banyard, 1997).

The biological mechanism underlying this relationship between history of adversity and maternal behavior remains unclear. The literature on early adversity and OT provides some interesting clues about potential mechanisms of action: Multiple experimental studies indicate that early adversity such as harsh parenting moderated the effects of intranasal OT on a range of outcomes relevant to maternal behavior, including reaction to infant cries and perception of social stimuli (Bakermans-Kranenburg, van IJzendoorn, Riem, Tops, & Alink, 2012; Bhandari, van der Veen, et al., 2014; Riem, Bakermans-Kranenburg, et al., 2013; Riem, Bakermans-Kranenburg, Voorthuis, & van IJzendoorn, 2014; Riem, van IJzendoorn, et al., 2013; van IJzendoorn, Huffmeijer, Alink, Bakermans-Kranenburg, & Tops, 2011). These results indicate that exposure to adversity early in life can have an enduring influence on the OT system,

potentially through epigenetic processes such as OTR gene methylation (Bakermans-Kranenburg & van IJzendoorn, 2013; Fries et al., 2005; Heim et al., 2009; Riem, Bakermans-Kranenburg, et al., 2013; Riem, van IJzendoorn, et al., 2013). Indeed, a recent study found that early adversity in the form of less optimal maternal care was related to higher levels of methylation of a DNA sequence located within exon III of the OTR gene (Unternaehrer et al., in press).

In addition, multiple studies have found an inverse association between OT and early adversity. For instance, lower levels of cerebrospinal fluid (CSF) OT were found in rhesus monkeys that had been raised separately from their mothers (Winslow, Noble, Lyons, Sterk, & Insel, 2003). In addition, female rats exposed to lower levels of maternal care early in life showed less binding of the OTR in the bed nucleus of the stria terminalis (though this was not true of male rats; Francis, Young, Meaney, & Insel, 2002) as well as in the central nucleus of the amygdala (Francis, Champagne, & Meaney, 2000) in adulthood. In humans, lower levels of CSF OT were linked to more experiences of childhood maltreatment, especially emotional abuse (Heim et al., 2009). In women, plasma OT was inversely related to childhood trauma, particularly emotional abuse and neglect (Bertsch, Schmidinger, Neumann, & Herpertz, 2013). In postpartum women, plasma OT was inversely associated with paternal abuse endured by age 16 (Eapen et al., 2014). In men, adversity endured during childhood was associated with more emotional suppression, which was in turn associated with lower levels of plasma OT (Mohiyeddini, Opacka-Juffry, & Gross, 2014). In another study of men, levels of plasma OT were negatively related to stress such as abuse endured by age 12; trait anxiety moderated this relationship (Opacka-Juffry & Mohiyeddini, 2012). In sum, early adversity is associated with lower OT concentrations, which have been linked to poorer maternal behavior. Thus, it is possible that OT mediates the relationship between early adversity and maternal behavior, that is,

early adversity may predict lower levels of OT which in turn may contribute to poorer maternal behavior.

However, several investigations have detected positive correlations between OT and early adversity (Bhandari, Bakermans-Kranenburg, et al., 2014; Crowley, Pedersen, Leserman, & Girdler, 2015; Mizuki & Fujiwara, 2015; Pierrehumbert et al., 2010), suggesting that not every person with a background of adversity will have lower concentrations of OT. Rather, experiences occurring later in life, such as attachment relationships with close friends or dating partners, may likewise contribute to individual differences in circulating concentrations of OT. Indeed, early adversity such as childhood abuse has also been linked to adult attachment insecurity (Bradley et al., 2011; Gwadz, Clatts, Leonard, & Goldsamt, 2004; Muller, Sicoli, & Lemieux, 2000; Riggs & Jacobvitz, 2002; Twaite & Rodriguez-Srednicki, 2004), which has likewise been linked to OT levels and poorer maternal behavior. These relationships between insecure attachment, maternal behavior, and OT are described next.

Adult Attachment

Attachment theory argues that, based on past experiences with significant others, people develop internal working models of themselves and of others that impact the way in which they perceive and approach future relationships (Bowlby, 1969, 1982). Attachment is first developed toward primary attachment figures who are typically parents, and later toward secondary attachment figures including best friends or dating partners (Bowlby, 1969, 1982). Consistent with Bowlby's proposition that internal working models can be modified, meta-analytic findings suggest that attachment is only moderately stable over time (Fraley, 2002; Pinquart, Feussner, &

Ahnert, 2013); as such, some insecurely attached children may later become securely attached in adulthood, and vice versa.

According to Bartholomew and Horowitz (1991), attachment in adults can be viewed along 2 dimensions. One dimension is attachment anxiety; individuals with a negative model of self tend to perceive themselves as undeserving of love and worry about the availability of others (Bartholomew & Horowitz, 1991). The second dimension is attachment avoidance; individuals who have a negative model of others tend to feel uncomfortable trusting and counting on others (Bartholomew & Horowitz, 1991). Securely attached individuals have positive models of both self and others; they believe that they deserve to be loved and consider others to be reliable and trustworthy (Bartholomew & Horowitz, 1991). Preoccupied adults have positive models of others but negative models of self; they perceive themselves as undeserving of the love that they eagerly desire from other individuals (Bartholomew & Horowitz, 1991). Dismissing adults have positive models of self but negative models of others; they believe that they deserve to be loved but value their own independence over relationships with others (Bartholomew & Horowitz, 1991). Fearful adults have negative models of both self and others; they believe that they are undeserving of love and view others as unreliable and untrustworthy (Bartholomew & Horowitz, 1991). Preoccupied, dismissing and fearful attachment are considered kinds of insecure attachment (Bartholomew & Horowitz, 1991). Although individuals are sometimes classified as securely or insecurely attached, researchers generally view attachment as a continuous construct wherein individuals vary along dimensions of attachment anxiety and avoidance as opposed to mapping directly onto one attachment classification (Fraley & Waller, 1998).

Studies suggest that insecurely attached mothers exhibit poorer interactive behavior than securely attached mothers. An early meta-analysis found that securely attached adults were more

responsive with their children than insecurely attached adults (van IJzendoorn, 1995). During interactions with their 2-year-old children, preoccupied mothers exhibited more intrusive/angry behavior than dismissing or secure mothers (Adam, Gunnar, & Tanaka, 2004). An inverse relationship was reported between dismissing attachment and maternal sensitivity (Haltigan et al., 2014; Whipple, 2009).

OT may represent a biological mechanism linking adult attachment and maternal behavior. OT was shown to augment activation in brain areas related to empathy (Riem et al., 2011), and OT administration was found to enhance generosity, trust, and emotion recognition (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005; Lischke et al., 2012; Zak, Stanton, & Ahmadi, 2007); as such, individuals with higher concentrations of OT may have better social-cognitive skills, which are important for connecting with others. OT was shown to stimulate dopamine secretion within brain areas including the nucleus accumbens (Shahrokh et al., 2010), suggesting that individuals with higher concentrations of OT may derive a greater sense of reward from their relationship partners (see Carter, 1998; Strathearn et al., 2009). Moreover, because OT decreases anxiety and distress (Carter, 1998; Ditzen et al., 2009; Heinrichs et al., 2003; Neumann, 2002), individuals with higher concentrations of OT may feel calmer and better able to initiate and navigate social relationships. Via its links to secure attachment, OT may enhance the quality of maternal interactive behavior.

Indeed, experimental studies indicate that OT is positively associated to attachment security. Following OT administration, insecurely attached men construed pictures in a manner that was more consistent with attachment security (Buchheim et al., 2009), and more men categorized themselves as securely attached (De Dreu, 2012). Some studies of circulating OT have found similar results. For instance, higher concentrations of plasma OT were found in

securely than insecurely attached adults (Pierrehumbert et al., 2012). In postpartum women, higher levels of plasma OT were associated to lower levels of attachment anxiety and avoidance (Eapen et al., 2014). Higher levels of salivary OT were also associated with less romantic attachment avoidance and anxiety among parents in the postpartum period (Feldman et al., 2011).

However, some studies employing similar methodologies have failed to find convergent results (Marazziti et al., 2006; Weisman et al., 2013). Thus, it is important to account for why OT may be negatively associated with attachment insecurity in certain people but not in others.

In addition to predicting insecure attachment, early adversity has also been shown to predict mental health problems in adulthood, which have likewise been linked to lower concentrations of OT and poorer maternal behavior. Indeed, there is evidence of a positive relationship between childhood adversity and psychopathology in adulthood. A meta-analysis found that childhood maltreatment was related to a greater risk of experiencing more depressive episodes, longer-lasting depressive episodes, and poorer treatment outcomes for depression (Nanni, Uher, & Danese, 2012). In childbearing women, early adversity including abuse and neglect has been linked with mental health problems, such as postpartum PTSD and perinatal depression (Alvarez-Segura et al., 2014; Muzik et al., 2013; Plant, Barker, Waters, Pawlby, & Pariante, 2013; Stacks et al., 2014). These relationships between mental health problems, maternal behavior and OT are described next.

Mental Health Problems

Perinatal mental health problems are both prevalent and associated with poorer caregiving behaviors. In a review of studies on depression diagnosed using clinical interviews,

point prevalence was found to be 6.5-12.9% at various points in the perinatal period, with a period prevalence of up to 18.4% in pregnancy and up to 19.2% in the first 3 postpartum months (Gavin et al., 2005). Moreover, 14.6% of participants exceeded the cut-off on a self-report measure of anxiety assessed at 18 weeks gestation, 15.6% at 32 weeks gestation, 8.1% at 8 weeks postpartum, and 9.1% at 8 months postpartum (Heron et al., 2004).

Maternal depression. As a group, depressed mothers have greater difficulty bonding with their infants. Depressed mothers reported less attachment toward their 2-month-old infants, which was in turn related to maternal reports of less satisfying interactions with their offspring (Mason, Briggs, & Silver, 2011). Among postpartum mothers from a psychiatric hospital program, those with more depressive symptoms reported more severe impairments related to bonding with their infants, as well as more anger directed toward their infants (Sockol, Battle, Howard, & Davis, 2014). Indeed, mothers with severe depressive disorders reported more impaired bonding with their 0- to 7-month-old infants than did psychotic mothers, though lack of insight in the latter group could have contributed to this finding (Hornstein et al., 2006).

Moreover, depressed mothers have been shown to exhibit poorer interactive behaviors than non-depressed mothers. In a meta-analysis of studies on maternal depression and interactive behavior, depressed mothers displayed more negative behaviors such as intrusiveness, and more disengaged behaviors such as withdrawal (Lovejoy et al., 2000). This study also found that depressed mothers exhibited fewer positive behaviors such as praise, but only when they experienced financial strain, suggesting that economic difficulties may aggravate the effects of maternal depression on positive interactive behaviors (Lovejoy et al., 2000).

Maternal anxiety. Although comparatively fewer studies have explored the interactive behavior of anxious mothers, the existing literature indicates that they exhibit poorer bonding and interactive behaviors than non-anxious mothers. For instance, postpartum mothers who had been diagnosed with anxiety disorders reported poorer bonding with their infants than did a comparison group of healthy mothers without past or present psychopathology; part of the variance was explained by severity of anxiety as well as by subclinical symptoms of depression (Tietz, Zietlow, & Reck, 2014), which makes sense given the comorbidity among these disorders (Pollack, 2005).

In mothers and their low birthweight children, high maternal trait anxiety during the newborn's stay in the neonatal intensive care unit predicted poorer maternal sensitivity and structuring, as well as less child involvement of the mother, at the corrected age of 24 months (Zelkowitz et al., 2009). Mothers diagnosed with anxiety disorders were found to be less warm during interactions with their offspring than were a comparison group of mothers who had not experienced depressive or anxiety disorders since delivery; this relationship remained significant when controlling for the effects of maternal depression, child anxiety, and strain endured over the previous 6 months (Whaley et al., 1999). Relative to mothers with low trait anxiety, mothers with high trait anxiety exhibited lower levels of sensitive responsivity, less emotional tone including tone of voice and facial expression, and more non-contingent utterances such as utterances that were not aligned with the child's behavior, during interactions with their 10- to 14-month-old infants; these differences persisted when mothers with elevated depressive symptoms were excluded from analysis, specifying the role of maternal anxiety in interactive behavior (Nicol-Harper et al., 2007). The authors suggested that maternal anxiety might increase

attention to negative or threatening cues, which could in turn impair maternal responsiveness toward the child (Nicol-Harper et al., 2007).

OT may represent a biological mechanism linking maternal mental health with interactive behavior. As explained above, OT was found to dampen HPA axis activation (Carter, 1998; Neumann, 2002), and to decrease levels of ACTH (Legros, 2001; K. J. Parker et al., 2005) and cortisol (Ditzen et al., 2009). OT was also shown to dampen amygdala activation (Kirsch et al., 2005). In these ways, OT may diminish the physiological response to stressors encountered during adulthood, potentially reducing stress and exerting antidepressant or anxiolytic effects. Via its links with mental health, maternal OT may enhance the quality of maternal interactive behavior.

Indeed, studies have found inverse associations between OT and mood or anxiety disorders. Human studies have detected lower OT levels among depressed individuals than healthy controls (Anderberg & Uvnas-Moberg, 2000; Ozsoy et al., 2009; Yuen et al., 2014), as well as inverse associations between OT and depressive symptomatology in diverse samples (Anderberg & Uvnas-Moberg, 2000; Gordon et al., 2008; Scantamburlo et al., 2007), including childbearing women (Eapen et al., 2014; Garfield et al., 2015; Skrundz et al., 2011; Stuebe et al., 2013). In addition, there are multiple reports of negative associations between OT and anxious symptomatology (Anderberg & Uvnas-Moberg, 2000; D. S. Carson et al., 2014; Scantamburlo et al., 2007; Weisman et al., 2013), including research on childbearing women (Eapen et al., 2014; Stuebe et al., 2013).

However, research on OT and anxiety or depression have yielded divergent results (for a review, see Kim, Soeken, et al., 2014), with some reporting no relationship (Barraza et al., 2013; Clarici et al., 2015; Gordon et al., 2008; Guastella, Howard, Dadds, Mitchell, & Carson, 2009;

Hoge et al., 2008; Keating, Dawood, Barton, Lambert, & Tilbrook, 2013; Meynen, Unmehopa, Hofman, Swaab, & Hoogendijk, 2007; Pitts et al., 1995) and others finding positive relationships (Cyranowski et al., 2008; Hoge et al., 2008; K. MacDonald et al., 2013; K. J. Parker et al., 2010; Purba, Hoogendijk, Hofman, & Swaab, 1996; Taylor et al., 2010; Tops, van Peer, Korf, Wijers, & Tucker, 2007; Weisman et al., 2013). Some investigators have reported that depressed individuals exhibit a broader and more variable range of plasma OT levels, suggesting a general dysregulation of the OT system (Cyranowski et al., 2008; van Londen et al., 1997). A recent study suggested that dysregulation of both OT secretion and the HPA axis could contribute to depressive and anxious symptomatology in postpartum breastfeeding women (E. Q. Cox et al., 2015). Additional research is required to explore why OT is negatively related to depression and anxiety in some adults but not others.

Divergent Findings

What might account for the discrepant relationships reported between OT and attachment insecurity or mental health problems? Methodological discrepancies between studies may be playing a role. Some studies had small sample sizes of fewer than 20 participants, limiting the generalizability of the results (e.g. Keating et al., 2013; Meynen et al., 2007; Purba et al., 1996; Tops et al., 2007). In addition, participant gender may play a role; for instance, Weisman et al. (2013) found that OT was negatively related to anxiety for men but not women (Feifel et al., 2011). Even in studies of women, factors such as breastfeeding status or menstrual cycle may impact hormone levels and contribute to variability across studies; for instance, Eapen et al. (2014) showed that OT concentrations were inversely related with attachment insecurity during the postpartum – but not the prenatal - period. Genetic differences between participants may also

impact the results; for instance, the rs2254298 GG genotype on the OTR gene was linked with depression and lower levels of salivary OT (Apter-Levy, Feldman, Vakart, Ebstein, & Feldman, 2013).

Variability in OT measurement between studies could also contribute to the conflicting findings; for instance, some studies of attachment or mental health have measured OT in post-mortem brain tissue (e.g. Purba et al., 1996), cerebrospinal fluid (e.g. D. S. Carson et al., 2014; Pitts et al., 1995), plasma (e.g. Tops et al., 2007; Yuen et al., 2014), saliva and urine (e.g. Feldman et al., 2011). However, studies suggest that plasma and salivary OT levels are not associated with urinary OT levels (Feldman et al., 2011), and researchers have argued that peripheral levels may not correspond to central concentrations of OT (McCullough, Churchland, & Mendez, 2013). In addition, some researchers (e.g. Stuebe et al., 2013) used a technique called extraction, which removes circulating plasma components such as clotting factors (e.g. fibrinogen), protein and lipid carriers (e.g. albumin and globulins) and other hormones from the sample matrix prior to measurement (Szeto et al., 2011). However, others did not extract prior to measurement (e.g. Taylor et al., 2010), and there is some evidence to suggest that extracted samples are not associated to unextracted samples (Szeto et al., 2011). Finally, to quantify OT levels, some researchers (e.g. Cyranowski et al., 2008) used radioimmunoassay (RIA), in which an unknown amount of antigen (OT) from the participant's sample competes with a known amount of radioactive antigen for binding sites on an animal antibody designed specifically against human OT (Darwish, 2006). Next, the quantity of free radioactive antigen is assessed to deduce the quantity of OT in the participant's sample (Darwish, 2006). In contrast, others (e.g. Weisman et al., 2013) have used a comparable technique called an enzyme-linked immunosorbent assay (ELISA or EIA), which does not require the use of radioactivity (Darwish,

2006). In this approach, the final antigen-antibody complex is linked to an enzyme which reacts with a substrate to generate color relative to the concentration of antigen (OT) in the participant's sample (Darwish, 2006).

Importantly, even studies employing similar methods of OT measurement, such as extracted plasma OT with RIA, have yielded divergent relationships with attachment (e.g. Eapen et al., 2014; Marazziti et al., 2006; Pierrehumbert et al., 2012) and with mental health (e.g. Anderberg & Uvnas-Moberg, 2000; Cyranowski et al., 2008; Eapen et al., 2014; K. J. Parker et al., 2010; Tops et al., 2007). Thus, it is likely that non-methodological factors are also playing a part in the divergent results.

One possibility is that the association between OT and psychosocial factors like mental health problems or attachment insecurity may differ for adults with versus without a history of adversity. Research indicates that OT is released as a response to stress. However, some individuals experience prolonged exposure to stress, such as neglectful or abusive parenting throughout childhood. Because OT is secreted in response to stress, prolonged stress may place significant demands upon the OT system. Importantly, studies suggest that prolonged exposure to OT may result in a dampening of the OT system. For instance, in cell culture, sustained exposure of renal cells to synthetic OT resulted in OTRs being internalized (Gimpl & Fahrenholz, 2001). In mice, intranasal OT administration for 1 to 3 weeks was shown to reduce the quantity of central OTRs (Huang et al., 2014). In another mouse study, high doses of central OT administration resulted in decreased OTR binding in multiple brain regions, such as the median raphe nucleus and the medial and basolateral amygdala (Peters, Slattery, Uschold-Schmidt, Reber, & Neumann, 2014). Thus, repeated release of OT as might be expected in cases of early adversity could lead to a dampening of the OT system, including internalizing of OTR,

decreases in the number of OTRs, and decreased OTR binding. Lower concentrations of OT may then be produced as a result of biofeedback. Thus, in individuals with a history of adversity, the OT system might be unable to mount an OT response to stress; for this reason, OT may be negatively related to stress among individuals with a history of adversity, but not in those without a history of adversity. In keeping with this idea, researchers have suggested that the OT system might be less responsive following early adversity, leading to decreased resilience in the face of subsequent stressors (Buisman-Pijlman et al., 2014).

Among mood or anxiety disordered adults without a background of adversity, OT may be released to counteract their distress, resulting in concentrations of OT that are comparable to - or even higher than - those in mentally healthy adults. In contrast, in mood or anxiety disordered individuals with a history of early adversity, the OT system might be less able to release OT to counteract stress (as a result of negative biofeedback as described above), resulting in lower concentrations of OT; as such, OT concentrations might be inversely related to depression or anxiety in mothers with a history of adversity. Indeed, a recent investigation found that OT was negatively related to depressive symptomatology, but only in mothers reporting high degrees of psychosocial adversity throughout life (Zelkowitz et al., 2014). Moreover, in women experiencing menstrually-related mood disorders, OT was inversely associated with a range of symptoms (e.g. rejection sensitivity, mood swings), but only in those who reported early sexual abuse (Crowley et al., 2015).

Although the OT system might be dampened in many people with a history of adversity, a small number of studies have detected higher concentrations of OT in individuals with this background. This suggests that experiences that take place later in life, such as attachment relationships with close friends or romantic partners, may likewise contribute to individual

differences in circulating concentrations of OT. Interestingly, although early adversity predicts adult attachment insecurity, some individuals with this background become securely attached adults. Thus, early adversity and adult attachment insecurity might interact to predict endogenous levels of OT. Additional research is required to ascertain whether history of adversity moderates the relationship between OT and attachment, that is, whether the link between OT and attachment insecurity differs in adults with versus without a history of adversity.

In the last component of the proposed model, these lower concentrations of OT contribute to poorer maternal behaviors. As such, this literature review ends with a description of studies linking OT and maternal behavior.

OT and Maternal Behavior

OT has been linked with maternal behavior in studies of both animals and humans (Bosch & Neumann, 2012; Galbally, Lewis, van IJzendoorn, & Permezel, 2011).

Animal studies. Decades of animal research have demonstrated that OT promotes the initiation of maternal behavior. In virgin rats, OT administered to the lateral intracerebral ventricle enhanced maternal behavior relative to saline (Pedersen & Prange, 1979). In virgin rats who had had their ovaries surgically removed and who had been treated with estrogen, central OT injections increased maternal behaviors (e.g. pup licking and retrieval; Pedersen, Ascher, Monroe, & Prange, 1982), and the infusion of OT into the olfactory bulb elicited maternal behavior as well (Yu, Kaba, Okutani, Takahashi, & Higuchi, 1996). In female rats bred for low anxiety-linked behavior, chronic intracerebroventricular infusion of OT beginning on lactation day 1 enhanced arched back nursing during lactation days 2 to 6 (Bosch & Neumann, 2008).

This evidence is strengthened by studies showing impaired maternal behavior in knockout mice or in rodents following the administration of OT antagonists. OTR knockout mice were found to exhibit more pup abandonment than controls (Rich, deCardenas, Lee, & Caldwell, 2014). In rats, administration of an OT antagonist into the olfactory bulb (both following the birth of a first pup and prior to assessment) was found to delay maternal behavior (Yu et al., 1996). Arched back nursing was reduced in lactating rats following infusion of an OTR antagonist into the medial preoptic area (Bosch & Neumann, 2012), and in rat dams following intracerebroventricular administration of an OT antagonist (Pedersen & Boccia, 2002).

Human studies. In human studies, maternal caregiving behaviors have been linked to polymorphisms of the OT peptide gene (OXT) and of the OTR gene. Statistically adjusting for maternal depression, education and marital discord, community sample mothers who were homozygous for the G allele of the OTR rs53576 genotype were more sensitive toward their children than mothers who were homozygous for the A allele or those who were heterozygous (Bakermans-Kranenburg & van IJzendoorn, 2008). Mothers who were homozygous for the A allele of the OTR rs53576 genotype exhibited less warmth with their 6- to 10-year-old children than those who were homozygous or heterozygous for the G allele, even after statistically adjusting for child genotype (Klahr, Klump, & Burt, 2014). Mothers who were homozygous for the C allele of the OXT rs2740210 genotype, and those who were homozygous for the G allele of the OXT rs4813627 genotype, exhibited longer vocalizations with their 6-month-old infants; this aspect of maternal behavior was not related to the OTR rs237885 genotype (Mileva-Seitz et al., 2013).

Experimental studies using intranasal OT suggest that OT may enhance parental behavior. For example, fathers who were administered intranasal OT were better able to structure interactions with their offspring than fathers who were administered placebo (Naber, van IJzendoorn, Deschamps, van Engeland, & Bakermans-Kranenburg, 2010). In addition, following OT administration, depressed women described more positive relationships with their infants (though they also described their infants as more difficult; Mah, van IJzendoorn, Smith, & Bakermans-Kranenburg, 2013), and exhibited more protective behavior when an unfamiliar adult approached their infant in an intrusive manner (Mah, Bakermans-Kranenburg, van IJzendoorn, & Smith, 2014).

Maternal behavior was also positively associated with levels of circulating OT. Rising levels of prenatal plasma OT from the first to third trimester were associated with maternal reports of bonding toward her fetus (Levine et al., 2007). Plasma OT during early pregnancy and postpartum was positively related to maternal feelings of attachment toward the infant, as well as with maternal gaze, affectionate touch, positive affect and motherese vocalizations during interactions with their infants (Feldman et al., 2007). Parents with higher levels of plasma or salivary OT exhibited more coordination/synchrony with their infants (Atzil et al., 2011; Feldman et al., 2011). Parents with higher concentrations of plasma OT also synchronized gaze with their infants for greater periods of time than parents with lower levels (Feldman et al., 2012). Parental concentrations of plasma OT also predicted synchrony in father-mother-child interactions in the postpartum period (Gordon et al., 2010b). Concentrations of plasma or salivary OT were associated with affectionate behavior in mothers, and stimulatory behavior in fathers, during interactions with their infants (Feldman, Gordon, Schneiderman, et al., 2010; Gordon et al., 2010a).

Peripheral OT responses have also been positively associated with maternal behavior. Mothers who showed greater increases in circulating OT following interactions with their 7-month-olds tended to gaze at their infants for longer, and to look away from their infants less frequently (Kim, Fonagy, Koos, Dorsett, & Strathearn, 2014). Foster mothers who exhibited more delight during interactions with their foster infants exhibited a greater urinary OT response after cuddling with them (Bick, Dozier, Bernard, Grasso, & Simons, 2013). Thus, numerous investigations have linked maternal caregiving behavior to polymorphisms of the OXT and OTR genes, intranasal administration of OT, and peripheral OT levels.

Only a few studies have found an inverse relationship between circulating OT levels and maternal behavior (Elmadih et al., 2014; Feldman et al., 2011; Miura, Fujiwara, Osawa, & Anme, 2014). It is noteworthy that two of these three studies included urinary samples of OT. Though some have described urinary OT as reflecting "interactive stress" (Feldman et al., 2011), it is unclear why urinary OT would be differentially linked to maternal behavior relative to plasma or salivary OT. Another possibility is that psychosocial factors may moderate the relationship between OT and maternal behavior. For instance, a recent investigation found that OT was related to greater maternal sensitivity, but only for mothers who experienced high degrees of psychosocial adversity throughout life (Zelkowitz et al., 2014). Additional research is required to explore the potential moderating roles of other psychosocial factors that have been related to both OT and maternal behavior, including maternal mental health.

To date, most human research on circulating OT and maternal behavior has focused on community sample mothers, excluding those with mental health problems. The few studies that have examined endogenous OT and interactive behaviors among mood or anxiety disordered mothers (e.g. Mah et al., 2014; Mah et al., 2013) have lacked a control group of mothers without

mental health problems, making it difficult to decipher whether mental health played a role in the reported relationships. However, it is especially important to investigate the association between OT and behavior in mothers with mental health problems because, as described above, they have been found to display poorer interactive behaviors, and some research suggests that they have lower concentrations of endogenous OT. Given the anti-stress, anxiolytic, and antidepressant effects of OT, OT may play an especially valuable role in the caregiving behavior of these mothers. Thus, future research should explore if maternal mental health moderates the link between OT and interactive behavior. Indeed, previous research suggests that mental health moderates the association between OT and a number of outcomes relevant to maternal behavior, including the stress response (Bartz, Simeon, et al., 2011; Bartz, Zaki, et al., 2011; Cardoso et al., 2014; Olff et al., 2013; Simeon et al., 2011). Another recent study found that maternal mental health moderated the relationship between early adversity and OT response to interactions with their infants; mothers with high degrees of both depressive symptoms and childhood maltreatment exhibited lower OT responses to interactions with their infants (Gonzalez et al., 2015).

Thesis Outline

Given the role of OT in maternal behavior, it is important to investigate which childbearing women are likely to have high or low concentrations of endogenous OT. As such, the first goal of the present thesis was to explore the psychosocial factors associated with individual differences in OT concentrations. Because OT has been found to play a role in affiliation, bonding and stress reduction, individual differences in attachment style and mental health may be associated with endogenous levels of OT. However, research on OT and these

psychosocial factors have yielded inconsistent results. Additional research is required to investigate why OT is negatively related to psychosocial factors like attachment insecurity in certain adults but not others.

As described above, one possibility is that history of adversity moderates the relationship between OT concentrations and attachment security. To test this hypothesis, Study 1 examined whether OT would be negatively related to insecure attachment in pregnant women who experienced high levels of psychosocial adversity throughout life. To build upon this study, Study 3 investigated the association between OT and attachment insecurity in mothers both with and without a background of early adversity.

Having explored some of the psychosocial variables associated with individual differences in circulating concentrations of OT, we then examined the role of OT in maternal behavior. Mothers with mental health problems exhibit poorer interactive behavior with their children, and some studies indicate that they have lower concentrations of OT. However, most research on OT and maternal behavior has excluded mothers with mental health problems. Given its anti-stress, anxiolytic and antidepressant properties, OT may play an especially advantageous role in the interactive behaviors of mothers with mood or anxiety disorders. Thus, the second goal of the present thesis was to examine the relationship between OT and interactive behaviors in mothers both with and without mood or anxiety disorders. To this end, Study 2 investigated whether mental health moderated the association between OT and caregiving behaviors in the postpartum period.

Manuscript 1: Attachment security and recent stressful life events predict oxytocin levels: A pilot study of pregnant women with high levels of cumulative psychosocial adversity.

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Abstract

Purpose: Recent reports indicate that prenatal levels of the neuropeptide oxytocin (OT) are inversely related to depressive symptomatology and positively associated with more optimal interactive behaviors in mothers with high levels of cumulative psychosocial adversity (CPA). In the present pilot study, we aimed to identify factors associated with high versus low levels of OT in pregnant women with high levels of CPA. We hypothesized that insecurely attached women, and those who recently experienced stressful life events (SLE), would have lower levels of prenatal OT. **Methods:** Thirty pregnant women with mood and anxiety disorders and high levels of CPA were recruited from the perinatal mental health service of a general hospital. Participants completed self-report measures of psychosocial stress and adult attachment style, and blood was then drawn to assess OT. **Results and Conclusions:** Lower OT levels were found among those who were insecurely attached, and among those who experienced SLE within the last year. In a multiple linear regression, both attachment security and SLE significantly contributed to a model of prenatal OT levels. These individual difference factors explained 38% of the variance in prenatal OT, which may in turn predict poorer maternal mental health and caregiving outcomes during the postpartum period.

Keywords: Oxytocin, attachment, adversity, pregnancy, mood and anxiety disorders

Introduction

Oxytocin (OT), a neuropeptide synthesized in the supraoptic and paraventricular nuclei of the hypothalamus, is implicated in labour, delivery, and lactation (Carter, 1998, 2014). Lower levels of OT during pregnancy and postpartum are associated with poorer perinatal mental health (Skrundz et al., 2011; Stuebe et al., 2013) as well as with less optimal bonding and caregiving behaviors (Feldman et al., 2011; Feldman et al., 2007; Levine et al., 2007). Factors contributing to individual differences in prenatal OT levels remain to be identified.

A small but growing body of literature suggests that adult attachment security may be one such factor. Endogenous OT levels are positively associated with secure attachment, and inversely related to insecure attachment in adults (Eapen et al., 2014; Pierrehumbert et al., 2012). Endogenous OT levels are also associated with attachment-related prosocial behaviors including sharing feelings with peers (Tops et al., 2007). Attachment style moderated the effects of exogenous OT administration on memories of maternal care (Bartz, Zaki, Ochsner, et al., 2010). Relative to placebo, more men who were administered OT classified themselves as securely attached (De Dreu, 2012), and insecurely attached men interpreted images in a manner more consistent with secure attachment after OT administration (Buchheim et al., 2009).

Several mechanisms have been proposed to explain the relationship between insecure attachment and lower OT levels. OT has been shown to inhibit activation of the hypothalamic–pituitary–adrenal (HPA) axis (Carter, 1998; Neumann, 2002) and of the amygdala (Kirsch et al., 2005; Riem et al., 2011), and to decrease levels of cortisol (Ditzen et al., 2009; Heinrichs et al., 2003) and adrenocorticotropic hormone (Legros, 2001; K. J. Parker et al., 2005). As such, OT may reduce the anxiety and stress involved in the initiation of attachment relationships, enhancing approach (rather than withdrawal) responses (Francis et al., 2000). In addition, OT

may promote the release of dopamine in the ventral striatum, enhancing the rewarding nature of interactions with attachment figures (Carter, 1998; Liu & Wang, 2003; Pedersen, 1997; Strathearn et al., 2009). OT may also play a role in attachment relationships by enhancing activation in areas of the brain that are linked to empathy and bonding (i.e. the insula and inferior frontal gyrus pars triangularis; Riem et al., 2011), and by enhancing functional connectivity between regions of the brain involved in touch, emotion and understanding the minds of others (i.e. the cerebellum, posterior cingulate cortex, and postcentral gyrus in those who had supportive upbringings; Riem, van IJzendoorn, et al., 2013). Indeed, OT administration has been shown to increase trust (Kosfeld et al., 2005), generosity (Zak et al., 2007), and emotion recognition (Lischke et al., 2012), all of which are attachment-related constructs.

Another individual difference factor that may predict levels of prenatal OT is a history of psychosocial adversity. Early adversity, such as neglect or abuse during childhood, is thought to have lasting effects on the oxytocinergic system (Bakermans-Kranenburg & van IJzendoorn, 2013). In both human and animal studies, lower levels of OT in plasma and cerebrospinal fluid have been found in adults who endured stress and maltreatment early in life (Bertsch et al., 2013; Eapen et al., 2014; Heim et al., 2009; Mohiyeddini et al., 2014; Opacka-Juffry & Mohiyeddini, 2012; Winslow et al., 2003, but see Olff et al., 2013). Epigenetic factors may account for the link between greater adversity and lower OT levels. For instance, researchers have proposed that early adversity may impact oxytocin receptor (OTR) gene methylation (Bakermans-Kranenburg & van IJzendoorn, 2013), and animal studies have linked early adversity (in the form of less maternal care) to decreased OTR levels (Francis et al., 2000; Francis et al., 2002; Pedersen & Boccia, 2002). In contrast, other human studies have found *higher* levels of plasma or salivary OT in adults who endured adversity early in life in the form of maltreatment or cancer (Bhandari,

Bakermans-Kranenburg, et al., 2014; Pierrehumbert et al., 2010). Although methodological differences between studies (e.g. plasma versus cerebrospinal fluid OT) may have contributed to these discrepant findings (Bhandari, Bakermans-Kranenburg, et al., 2014), an exploration of additional moderating factors may also help to shed light on the relationship between OT and adversity.

Indeed, it has been suggested that an individual's history of stressful experiences may play a role in the OT stress response (Pierrehumbert et al., 2010). One possibility is that OT may be released in response to stress in individuals without a history of adversity, increasing endogenous OT levels and serving anxiolytic and stress-reducing functions. Past studies have linked higher levels of OT to interpersonal stress (e.g. poorer quality interactions) in samples of women not selected for a history of adversity (Taylor et al., 2006; Turner et al., 1999).

In contrast, the OT system may be dampened in those with a history of adversity, reflected by lower levels of endogenous OT following stress. In adult male rats exposed to a stressor on 3 successive days, peak plasma levels of post-stress OT were lower on day 2 and 3 than day 1 (Wotjak et al., 1998). In a human study, adults who endured sexual abuse early in life had somewhat lower levels of OT than those without this history of abuse following an acute experimental stressor (though cancer survivors exposed to this experimental stressor had higher levels of OT; Pierrehumbert et al., 2010). Thus, additional studies of OT and current stress in those with a history of adversity may help to account for past discrepant findings.

A recent longitudinal study found that cumulative psychosocial adversity (CPA; i.e. adversity experienced across the lifespan) moderated the relationship between OT and depression, as well as the relationship between OT and maternal behavior, in a community sample of pregnant women (Zelkowitz et al., 2014). In particular, prenatal OT levels were inversely related to

depressive symptomatology and positively associated with sensitive maternal behavior only in women who reported high rates of CPA. Importantly, there was considerable variability in OT levels among women reporting high levels of CPA.

Thus, it remains unclear which pregnant women - *among those with high levels of CPA* - are likely to have high versus low levels of OT. To shed light on this question, we examined the contributions of attachment security and recent stressful life events (SLE) to OT levels in pregnant women who reported high rates of CPA. In contrast to the community sample described in the study by Zelkowitz et al. (2014), we recruited pregnant women who were referred to a perinatal psychiatry service, where we would be more likely to find participants with high rates of CPA.

Whereas past studies have examined the relationship between OT and either attachment or psychosocial stress separately, the current study is the first to examine both factors in a sample reporting high levels of CPA. Given the potential for overlap between psychosocial stress and insecure attachment (i.e. insecurely attached individuals may have experienced more psychosocial adversity than securely attached adults; Bifulco et al., 2006), it is particularly important to examine the independent effects of both factors in one model.

The present pilot study had three hypotheses. First, we hypothesized that participants with insecure adult attachment styles would have lower OT levels than those with a secure adult attachment style. We also hypothesized that those who recently experienced SLE would have lower levels of OT than those who did not report these experiences. Finally, we predicted that attachment insecurity and recent SLE would each independently predict lower levels of prenatal OT in a sample of women with high levels of CPA.

Methods

Participants

Recruitment took place at the Perinatal Mental Health Service in a psychiatry department of a large tertiary care hospital in Montreal, Canada. This service provides outpatient care (e.g. risk assessment, treatment) for women from pregnancy to 6 months postpartum. During an intake interview, the medical doctor asked pregnant women if they would like to participate in this study.

In order to obtain a sample of pregnant women who experienced a high degree of CPA, we recruited participants who scored above the clinical cut-off of 23 on a measure of CPA called the Antenatal Risk Questionnaire (ANRQ; Austin, Colton, Priest, Reilly, & Hadzi-Pavlovic, 2013), described below. Of those who scored above the cut-off on the ANRQ, we included all those with mood, anxiety or adjustment disorders in an effort to obtain a relatively diagnostically homogenous sample, given the overlap in symptoms and the established comorbidity between depression and anxiety (Pollack, 2005; Young, Abelson, & Cameron, 2004). As such, our final sample consisted of 30 women who were diagnosed with mood disorders (15), anxiety disorders (8), comorbid mood and anxiety disorders (5), or adjustment disorders with depressed, anxious or irritable mood (2).

Demographic characteristics of the final sample are presented in Table 1. The majority were partnered. They had a broad range of educational levels. On average, they were 24 weeks gestation. They were all singleton pregnancies, and about two-thirds were multiparous. Seven participants were taking psychotropic medication at the time of assessment.

Measures

A registered nurse drew 10 milliliters of blood from the cubital vein of each participant into a heparinized tube, which was immediately placed on ice. Samples were cold centrifuged at 1600 x *g* for 15 minutes. The plasma portion was then pipetted off and immediately frozen at -80°C. Samples were then sent to the laboratory of Dr. Sue Carter at the University of Illinois, Chicago. Unextracted plasma was assayed using an enzyme-linked immunosorbent assay purchased from Enzo Life Sciences (Farmingdale, New York; catalogue # ADI-900-153-0001). Samples were diluted 1:2 or 1:4 in order to obtain values falling within the sensitive part of the standard curve. The samples were de-identified, and the laboratory technician was blind to the hypothesis of this study and to all other participant values. Samples were assayed in duplicate; the intra-assay and inter-assay coefficients of variation were under 10%. The assay has been validated (Carter et al., 2007; Kramer et al., 2004), and this protocol has been used extensively (Ebstein, Knafo, Mankuta, Chew, & Lai, 2012) with stable individual values (Gouin et al., 2010; Weisman et al., 2013). The OT values in the present sample fall within the range reported in other samples of pregnant women using this protocol (Prévost et al., 2014).

Participants completed a set of self-report questionnaires. They provided demographic information including parity, age, relationship status, weeks of gestation, and educational level. They also reported if they were currently taking psychotropic medications.

The Relationship Questionnaire (RQ; Bartholomew & Horowitz, 1991) is a two-part measure of adult attachment. In the categorical component, respondents are presented with descriptions of four attachment styles (secure, preoccupied, dismissing, and fearful) and are asked to indicate which one best describes them in their close relationships. In the dimensional component, respondents rate the degree to which each of the four categories corresponds to their

overall relationship style on a scale from 1 (not at all like me) to 7 (very much like me). These attachment styles have been found to be moderately stable for 8 months (Scharfe & Bartholomew, 1994). Responses on the RQ converge with scores on interview measures of attachment style (Bartholomew & Horowitz, 1991). The RQ has been employed with samples of pregnant women (e.g. van Bussel, Spitz, & Demyttenaere, 2009, 2010a, 2010b). Our analyses focused solely on the categorical component of the RQ because we sought to examine differences in OT levels in those with secure versus insecure attachment styles, as opposed to those with different degrees of secure or insecure attachment. Thus, those who selected the preoccupied, dismissing or fearful categories were considered to be insecurely attached.

The ANRQ (Austin et al., 2013) is a screening tool used to assess CPA, and to identify pregnant women who are at risk for developing mental health problems during the perinatal period. This measure inquires about a broad range of adversities, including early relationship with one's own mother, mental health problems, degree of emotional support in the romantic relationship, tendencies to worry and require order, anticipated social support with the baby, experiences of abuse, as well as recent SLE (stressors, changes, or losses in the last 12 months). Continuous and categorical questions on the ANRQ yield scores ranging from 5 to 62, where higher scores are indicative of greater CPA (Austin et al., 2013). The ANRQ has been shown to be very acceptable to pregnant women (Austin et al., 2013). Relative to five other tools used to assess perinatal mental health risk (e.g. Pregnancy Risk Questionnaire), the ANRQ was judged to satisfy psychometric requirements (e.g. validity and reliability, specificity and sensitivity, negative and positive predictive values) more thoroughly (Johnson et al., 2012). Because the ANRQ assesses cumulative risk across a broad range of domains, an individual may not necessarily score high on all items. Specific subscales have not been established for the ANRQ,

and assessment of internal consistency using Cronbach's alpha is not reported for this measure (Austin et al., 2013; Johnson et al., 2012). We administered all ANRQ items in order to obtain the CPA scores, and to determine that all participants in the present study were above the cut-off of 23 established in the literature (indicating that they had high levels of CPA). We measured recent SLE by examining responses to the following individual ANRQ item: "Have you had any stresses, changes or losses in the last 12 months (e.g. separation, domestic violence, unemployment, bereavement?)". Responses for this item were categorical (yes or no).

Procedure

This study was approved by the research ethics committee at the tertiary care hospital where the study took place. Participants provided written informed consent before being included in this study. A medical doctor at the Perinatal Mental Health Service conducted a clinical interview to diagnose mental health problems using the Diagnostic and Statistical Manual (DSM-IV-TR; American Psychiatric Association, 2000).

While at the hospital, participants completed a background questionnaire as well as the RQ and ANRQ. As in past studies (Strathearn et al., 2009), we assessed participants' attachment styles during pregnancy, rather than postpartum, to avoid the possibility that their interactions with their newborns would impact their responses on the attachment measure. A nurse then drew 10 ml of blood from each participant to assay for endogenous OT.

Data Analysis

Visual inspection of a histogram of raw OT values revealed a positive skew. Thus, in keeping with other OT studies (e.g. Gordon et al., 2010a; Gordon et al., 2008; Opacka-Juffry &

Mohiyeddini, 2012), OT data were log-transformed. These transformed values were then used in all statistical analyses.

Although one participant's log OT value corresponded to standardized score of -3.09, we retained her data in the final analyses because excluding it did not change the results. Moreover, values below her raw OT value of 61.68 pg/ml have been reported in other studies of OT in pregnant women (e.g. Prévost et al., 2014). Finally, her standardized score was above the cut-off of -3.29 for a univariate outlier (Tabachnick & Fidell, 2006).

We computed descriptive statistics to obtain the means and standard deviations for continuous variables, as well as the frequencies and percentages for nominal variables. We then computed bivariate Pearson correlations, independent samples t-tests, and chi square tests to determine whether log OT, recent SLE, and attachment security were significantly associated with demographic variables (parity, age, marital status, educational level, and weeks of gestation) or with medication use. Educational level was analyzed as a continuous variable in which years of schooling were assigned to the highest completed degree: 11 for high school, 13 for junior college or trade school, 16 for bachelor's degree, and 18 for master's degree.

First, an independent samples t-test was calculated to determine whether participants who classified themselves as insecurely attached on the RQ had significantly lower levels of OT than those who classified themselves as securely attached. We ran another independent samples t-test to determine whether participants who reported experiencing stresses, changes or losses within the last year on the ANRQ had significantly lower levels of OT than those who did not report such experiences.

Finally, we ran a multiple linear regression. According to Stevens (1996), 15 participants are required for each predictor in a multiple regression. Therefore, our sample size of 30 was

adequate for a regression analysis with 2 predictors: attachment security and recent SLE. Attachment security was dummy coded as 0 (securely attached) or 1 (insecurely attached). Experience of recent stresses, changes, or losses was also dummy coded as 0 (no) or 1 (yes).

We used an alpha level of .05 for each statistical test. Cohen's *d* was computed to measure effect size.

Results

Descriptive Statistics

Descriptive statistics of raw OT, log OT, total ANRQ scores, RQ categories, and recent SLE are reported in Table 2. On the ANRQ, all participants had a total score above the clinical cut-off of 23, indicating that they experienced a high degree of CPA. When participants were asked to describe their recent SLE, they listed a range of stressors, changes and losses, such as marital difficulties and the death of loved ones. Log OT, recent SLE, and attachment security were not significantly associated with demographic variables (parity, age, marital status, educational level, and weeks pregnant) or with medication use.

Eight securely attached participants, and 13 insecurely attached participants, had recently experienced SLE. Collinearity statistics (tolerance = .976; VIF = 1.024; condition index = 1.00-4.897) confirmed that the data satisfy the regression assumption of multicollinearity, and that attachment security was not significantly related to recent SLE.

Attachment Security and OT

On the categorical component of the RQ, those who classified themselves as insecurely attached had lower levels of endogenous OT ($M = 5.33$, $SD = .45$) than those who classified

themselves as securely attached (M = 5.68, SD = .26); t (28) = 2.23, p = .034. The effect size for this finding was large (d = 0.86). Raw levels of OT in securely versus insecurely attached participants are presented in Figure 1.

Recent SLE and OT

There was a relationship between OT and recent SLE; women who reported experiencing stresses, changes or losses in the last 12 months had significantly lower OT levels (M = 5.33, SD = .41) than those who had not had these experiences (M = 5.71, SD = .37); t (28) = 2.391, p = .024. The effect size for this finding was large (d = 0.95). Raw levels of OT in participants without and with SLE are presented in Figure 2.

Attachment Security, Recent SLE and OT

A multiple linear regression was conducted to test the third hypothesis that attachment security and recent SLE would both make significant contributions to prenatal levels of plasma OT (Table 3). The overall model was significant; F (2, 27) = 8.214, p = .002. Thirty-eight percent of the variance in OT was explained by attachment security and recent SLE. Both factors had significant negative weights, indicating that insecure attachment and recent SLE both predicted lower levels of prenatal OT.

Discussion

A growing body of literature has highlighted the importance of considering the interplay of biological and psychosocial factors in trying to understand perinatal mental illness, and its implications for the mother-infant relationship. Recent reports have indicated that prenatal OT

may be protective in women who reported high levels of CPA; higher levels of OT were positively associated with sensitive maternal behavior, and inversely related to depressive symptomatology, in women who reported high rates of CPA (Zelkowitz et al., 2014). The present study aimed to determine which individual difference factors predict who, among those with high levels of CPA, will have high versus low levels of prenatal OT. Our principle finding was that attachment insecurity and recent SLE each independently, and significantly, predicted lower levels of plasma OT in a sample of pregnant women who reported high levels of CPA.

We found that participants with insecure adult attachment styles had lower OT levels than those with a secure adult attachment style. This is consistent with past research showing that endogenous OT levels are positively associated with secure attachment, and inversely related to insecure attachment in community samples of men and women. The present study extended these past findings to a clinical sample of women with mood and anxiety disorders. This distinction in sample composition is important given that mental illness (along with other individual differences) has been found to moderate OT effects (Bartz, Zaki, et al., 2011; Olff et al., 2013; Simeon et al., 2011). One previous report linking higher OT levels and secure attachment in adults included some community sample participants and others who were exposed to early trauma (Pierrehumbert et al., 2012). However, participants with significant psychopathology were excluded. Thus, to our knowledge, the present study is the first to demonstrate a relationship between adult attachment security and circulating OT levels in a clinical sample.

It is not fully known how OT exerts an influence on social affiliation and bonding. Through a bio-behavioral feedback mechanism, women with lower levels of OT may be less likely to approach others (Francis et al., 2000) or to view their social interactions as rewarding (Carter, 1998; Liu & Wang, 2003; Pedersen, 1997; Strathearn et al., 2009). Their

resulting withdrawal may, in turn, further dampen the oxytocinergic system. However, as our study and past reports indicate, securely attached adults have higher levels of OT than insecurely attached adults. Their higher OT levels may promote approach and trust-related behaviors, and these affiliative interactions may in turn increase OT levels in a positive feedback loop. As such, attachment security may be a protective factor against social withdrawal or isolation in pregnant women reporting high levels of CPA.

Our finding that secure attachment predicts higher levels of prenatal OT has important implications because prenatal OT has been linked to more optimal maternal interactive behaviors and maternal mental health in postpartum women (Feldman et al., 2011; Feldman et al., 2007; Skrundz et al., 2011; Stuebe et al., 2013; Zelkowitz et al., 2014). Indeed, higher levels of prenatal OT may be especially important to mothers with mental illness because, as a group, they are at risk of exhibiting poorer interactive behaviors with their infants (Coyne, Low, Miller, Seifer, & Dickstein, 2007; Crockenberg & Leerkes, 2003; Lovejoy et al., 2000). Maternal interactive behaviors are linked, in turn, to a wide range of child development outcomes including attachment security (de Wolff & Van Ijzendoorn, 1997; Dexter et al., 2013; Laucht et al., 2002; Mäntymaa et al., 2004; Wang & Dix, 2013).

Much of the literature on stress and OT has focused on the impact of early life stress on OT levels, and our findings indicate that SLE endured during adulthood can affect the OT system as well. In particular, in a sample of pregnant women who reported high levels of CPA, we found that participants who recently endured SLE had lower levels of OT than those who did not report these experiences. The addition of a SLE in the context of already high CPA may overtax or dampen the OT system, resulting in lower endogenous levels. Without a background of CPA, the OT system may be better able to respond to SLE by releasing OT to perform anxiolytic and

stress-reducing functions. Although recent SLE in the present study are not equivalent to acute psychosocial stressors in experimental studies, our findings suggest that additional research is needed to investigate the possibility that an individual's background of stressful experiences may impact their OT stress response (Pierrehumbert et al., 2010).

A number of mechanisms may help to explain why recent SLE may be related to OT levels. Neumann and Landgraf (2012) proposed that a coordinated balance exists between OT and arginine vasopressin (AVP), whereby positive social cues may transfer the balance towards increased activity of the OT system (and its anti-depressant and anxiolytic effects). Conversely, risk factors such as adversity may transfer the balance towards the AVP system (and its depressive and anxiogenic effects). Thus, in our sample of women, the experience of a recent stressor in the context of already high CPA may have further transferred the balance toward AVP and away from OT, explaining the lower OT levels.

Moreover, it has been suggested that individuals who are repeatedly exposed to psychosocial stressors may exhibit cumulative and greater changes in DNA methylation, and that individuals who endured early adversity may exhibit heightened sensitivity to stress and may be more likely to experience changes in OTR gene methylation when faced with an acute stressor (Unternaehrer et al., 2012).

Limitations

As has been done in other research, we assessed plasma OT to approximate central OT (Feldman et al., 2012); central OT is thought to regulate social constructs (e.g. trust) related to attachment but cannot be readily assessed in humans. Although it is currently unknown whether peripheral OT levels reflect brain activity, administration of intranasal OT has been shown to

elicit increases in plasma OT (Burri, Heinrichs, Schedlowski, & Kruger, 2008). Moreover, a recent human study found that OT levels in plasma are positively associated with OT levels in cerebrospinal fluid, further supporting the use of plasma OT as a proxy for central OT in human studies (D. S. Carson et al., 2014).

Although some have argued in favor of sample extraction (Szeto et al., 2011), we opted for un-extracted samples because extraction can result in undetectable OT levels (Zhong et al., 2012). A strong correlation has been reported between extracted and non-extracted serum OT levels in rhesus monkeys (Michopoulos, Checchi, Sharpe, & Wilson, 2011). In addition, recent research using mass spectrometry has indicated that the actual values for OT are at least 1000 times higher than those reported using enzyme-based assays (Martin & Carter, 2013). The use of an extraction procedure discards most of these peptides because they bind to plasma proteins, such as albumin.

Finally, although recent studies of OT and attachment (e.g. Strathearn et al., 2009), and OT and adversity (e.g. Heim et al., 2009; Meinlschmidt & Heim, 2007), have employed small sample sizes comparable to ours, our study should be considered an exploratory pilot study, and our findings require replication in larger samples. Given that the ANRQ is a self-report screening tool designed to assess a broad range of adversities across the lifespan, future studies are needed to investigate the relationship between OT and adversity using more comprehensive measures of early life stress and current stressors.

Conclusions

The present study is the first to examine the contributions of attachment security and recent SLE to levels of plasma OT in a sample of pregnant women with high levels of CPA. We

found lower levels of prenatal OT in women with insecure attachment styles, and in those who experienced recent SLE in the context of already high CPA. As such, this study represents a step towards identifying which pregnant women with high levels of CPA are likely to have high versus low levels of OT, which have in turn been linked to perinatal mental health and caregiving behaviors in women with high levels of CPA.

Future Directions

Since the participants in this study were pregnant, it was not yet possible to determine how their OT levels and attachment styles related to their maternal behaviors. To this end, a follow-up study of these women and their now 2.5-year-old children is underway to assess the mother-child relationship, including interactive behavior and child's attachment security. This will enable us to examine the intergenerational transmission of attachment, as well as its relation to maternal OT and adversity.

Table 1

Demographic Characteristics

	M	*SD*	Range
Age (years)	32.87	4.29	25-41
Weeks pregnant	24.01	6.90	9-37
Years of schooling	15.00	2.27	11-18
Highest degree of education			
High school		10% (n = 3)	
Junior college/trade degree		30% (n = 9)	
Bachelor's degree		40% (n = 12)	
Master's degree		20% (n = 6)	
Relationship status			
Single		6.7% (n = 2)	
Partnered		93.3% (n = 28)	
Cohabiting		13.3% (n = 4)	
Married		80% (n = 24)	
Parity			
Never given birth before		36.7% (n = 11)	
One to five other children		63.3% (n = 19)	
Psychiatric diagnoses			
Mood disorders		50% (n = 15)	
Anxiety disorders		26.67% (n = 8)	
Comorbid mood and anxiety		16.67% (n = 5)	
Adjustment disorders		6.67% (n = 2)	
Psychotropic medication			
None		76.7% (n = 23)	
Selective serotonin re-uptake inhibitor		16.6% (n = 5)	
Serotonin–norepinephrine reuptake inhibitor		3.3% (n = 1)	
Atypical antipsychotic, benzodiazepines		3.3% (n = 1)	

Table 2

Descriptive Statistics

	M	*SD*	Range
Raw OT (pg/ml)	252.24	103.06	62-538
Log OT	5.45	.43	4.12-6.29
Total ANRQ	36.87	6.26	26-54
RQ category			
Securely attached	33.3% (n = 10)		
Insecurely attached	66.7% (n = 20)		
Fearful	40% (n = 12)		
Preoccupied	23.3% (n = 7)		
Dismissing	3.3% (n = 1)		
Recent SLE (stresses, changes or losses in the last 12 months)			
Yes	70% (n = 21)		
No	30% (n = 9)		

Note. OT = oxytocin; ANRQ = Antenatal Risk Questionnaire; RQ = Relationship Questionnaire; SLE = stressful life events; pg/ml = picograms per millilitre.

Table 3

Multiple Linear Regression Model of Prenatal OT

Predictors	B	SE	β	*t*	*p*
Attachment security	-.413	.137	-.462	-3.011	.006
Recent SLE	-.444	.141	-.483	-3.146	.004

Note. SLE = stressful life events.

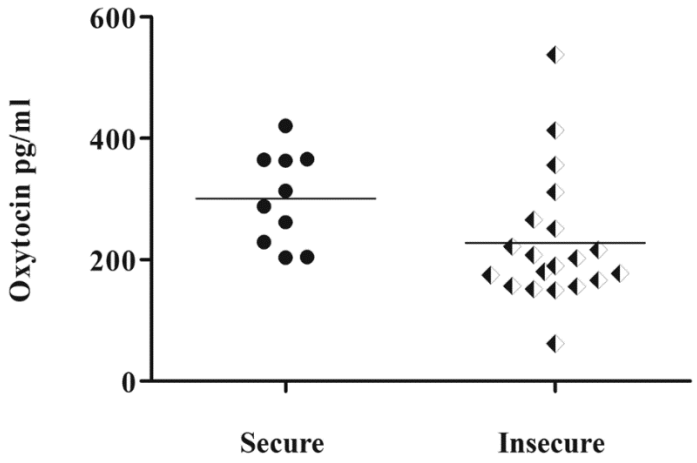

Figure 1. Raw OT levels (pg/ml) of securely and insecurely attached participants. pg/ml = picograms per millilitre. Raw OT levels ranged from 203.74 to 420.77 pg/ml for securely attached participants (M = 301.44, SD = 76.29). Raw OT ranged from 61.68 to 537.56 pg/ml for insecurely attached participants (M = 227.65, SD = 107.44).

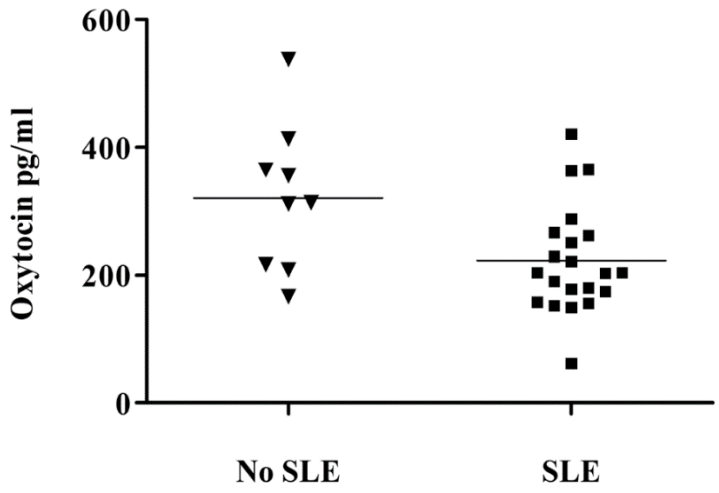

Figure 2. Raw levels of OT in participants without and with SLE. SLE = stressful life events; pg/ml = picograms per millilitre. Raw OT levels ranged from 166.84 to 537.56 pg/ml for participants who did not report recent SLE (M = 321.02, SD = 115.13). Raw OT ranged from 61.68 to 420.77 pg/ml for participants who did report recent SLE (M = 222.77, SD = 84.01).

Transition to Manuscript 2

Study 1 aimed to explore why oxytocin (OT) is inversely related to a history of adversity in some individuals but not others. We posited that experiences occurring later in life may also contribute to individual differences in levels of OT in childbearing women with a history of adversity. We recruited a clinical sample of pregnant women with mood, anxiety or adjustment disorders, all of whom reported high rates of psychosocial adversity across the lifespan. We found that those with recent stressful life events or insecure attachment styles had lower levels of OT.

Because mothers in Study 1 were pregnant, it was not yet possible to evaluate their interactive behaviors with their infants. Although multiple studies have linked maternal OT levels to interactive behavior in community samples of healthy mothers, few have examined this relationship in mothers with mental health problems. However, there is reason to believe that OT may play an especially important role in the interactive behaviors of mothers with mental health problems. In particular, mothers with mood or anxiety disorders have been shown to exhibit poorer interactive behaviors, and some studies suggest that they may have lower levels of OT than mothers without these mental health problems. In addition, mothers with these mental health problems tend to exhibit more depressive (e.g. tense, self-focused, or lethargic) interactive behaviors with their infants, and animal and human studies indicate that OT may exert anti-depressant and anxiolytic effects. As such, OT may help to buffer the effects of mood or anxiety disorders on the caregiving behaviors of mothers with these mental health problems.

To explore this possibility, Study 2 examined the association between OT and interactive behaviors in mothers with and without mental health problems. It was expected that maternal mental health would moderate the association between OT levels and interactive behaviors, such

that mothers with mood or anxiety disorders who had higher levels of OT would exhibit less depressive interactive behaviors than those with lower levels of OT. As mothers without these mental health problems were not expected to exhibit many depressive interactive behaviors, these antidepressant or anxiolytic roles of OT were expected to be less evident in this group of mothers.

Manuscript 2: Maternal Mental Health Moderates the Relationship between Oxytocin and Interactive Behavior

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Abstract

Purpose: Mothers with mood or anxiety disorders exhibit less optimal interactive behavior. The neuropeptide oxytocin (OT) has been linked to more optimal interactive behaviors in mothers without mental illness, and it may play a particularly beneficial role in mothers with mood or anxiety disorders given its anti-depressant and anxiolytic functions. We compared the relationship between OT and interactive behavior in mothers with and without mental health problems. **Methods:** Participants included 20 women diagnosed with postpartum mood or anxiety disorders (clinical sample), and 90 women with low levels of depression and anxiety during pregnancy and postpartum (community sample). At 2 months postpartum, blood was drawn to assess maternal OT levels, and mother-infant interaction was coded for maternal sensitivity, intrusiveness, remoteness and depressiveness. **Results:** Clinical mothers exhibited less sensitive, more intrusive and more depressive interactive behaviors than community mothers. The groups did not differ in OT levels. Mothers with higher OT levels were less intrusive with their infants. Higher OT levels were associated with less depressive interactive behavior only in clinical mothers. **Conclusions:** OT was associated with positive interactive behaviors in both groups. In clinical mothers, the calming and soothing effects of OT may promote more relaxed, energetic, and infant-focused interactive behaviors.

Keywords: Oxytocin, interactive behavior, mood and anxiety disorders

Introduction

Mothers with postpartum mood or anxiety disorders are at greater risk for exhibiting poor interactive behaviors (McErlean & Eapen, 2012). For instance, depressed mothers have been shown to be less sensitive with their 6- to 30-month-olds (Coyne et al., 2007; Crockenberg & Leerkes, 2003). They also exhibit fewer matched states and less synchrony with their children (for a review, see Feldman, 2007). In a meta-analysis of studies with children up to 16 years of age, depressed mothers were found to exhibit less enthusiastic and pleasant behaviors, as well as increased negative affect and more coercive, hostile, disengaged, and uninvolved behaviors (Lovejoy et al., 2000). Similarly, during interactions with their infants, anxious mothers exhibited less sensitivity (Feldman et al., 2009; Nicol-Harper et al., 2007), less structuring (Zelkowitz et al., 2009), and more exaggerated (e.g. excessively frequent) behavior (Kaitz, Maytal, Devor, Bergman, & Mankuta, 2010). Maternal interactive behaviors have important implications in that they predict various child outcomes, such as attachment style (Dexter et al., 2013), internalizing and externalizing symptoms (Laucht et al., 2002; Mäntymaa et al., 2004), as well as linguistic and cognitive development, socio-emotional competence, and responsiveness toward their mothers (Wang & Dix, 2013).

A consideration of hormonal factors associated with both maternal mood and behavior may be useful in elucidating how maternal mental health impacts the mother-infant relationship. One such factor that has received increased attention in recent decades is oxytocin (OT), a neuropeptide primarily produced in the supraoptic and paraventricular nuclei of the hypothalamus (Brunton & Russell, 2008a). OT has been linked to maternal caregiving behaviors in both animal and human studies (for reviews, see Galbally et al., 2011; Rilling & Young, 2014). In animal studies, female rats who were more responsive toward pups and exhibited

higher levels of pup licking/grooming had higher OT receptor levels in certain brain regions, including the central nucleus of the amygdala and the bed nucleus of the stria terminalis (Champagne, Diorio, Sharma, & Meaney, 2001). Moreover, oxytocin knockout mice licked their pups less frequently (Pedersen, Vadlamudi, Boccia, & Amico, 2006). Similarly, in human studies, maternal levels of OT during the first postpartum year have been positively associated to synchrony with infant cues (Atzil et al., 2011; Feldman et al., 2011; Gordon et al., 2010b), touch, gaze, positive affect, vocalizations (Feldman et al., 2007; Feldman et al., 2012; Gordon et al., 2010a), and positive interactive sequences (Feldman et al., 2011). Thus, OT has been linked to more optimal interactive behaviors in community samples of mothers without mental illness.

Multiple mechanisms may explain the association between OT and maternal behavior. In humans, OT has been shown to enhance activation in brain areas related to bonding and empathy (i.e. the insula and inferior frontal gyrus pars triangularis; Riem et al., 2011), and functional connectivity between brain areas related to emotion, touch and understanding another's mind (i.e. the cerebellum, postcentral gyrus, and posterior cingulate cortex in adults with supportive upbringings; Riem, van IJzendoorn, et al., 2013). Moreover, the administration of OT has been found to increase emotion recognition (Lischke et al., 2012), as well as the capacity to decipher the mental states of others using information from the eye area (Domes et al., 2007).

Individuals with mood or anxiety disorders, who tend to exhibit impaired interactive behavior, have also been shown to have lower levels of endogenous OT. In particular, researchers have noted a negative relationship between OT levels and both anxiety (Eapen et al., 2014; Scantamburlo et al., 2007) and depression (Anderberg & Uvnas-Moberg, 2000; Apter-Levy et al., 2013; Gordon et al., 2008; Ozsoy et al., 2009; Scantamburlo et al., 2007; Skrundz et al., 2011; Stuebe et al., 2013; Zetzsche, Frasch, Jirikowski, Murck, & Steiger, 1996). Given that

OT has been linked to both maternal interactive behavior and mental health, it may help to explain why mothers with mental health problems exhibit less optimal interactive behaviors with their infants.

A few studies of OT and interactive behavior in depressed samples have emerged in recent years. Relative to non-depressed mothers and their children, depressed mothers had lower OT levels and their 6-year-old children exhibited decreased social engagement during interactions (Apter-Levy et al., 2013). In addition, depressed mothers who were administered OT (versus placebo) were more protective when an intrusive stranger approached their infant (Mah et al., 2014), and tended to describe their relationship with their child more positively (Mah et al., 2013). However, the latter two studies lacked a control group of non-depressed mothers, making it impossible to tease apart the roles that maternal mental health and OT played in interactive behavior during infancy. Thus, no studies to our knowledge have compared the relationship between endogenous OT levels and interactive behaviors during the postpartum period in mothers with and without mental health problems.

It is possible that OT plays a particularly beneficial role in mothers with mood or anxiety disorders due to its anxiolytic and stress-reduction properties. Research suggests that OT may inhibit activation of the amygdala (Kirsch et al., 2005; Riem et al., 2011), and of the hypothalamic–pituitary–adrenal axis (Carter, 1998; Neumann, 2002). OT has also been found to decrease levels of adrenocorticotropic hormone (K. J. Parker et al., 2005; also see Legros, 2001) and cortisol (Ditzen et al., 2009; when combined with social support in Heinrichs et al., 2003). Given the anxiolytic effects of OT (de Oliveira et al., 2012; Heinrichs et al., 2003; McRae-Clark, Baker, Maria, & Brady, 2013; for males but not females in Feifel, Macdonald, McKinney, Heisserer, & Serrano, 2011), mothers with higher OT levels might be less tense during

interactions with their infants. Moreover, in light of animal studies demonstrating anti-depressant effects of OT (Arletti & Bertollni, 1987; Nowakowska et al., 2002; for a review, see Slattery & Neumann, 2010), mothers with higher OT levels might be less withdrawn, remote and self-focused during interactions with their infants.

In sum, previous literature has demonstrated that mothers with mood and anxiety disorders show deficits in interactive behaviors, and lower levels of OT, a neuropeptide which has been linked to more optimal caregiving behaviors in community samples of mothers without mental health problems. OT may play a particularly beneficial role in mothers with mood or anxiety disorders given its anti-depressant and anxiolytic functions, raising the question of whether mental health moderates the association between OT levels and interactive behavior.

Thus, the current study aimed to test 3 hypotheses: (1) Mothers with mood or anxiety disorders will interact less optimally (more insensitive, intrusive, remote and depressive) with their infants; (2) Mothers with mood or anxiety disorders will have lower levels of OT than mothers without these mental health problems; (3) In light of previous research linking OT to responsiveness, engagement, emotion recognition and synchrony, we expected that higher OT levels would be linked to more sensitive and less intrusive behaviors in both mothers with and without mental health problems. In light of the anxiolytic and anti-depressant effects of OT, we expected that higher OT levels would also be linked to less tense, remote, self-conscious, withdrawn, or lethargic behaviors in mood or anxiety disordered mothers. In contrast, we expected that these roles of OT would be less necessary, and thus less evident, in mothers without mood or anxiety disorders. To test the latter hypothesis, we examined whether maternal mental health moderated the relationship between OT levels and (tense, remote, self-conscious, withdrawn, or lethargic) interactive behaviors.

Methods

Participants

The present study represents a subsample of a larger study on maternal OT, mental health and the developing mother-infant relationship. Women who sought outpatient care for mental health problems at the Perinatal Mental Health Service of a psychiatry department were recruited to participate in the larger study.

A physician conducted a psychiatric interview in order to obtain a diagnosis of mental health problems in accordance with the Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition – Text Revision (DSM-IV-TR; American Psychiatric Association, 2000). Of the 45 women who were approached, 9 (20%) refused to participate in the study. Reasons for refusal included feeling better, feeling overwhelmed, lack of time or interest, and husband not wanting his spouse to participate.

Because the present analysis pertained to OT and interactive behaviors in mothers with mood or anxiety disorders, our inclusion criteria were a diagnosis of mood, anxiety or adjustment disorder with depressed and/or anxious features, as well as participation in the blood draw and interaction session portions of the study. Twelve of the 36 participants did not meet these inclusion criteria. Of the remaining 24 women, four mother-infant interactions could not be scored because the mothers declined to be filmed or because their video could not be coded. Thus, the final sample consisted of 20 women (9 mood disorders, 5 anxiety disorders, 4 comorbid mood and anxiety disorders, 2 adjustment disorders with depressed and/or anxious features). For brevity, we refer to this group as the clinical sample.

The comparison group was derived from a longitudinal study of 341 pregnant women recruited during a routine obstetrical visit (Zelkowitz et al., 2014). They completed the Edinburgh Postnatal Depression Scale (EPDS; J. L. Cox, Holden, & Sagovsky, 1987), a measure of depressive symptomatology during the perinatal period, at 12-14 weeks gestation, 32-34 weeks gestation, one week postpartum, and 2 months postpartum. They also completed the Generalized Anxiety Disorder 7-item scale (GAD-7; Spitzer, Kroenke, Williams, & Lowe, 2006), a measure of anxious symptomatology, at 12-14 weeks gestation, 32-34 weeks gestation, and 2 months postpartum. Because other researchers have used EPDS cut-off scores as low as 9/10 (Affonso, De, Horowitz, & Mayberry, 2000; Seimyr, Edhborg, Lundh, & Sjögren, 2004), we included all women with EPDS scores below 8 at all four time points. They also scored at or below the cut point for mild anxiety (0-5; Spitzer et al., 2006) on the GAD-7 *at all three time points.* As such, we obtained a community sample of women who were neither depressed nor anxious during the perinatal period. The final sample consisted of 90 women with low scores on both the EPDS and GAD-7, and who completed both the interaction session and the postpartum blood draw. We refer to this group as the community sample.

Demographic characteristics are reported in Table 1. Most women were partnered. On average, participants were in their early thirties. The majority had a university degree. The participating infant was the firstborn for almost half of the mothers. Most of the infants were breastfed (either exclusively or in combination with formula). Eight (40%) of the 20 clinical sample participants reported taking psychotropic medication when they were interviewed by the medical doctor: 3 were taking selective serotonin reuptake inhibitors (SSRIs), 2 were taking benzodiazepines, 1 took an SSRI and benzodiazepine, 1 took an SSRI, benzodiazepine and

cyclopyrrolone, and 1 took a selective norepinephrine reuptake inhibitor (SNRI), atypical antipsychotic, and benzodiazepine.

Measures

OT measurement has been described elsewhere (Samuel et al., 2015a).

The Global Rating Scales (GRS; Murray, Fiori-Cowley, Hooper, & Cooper, 1996) is a coding system used to assess mother-infant interactive behaviors. Scores have been shown to predict cognitive outcomes in 18-month-old infants (Murray et al., 1996) and to converge with the Infant-Toddler version of the Home Observation for the Measurement of the Environment (Gunning et al., 2004). This measure has been used with mothers with mental health problems, including schizophrenia (Riordan, Appleby, & Faragher, 1999) and borderline personality disorder (Crandell, Patrick, & Hobson, 2003). It has also been employed in multiple countries, including four European cities (Gunning et al., 2004).

The four maternal scales were calculated (Fiori-Cowley, Murray, & Gunning, 2000), for which scores range from 1 (non-optimal) to 5 (optimal). The maternal sensitivity score was the average of 5 subscales: warm/positive (endearing and affectionate), accepting (uncritical), responsive (detects and responds to infant cues), non-demanding (attends to infant's interest rather than making requests of him/her), and sensitive (consistently empathic and responsive). The maternal non-intrusiveness score was the average of 2 subscales: non-intrusive behavior (does not impose on the infant in a way that elicits distress) and non-intrusive speech (does not interrupt infant). The maternal non-remote score was the average of 2 subscales: non-remote (very aware of infant) and non-silent (talking without prolonged silences). The maternal non-

depressive score was the average of 4 subscales: happy (smiling, joking, laughing), much energy (lively), absorbed in infant (focused on interaction), and relaxed (at ease).

To establish inter-rater reliability, a second coder coded 13 videos (3 clinical participants, and 10 community participants from the larger longitudinal study; MacKinnon et al., 2014). Intra-class correlation coefficients (absolute agreement, two-way random, single measures) were .52 for sensitivity, .69 for non-intrusiveness, .37 for non-remoteness, and .74 for non-depressive. This is considered satisfactory agreement as 50.3% of items were rated identically by both coders, and 89.9% of items were within one point for both coders (R. Costa & Figueiredo, 2011), which is in line with other studies using this measure (e.g. Wan et al., 2007).

Procedure

Approval was obtained for this research project by the research ethics committee of the hospital where the research was conducted. Participants signed an informed consent form prior to beginning the study.

At approximately 2 months postpartum, a nurse and research assistant visited the mother-infant dyad at home. The nurse performed a blood draw to assess endogenous OT levels. Consistent with past research (Feldman et al., 2011; Gordon et al., 2010a), blood was drawn 30 minutes or more after breastfeeding in order to minimize the impact of breastfeeding on OT levels (White-Traut et al., 2009).

Demographic information (parity, age, marital status, educational level, infant gender, and breastfeeding status) was obtained from participants. In addition, mother-infant interaction was filmed for five minutes. Mothers were instructed to interact with their babies as they typically do at home but without toys. The mother sat facing her infant, who was in a baby seat.

In order to film both members of the dyad, a mirror was placed near the infant and facing the mother. Maternal interactive behaviors were coded from these videos using the GRS.

Data Analysis

Visual inspection revealed that raw OT values were positively skewed. We therefore log-transformed OT levels, as was done in previous studies on OT and parent-infant interactions (e.g. Feldman et al., 2012; Gordon et al., 2010a). Analyses were performed on log OT levels rather than raw OT levels. In the community sample, 2 participants' log OT values corresponded to standardized scores of 3.50 and 3.54, which surpassed the cut-off of 3.29 for univariate outliers (Tabachnick & Fidell, 2006). We decided to retain their data in the analyses as excluding their data did not significantly change results of the regression analyses. Moreover, values above their raw OT values of 1971.18 and 2029.61 pg/ml have been reported in other studies of OT in pregnant and postpartum women (e.g. Feldman et al., 2007; Levine et al., 2007).

An alpha level of .05 was utilized in all statistical tests. We first conducted independent samples t-tests and chi square tests to confirm that the clinical and community samples were comparable in terms of demographic variables (parity, age, educational level, infant gender) as well as breastfeeding status. Level of education was computed as a continuous variable; years of schooling were determined based on participants' highest completed degree (11 years for high school, 13 for junior college or trade school, 16 for bachelor's degree, 18 for master's degree, and 21 for doctorate degree).

We then conducted descriptive statistics for OT and GRS in each group. We also conducted Pearson bivariate correlations and independent samples t-tests to determine whether OT levels and GRS scores were related to the demographic variables.

To test our hypotheses, we conducted independent samples t-tests to compare the community and clinical samples on interactive behaviors (sensitivity, non-intrusive, non-remote, and non-depressive) and OT levels. Multiple linear regression analyses were conducted to test our hypothesis that maternal mental health would moderate the relationship between OT levels and interactive behaviors. Mental health group was dummy coded as 0 (community sample) or 1 (clinical sample). Log OT levels were entered as a continuous variable. To obtain the interaction term (i.e. the moderator term), mental health group (community versus clinical) and log OT levels were standardized, and their product was then computed.

Results

Descriptive Statistics

Descriptive statistics for OT and GRS in each sample are presented in Table 2. Clinical and community samples did not differ significantly in parity, age, marital status, educational level, or breastfeeding status (any versus none). However, the clinical sample had more female infants than the community sample (Chi Square = 5.492, $df = 1$, $p = .019$). In the clinical sample, OT levels and interactive behaviors were not significantly different in those who were taking psychotropic medication, versus those who were not.

Non-remoteness was negatively associated with parity ($r = -.233$, $p = .014$), such that mothers with more children were more remote during interactions with the participating infant. OT level and GRS scores were not related to any other demographic variables. Also, sensitivity scores were higher in those who breastfed (exclusively or in combination with formula; $M = 3.68$, $SD = .61$) relative to those who formula fed exclusively ($M = 3.26$, $SD = .57$); $t(108) = -2.10$, $p = .038$. However, OT levels did not differ significantly in those who breastfed

(exclusively or in combination with formula; $M = 285.64$, $SD = 319.97$) compared to those who formula fed exclusively ($M = 194.12$, $SD = 69.43$).

Group differences in interactive behavior and OT

The community sample exhibited significantly more sensitivity than the clinical sample (t (108) = 3.025, $p = .003$), even when controlling for breastfeeding status (any versus none) in a multiple regression analysis; F (2, 107) = 6.447, $p = .002$. The groups also differed in non-intrusiveness (t (24.057) = 2.339, $p = .028$) and non-depressive scores (t (108) = 4.347, $p = .000$). They did not differ significantly in their non-remoteness scores (t (108) = 1.769, $p > .05$), even when controlling for parity in a multiple regression analysis. They also did not differ in their levels of plasma OT (t (108) = -0.072, $p > .05$).

Relationship between OT and interactive behavior

As displayed in Table 3, OT levels were positively correlated with 2 of the 4 maternal scales (non-intrusive scores in both groups combined, and non-depressive scores in the clinical sample alone). Therefore, multiple regression analyses examined whether maternal mental health, OT levels, or their interaction contributed to non-intrusive and non-depressive behaviors.

Models of Interactive Behavior

Multiple linear regression analyses were conducted to test our moderation hypothesis. First, we examined whether maternal mental health moderated the relationship between OT levels and non-intrusive interactive behavior (Table 4). The overall model was significant; F (3, 106) = 4.724, $p = .004$. Twelve percent of the variance in maternal non-intrusive behavior was

explained by mental health group, OT levels, and their interaction term. There was a main effect of mental health on non-intrusiveness; community sample mothers exhibited less intrusive behavior than clinical sample mothers. There was also a main effect of OT on non-intrusiveness; mothers with higher OT levels exhibited less intrusive behavior than mothers with lower OT levels. The interaction term was not significantly related to non-intrusiveness.

Next, we examined whether maternal mental health moderated the relationship between OT levels and non-depressive interactive behavior (Table 5). The overall model was significant; F (3, 106) = 8.592, p = .000. Twenty percent of the variance in maternal non-depressive behavior was explained by mental health group, OT levels, and their interaction term. There was a significant main effect of mental health on non-depressive interactive behavior; community sample mothers exhibited less depressive behavior than clinical sample mothers. There was no main effect of OT on non-depressive interactive behavior. There was a significant interaction effect of mental health and OT on non-depressive interactive behavior, suggesting that maternal mental health moderated the relationship between OT levels and depressive interactive behaviors. Specifically, higher levels of OT were linked to less depressive behavior only in mothers with mood or anxiety disorders (Figure 1).

Discussion

The current study sought to determine whether the associations between OT and maternal behavior were similar in mothers with and without mental health problems. That is, does maternal mental health moderate the relationship between OT and interactive behaviors?

Consistent with past research and our first hypothesis, we found that the community sample mothers exhibited more optimal interactive behaviors (more sensitive, non-intrusive,

non-depressive) than clinical sample mothers. The groups did not differ significantly in non-remote behaviors; however, the measurement of this variable may have lacked precision, as reflected in a low level of inter-rater agreement.

In contrast to our second hypothesis, we did not find that community sample mothers had higher levels of endogenous OT than clinical sample mothers. Rather, both groups exhibited a range of OT levels. The findings linking OT and depression have been inconsistent (Bell, Nicholson, Mulder, Luty, & Joyce, 2006; Kim, Soeken, et al., 2014); relative to controls, mean OT levels in depressed participants have been found to be lower (Anderberg & Uvnas-Moberg, 2000; Ozsoy et al., 2009), higher (K. J. Parker et al., 2010; during an affiliation imagery task in Cyranowski et al., 2008), or not significantly different (Pitts et al., 1995; van Londen et al., 1997). Similarly inconclusive results have been reported regarding OT and anxiety (Eapen et al., 2014), with researchers finding negative (Scantamburlo et al., 2007) or no associations (Gordon et al., 2008).

Methodological differences across studies may play a role in these conflicting results. The relationship between OT and depression/anxiety in pregnant or postpartum women (Eapen et al., 2014; Skrundz et al., 2011; Stuebe et al., 2013) may be affected by the hormonal fluctuations that occur during the perinatal period. Some have examined the relationship between OT and degrees of self-reported symptomatology (e.g. Eapen et al., 2014; Gordon et al., 2008), the results of which may not extend to comparisons of OT in those meeting diagnostic criteria for a mood/anxiety disorder versus controls (e.g. Cyranowski et al., 2008; Ozsoy et al., 2009). In a study of childbearing women, prenatal levels of OT were shown to predict postpartum mood (Skrundz et al., 2011), indicating that these variables may be linked prospectively if not concurrently.

Methodological issues notwithstanding, these inconsistent findings suggest that the relationship between OT and mental health is not straightforward. Our data show that postpartum women with (and without) mood and anxiety disorders exhibit a range of OT levels. Indeed, OT levels have been found to vary greatly among women in the perinatal period (e.g. Feldman et al., 2007; Levine et al., 2007; Prévost et al., 2014; Zelkowitz et al., 2014), and researchers have begun to consider why some childbearing women have higher versus lower levels of OT. Individual differences in OT levels may be related to a range of factors, including polymorphisms of the OT receptor gene (Apter-Levy et al., 2013), attachment style, and abuse endured early in life (Eapen et al., 2014). As such, our understanding of why some mothers from both samples had lower levels of OT would have been strengthened had we evaluated the contributions of such additional factors to individual differences in OT. Further research is needed to investigate other factors, such as stress and early adversity that may underlie the relationship that is sometimes detected between OT levels and mental health problems.

We also did not find evidence that OT levels differed in women who breastfed compared to those who did not. This is consistent with past reports that baseline levels of OT do not differ in the two groups when OT is measured 30 minutes or more after breastfeeding (Feldman et al., 2011; Gordon et al., 2010a), as was the case in our study. Similarly, we found that OT levels and interactive behaviors were not significantly different in those who were, versus those who were not, taking psychotropic medication. This is consistent with a recent report of no difference in OT levels before versus after 12-week SSRI treatment in depressed patients (Keating et al., 2013). Moreover, although the clinical sample had more female infants than the community sample, the GRS scores were not significantly different in male versus female infants in both samples combined. This is consistent with other research using the GRS (Murray et al., 1996),

which likewise did not find gender differences on these interaction measures. Finally, although mothers with more children were found to be more remote during interactions with the participating infant, the correlation was weak and may therefore lack clinical significance in spite of its statistical significance.

Consistent with previous research, we found that mothers with higher levels of OT exhibited more optimal interactive behavior. In particular, they were less intrusive during interactions with their infants. OT may have improved the ability of mothers to recognize emotions (Lischke et al., 2012) and mental states (Domes et al., 2007) in their infants, thereby encouraging these mothers to consider their infants' cues rather than their own agendas (the latter being the hallmark of intrusiveness). This interpretation is in line with studies linking OT to more synchronous interactions (Atzil et al., 2011; Feldman et al., 2011; Gordon et al., 2010b).

Finally, our third hypothesis was confirmed; we found that higher OT levels were associated with less depressive behavior in the clinical sample (but not in the community sample who had very low levels of depressive and anxious symptomatology). In mothers with postpartum mood or anxiety disorders, higher levels of OT may have served anxiolytic and anti-depressant functions (Arletti & Bertollni, 1987; de Oliveira et al., 2012; Heinrichs et al., 2003; Nowakowska et al., 2002). This may have enabled clinical sample mothers to behave in a more relaxed, energetic, and infant-focused manner. These calming and soothing functions of OT may have been less necessary (and less evident) in community sample mothers with low levels of depressive and anxious symptomatology. This interpretation is in line with recent reports that OT administration had greater positive effects on stress or fear-related outcomes (e.g. dampened cortisol response and amygdala reactivity) in clinically diagnosed participants relative to controls (Cardoso et al., 2014; Labuschagne et al., 2010).

Limitations

The present study has several limitations. As in other human studies of OT and depression, anxiety and maternal behavior (e.g. Gordon et al., 2010b; Gordon et al., 2008), we measured circulating levels of plasma OT. For ethical and practical reasons, human research cannot directly assess central levels of OT in the brain. However, recent research has indicated a positive association between levels of OT in plasma and cerebrospinal fluid in humans, suggesting that circulating OT levels can be used to approximate central OT levels (D. S. Carson et al., 2014). Moreover, there is some debate in the literature regarding the use of extraction versus non-extraction techniques. We opted to use unextracted samples because mass spectrometry research has shown that extraction can remove a significant portion of the OT in plasma (Martin & Carter, 2013). Finally, our sample of clinical subjects is small and replication in larger samples is needed to determine whether it is representative of (and generalizable to) other postpartum women with mood or anxiety disorders.

Conclusions

Past research on OT and interactive behavior during the postpartum period was either limited to women from community samples (e.g. Atzil et al., 2011; Feldman et al., 2011; Feldman et al., 2007; Feldman et al., 2012; Gordon et al., 2010a, 2010b) or clinical samples of depressed women (Mah et al., 2014; Mah et al., 2013). The current study is the first to our knowledge to directly compare the relationship between OT levels and interactive behavior in postpartum women with and without mental health problems.

Overall, we found that higher OT levels were associated with more optimal interactive behaviors in both samples. As a group, mothers with mood or anxiety disorders exhibited less optimal interactive behavior, but did not have significantly lower levels of OT, than mothers without these mental health problems. Rather, clinical sample mothers had a range of OT values, and those with higher OT levels exhibited more optimal (i.e. relaxed, energetic, and infant-focused) interactive behaviors than those with lower OT levels. Thus, higher levels of maternal OT may buffer the negative effects of mental health problems on caregiving behaviors during interactions with their infants. As such, OT may be useful in elucidating why some depressed mothers exhibit more optimal interactive behaviors than others (Field, Diego, Hernandez-Reif, Schanberg, & Kuhn, 2003). In sum, this study represents a step toward understanding the biological underpinnings of the relationship between maternal mood and behavior, which is known to have important implications for infant and child development.

Table 1

Demographic Characteristics

	Clinical (*n* = 20)	Community (*n* = 90)
Age in years: *M* (*SD*)	30.85 (*SD* = 5.66)	32.68 (*SD* = 4.19)
Years of schooling: *M* (*SD*)	15.40 (*SD* = 2.80)	15.91 (*SD* = 2.42)
Highest degree of education (n,%)		
High school	3 (15.0)	6 (6.7)
Junior college/trade degree	4 (20.0)	16 (17.8)
Bachelor's degree	7 (35.0)	42 (46.7)
Master's degree	5 (25.0)	20 (22.2)
Doctorate degree	1 (5.0)	6 (6.7)
Relationship status (n,%)		
Partnered	20 (100.0)	86 (95.6)
Not partnered	0 (0.00)	4 (4.4)
Prenatal parity (n,%)		
Never given birth before	10 (50.0)	39 (43.3)
One to seven other children	10 (50.0)	51 (56.7)
Feeding (n,%)		
Breastfeeding exclusively	8 (40.0)	70 (77.8)
Breastfeeding and formula	9 (45.0)	13 (14.4)
Formula only	3 (15.0)	7 (7.8)
Gender of baby (n,%)		
Male	6 (30.0)	53 (58.9)
Female	14 (70.0)	37 (41.1)

Table 2

Descriptive Statistics

	Clinical (*n = 20*) *M* (*SD*)	Community (*n = 90*) *M* (*SD*)
OT	249.99 (172.19)	283.39 (329.69)
Sensitivity	3.28 (.60)	3.72 (.59)
Non-intrusiveness	3.55 (.93)	4.07 (.70)
Non-remoteness	4.25 (.73)	4.56 (.71)
Non-depressive	3.70 (.59)	4.34 (.59)

Note. OT = oxytocin.

Table 3

Bivariate Correlations for OT and Interactive Behaviors

	Both groups (n = 110)	Clinical (n = 20)	Community (n = 90)
Sensitivity	.123	.198	.118
Non-intrusiveness	.215*	.262	.221*
Non-remoteness	-.076	.028	-.095
Non-depressive	.055	.560**	-.023

Note. *$p < .05$. **$p \leq 0.01$.

Table 4

Multiple Linear Regression of Non-intrusive Interactive Behavior

	B	SE	β	*t*	*p*
Mental Health	-.521	.182	-.262	-2.869	.005
OT[a]	.275	.112	.227	2.455	.016
Mental Health * OT[a]	.053	.082	.060	.647	.519

Note. OT = oxytocin.

[a] Log-transformed.

Table 5

Multiple Linear Regression of Non-depressive Interactive Behavior

	B	SE	β	*t*	*p*
Mental Health	-.642	.144	-.389	-4.469	.000
OT[a]	.094	.088	.094	1.058	.292
Mental Health * OT[a]	.156	.065	.211	2.390	.019

Note. OT = oxytocin.

[a] Log-transformed.

Transition to Manuscript 3

Study 1 showed that there were individual differences in levels of oxytocin (OT) in a clinical sample of pregnant women with mood, anxiety or adjustment disorders. Study 2 found that individual differences in levels of OT were linked with the depressive interactive behaviors of mothers with these mental health problems during the postpartum period. In particular, higher levels of OT were associated with less depressive interactive behaviors in mothers from the clinical sample, but not in mothers from the community sample.

Additional research is needed to more fully comprehend individual differences in concentrations of OT. Research to date has found inconsistent associations between OT and attachment, leaving it unclear why OT is inversely related to attachment insecurity in some individuals but not others. Study 1 found that, in a sample of 30 pregnant women with mental health problems and high rates of cumulative psychosocial adversity, insecurely attached individuals had lower levels of OT than securely attached participants. However, because all participants in Study 1 had endured high rates of psychosocial adversity, it is important to examine whether the reported association between OT and attachment would extend to mothers without a history of adversity. Indeed, early adversity has been found to moderate the effects of intranasal OT, leading researchers to posit that early adversity can have a lasting impact on the OT system via epigenetic processes. Thus, it is possible that the relationship between OT and attachment may differ for individuals with versus without a history of adversity.

As such, in Study 3, we recruited a larger sample of childbearing women with and without a background of early adversity, and examined whether early adversity moderated the relationship between OT and attachment. Based on the results of Study 1, it is possible that OT is inversely related to attachment insecurity in those with – but not those without – a history of

adversity. Moreover, because all participants in Study 1 were pregnant and were diagnosed with mental health problems at the time of the study, we explored whether the results extended to non-pregnant and non-depressed childbearing women.

Manuscript 3: Oxytocin and Insecure Attachment in Mothers with and without a History of Early Life Stress

Samuel, S., Hayton, B., Gold, I., Feeley, N., Carter, C. S., Bartz, J. A., & Zelkowitz, P. (submitted). Oxytocin and insecure attachment in mothers with and without a history of early life stress. *Attachment & Human Development*.

http://www.tandfonline.com/loi/rahd20

Abstract

Background: The neuropeptide oxytocin (OT) is thought to be related to attachment. However, the nature of this relationship is unclear as studies have found negative, positive, and no associations between OT and attachment insecurity. In order to clarify the relationship between OT and attachment insecurity, it may be useful to consider moderators, such as early life stress (ELS). ELS, which has been linked to both OT levels and attachment insecurity, may have a lasting impact on the OT system via epigenetic modification. Thus, we hypothesized that ELS may moderate the relationship between OT and attachment insecurity. **Methods:** As part of a longitudinal study, 195 childbearing women participated in the present follow-up study at 2.5 years postpartum. Blood was drawn to measure OT levels, and participants completed questionnaires assessing ELS and attachment. **Results and Conclusions:** OT was not associated with ELS or attachment insecurity in the sample as a whole. However, a hierarchical linear regression revealed that ELS moderated the relationship between OT and attachment avoidance; OT was inversely related to attachment avoidance, but only in those with a history of ELS. These findings highlight the need to consider ELS in order to better understand the relationship between OT and attachment.

Keywords: Oxytocin, attachment, early life stress, childhood abuse, childbearing women

Introduction

Oxytocin (OT), a neuropeptide mainly produced in the paraventricular and supraoptic nuclei of the hypothalamus, has been shown to affect maternal physiology and behavior during the perinatal period. In particular, OT promotes labor and lactation (Carter, 1998, 2014), and is associated with the quality of mother-infant interactive behaviors (Atzil et al., 2011; Feldman, Gordon, Schneiderman, et al., 2010; Feldman et al., 2011; Feldman et al., 2007; Feldman et al., 2012; Gordon et al., 2010a, 2010b; Zelkowitz et al., 2014). In addition, some studies have found that OT levels are inversely related to maternal depressive and anxiety symptomatology during the postpartum period (Eapen et al., 2014; Skrundz et al., 2011; Stuebe et al., 2013; Zelkowitz et al., 2014). As such, an examination of the psychosocial factors linked to individual differences in levels of OT could aid in the identification of women who may be more likely to experience mental health problems or to exhibit poorer caregiving behaviors during the perinatal period.

One psychosocial factor that may be relevant is adult attachment, given that endogenous OT has been shown to play an important role in attachment relationships across the lifespan (Feldman et al., 2011). Indeed, OT has even been called a "neurohormone of attachment" (Strathearn et al., 2009). Attachment theory postulates that early life experiences with primary caregivers form the foundation upon which children build mental representations of themselves and others (Bowlby, 1969, 1982), and develop strategies to regulate their emotions (Mikulincer, Shaver, & Pereg, 2003). Consistent and responsive parenting is associated with secure attachment towards caregivers, while inconsistent, cold, or abusive parenting is associated with insecure attachment towards caregivers (Ainsworth, Blehar, Waters, & Wall, 1978).

Individual differences in attachment vary along the two dimensions of attachment anxiety and attachment avoidance, both of which reflect the mechanisms children adopt to cope with

inadequate caregivers (Mikulincer et al., 2003). The attachment system is thought to be hyperactivated in anxiously attached individuals; individuals high in attachment anxiety want to be close with others, but worry that others will not be consistently available (Mikulincer et al., 2003; Shaver & Mikulincer, 2002). In contrast, the attachment system is thought to be deactivated in avoidantly attached individuals; individuals high in attachment avoidance exhibit "compulsive self-reliance", valuing independence over closeness with others (Mikulincer et al., 2003; Shaver & Mikulincer, 2002). Securely attached individuals are low in attachment anxiety and avoidance; they consider themselves to be deserving of love, and view others as available and reliable (Bartholomew & Horowitz, 1991). There are three types of insecure attachment. Preoccupied adults are high in attachment anxiety and low in attachment avoidance; they feel unworthy of love but they yearn for acceptance from others (Bartholomew & Horowitz, 1991). Dismissing adults are high in attachment avoidance but low in attachment anxiety; they view themselves as worthy of love but they prioritize independence over closeness (Bartholomew & Horowitz, 1991). Fearful adults are high in both attachment anxiety and avoidance; they view themselves as unworthy of love, and expect that others will be rejecting and untrustworthy (Bartholomew & Horowitz, 1991).

Of note, although attachment is often conceptualized as a stable trait, individual differences in attachment can be revised or reworked in light of later experiences, including relationships with secondary attachment figures such as friends and romantic partners during adulthood. Indeed, supporting the malleability of attachment, research indicates moderate stability in attachment over time (for meta-analyses, see Fraley, 2002; Pinquart et al., 2013), that is, some individuals who are insecurely attached during childhood go on to become securely

attached adults, whereas others who are securely attached during childhood go on to become less secure in adulthood.

OT and attachment security may be linked via multiple mechanisms. In his social-evolutionary model, Crespi (2015) posited that the role of OT in maternal care and bonding may extend to other attachment relationships including friendships and romantic relationships. OT administration has been shown to improve communication in couples during a conflict situation (Ditzen et al., 2009) and to enhance social-cognitive skills important to social relationships, such as generosity, emotion recognition, and interpretation of social cues (Domes et al., 2007; Lischke et al., 2012; Zak et al., 2007). OT administration has been found to promote trust in others (for a meta-analysis, see van IJzendoorn & Bakermans-Kranenburg, 2012), which is an essential component of attachment security. OT may promote prosocial behavior via its effects on social cognition; for instance, OT administration improved the recognition of positive relationship words such as love (Unkelbach, Guastella, & Forgas, 2008). OT may enhance social interactions or relationships by making individuals more likely to view themselves as warm, trusting and altruistic (Bartz et al., in press; Cardoso, 2012). OT administration was found to heighten activation in brain areas related to bonding and empathy (Riem et al., 2011), which may promote the development and maintenance of attachment relationships. In addition, OT is released following stress (Brunton & Russell, 2008b; Taylor, 2006), and exerts anxiolytic and anti-stress functions (Carter, 1998; Ditzen et al., 2009; Heinrichs et al., 2003; Neumann, 2002), and as such could ease the stress related to the initiation and navigation of social relationships. Finally, by stimulating dopaminergic release in the mesocorticolimbic system, OT may also contribute to the sense of reward that individuals derive from their attachment relationships (Carter, 1998; Liu & Wang, 2003; Shahrokh et al., 2010; Strathearn et al., 2009).

Although oxytocin in general has been linked with attachment security, there have been inconsistencies in the human work. Some studies have detected a positive relationship between OT and attachment security. For instance, in a sample of healthy men, more participants who were administered OT classified themselves as securely attached, and fewer participants who were administered OT selected anxious or avoidant classifications (De Dreu, 2012). When presented with attachment-related images after OT administration, insecurely attached men provided more interpretations consistent with secure attachment, and fewer interpretations consistent with preoccupied attachment (Buchheim et al., 2009). Similar results have been shown with endogenous OT. In a sample of men and women, securely attached participants had higher levels, dismissing participants had moderate levels, and preoccupied ones had lower levels of endogenous OT (Pierrehumbert et al., 2012). OT has also been linked to greater attachment security in romantic relationships; salivary OT levels were found to be inversely related to romantic attachment avoidance and anxiety (Feldman et al., 2011).

However, other studies have found inconsistent or discrepant results for the OT-attachment association. For example, endogenous OT levels were negatively associated with attachment anxiety and avoidance in childbearing women during the postpartum period, but not during the prenatal period (Eapen et al., 2014). Another study found that OT and attachment anxiety were positively associated in women but inversely related in men (Weisman et al., 2013). Similarly, endogenous OT was positively associated with attachment anxiety in romantic relationships in a sample of medical professionals and trainees (Marazziti et al., 2006). In sum, studies examining the association between OT and attachment have yielded inconsistent findings, leaving the nature of this relationship unclear and suggesting that not all insecurely attached individuals will have lower levels of OT.

Moderating factors may help to account for these discrepant findings (Bartz, Zaki, et al., 2011). One such factor is early life stress (ELS), which is associated with both attachment insecurity (Bradley et al., 2011; Gwadz et al., 2004; Muller et al., 2000; Riggs & Jacobvitz, 2002; Twaite & Rodriguez-Srednicki, 2004), and levels of circulating and central OT (Bertsch et al., 2013; Bhandari, Bakermans-Kranenburg, et al., 2014; Heim et al., 2009) in adulthood. The animal literature indicates that early caregiving experiences can impact the OT system (Winslow et al., 2003), via binding of the OT receptor (OTR) and/or regulation of the OTR gene (for reviews, see Bales & Perkeybile, 2012; Veenema, 2012). In addition, experimental studies indicated that ELS may moderate the effects of intranasal OT, suggesting that ELS may have a lasting effect on the OT system, perhaps via epigenetic modification such as methylation of the OTR gene (Bakermans-Kranenburg & van IJzendoorn, 2013; Bartz, Simeon, et al., 2011; Riem, Bakermans-Kranenburg, et al., 2013; Riem, van IJzendoorn, et al., 2013). In a recent study, adults who reported early adversity in the form of poorer maternal care were found to have increased DNA methylation in a target sequence of the OTR gene (Unternaehrer et al., in press). Thus, the relationship between OT and attachment may differ for those with and without a history of ELS.

On the one hand, ELS such as abuse or neglect by a primary caregiver may make individuals more vigilant to subsequent relationship information with secondary attachment figures such as friends or romantic partners during adulthood; thus, OT levels may be associated with attachment security in those with a history of ELS. On the other hand, researchers have proposed that individuals with a history of ELS may be less sensitive to the effects of intranasal OT (Bakermans-Kranenburg & van IJzendoorn, 2013) and that the OT system may be less responsive after ELS (Buisman-Pijlman et al., 2014). Thus, the OT system may be dampened or

blunted by ELS, and the relationship between OT levels and attachment insecurity may be limited to those without a history of ELS.

To date, few studies measuring endogenous OT have examined both adult attachment and history of adversity. A recent pilot study from our group found that, in a sample of 30 pregnant women with mood, anxiety or adjustment disorders, OT levels were higher in securely attached than insecurely attached individuals (Samuel et al., 2015a). Importantly, all participants had endured high rates of adversity across the lifespan, suggesting that OT may be inversely related to attachment insecurity in childbearing women with a history of adversity.

The present investigation aimed to build upon the pilot study by recruiting a larger sample of women both with and without a history of ELS, the latter serving as a comparison group and enabling us to determine whether adversity played a moderating role in the relationship between OT and attachment. Next, since studies suggest that OT levels fluctuate throughout pregnancy (Levine et al., 2007; Prévost et al., 2014), and differ in depressed versus non-depressed individuals (Anderberg & Uvnas-Moberg, 2000; Ozsoy et al., 2009; Yuen et al., 2014), there is a need to consider whether the pilot study results might be generalizable to non-pregnant and non-depressed women. As such, we assessed women who were not pregnant at the time of the study, and examined whether the results changed when analyses were limited to non-depressed individuals. Although ELS can be operationalized in a number of ways, we assessed it in the form of maternal abuse during the first 16 years of life to be consistent with past OT studies, which operationalized ELS in terms of early parenting experiences such as harsh caregiving (e.g. Bakermans-Kranenburg et al., 2012). We hypothesized that ELS would moderate the relationship between OT and attachment insecurity, such that the association

between OT and attachment insecurity would differ in individuals with and without a history of ELS.

Methods

Participants

A community sample of 341 pregnant women were recruited during obstetrics appointments to participate in a study about OT, mental health and the developing mother-child relationship (Zelkowitz et al., 2014). A clinical sample of 75 women was also recruited when they sought help for mental health problems at the psychiatry department of a general hospital during pregnancy or postpartum (samples described in Samuel et al., 2015a, 2015b). Approximately 2.5 years postpartum, 227 mothers agreed to participate in a follow-up study. Those who participated at follow-up were not significantly different from those who did not participate at follow-up in terms of parity, age, marital status (partnered versus not), or group (community versus clinical). Years of education were assigned based on highest completed degree (11 for high school, 13 for college or trade school, 16 for bachelor's degree, 18 for master's degree, 21 for doctoral degree); those who participated at follow-up had more years of education (M = 15.71, SD = 2.61) than those who did not (M = 14.41, SD = 2.42); t (413) = -5.20, p = .000.

Of the 227 women who participated in the follow-up study, 21 were currently pregnant and were thus excluded from the present analyses. OT values were missing for an additional 11 participants, resulting in a final sample of 195 women. Of these 195 participants, 161 were from the original community sample, and 34 were from the original clinical sample.

Forty-six participants (23.6%) had 1 child, 103 participants (52.8%) had 2 children, and the remaining 46 participants (23.6%) had between 3 and 5 children. Mean age was 35.58 (*SD* = 4.41). The vast majority of participants (*n* = 176, 90.3%) were partnered. Seventeen (8.72%) reported currently taking psychotropic medication.

Measures

The measure of OT employed has been reported previously (Samuel et al., 2015a). The enzyme-linked immunosorbent assay was obtained from Enzo Life Sciences (Farmingdale, New York; catalogue # ADI-900-153A). Samples were diluted 1:6, and were assayed in duplicate; the intra-assay coefficient of variation was 8.9% and inter-assay coefficient of variation was 3.68%. However, the antibody used in the Enzo kit was changed in 2013. Based on this and a series of new studies and validations using the new kit, we have found that the new antibody yields OT values in unextracted samples about 2 to 3 times higher than in the past for comparable samples. Although the company identifies this as a highly specific antibody, it is possible that the antibody used in the present study is more sensitive or has a capacity to identify other forms of OT, including metabolic products that were not detectable with previous assays. Based on LC/mass spectrometry, over 90% of the OT in circulation is sequestered on proteins and other elements in blood (Martin & Carter, 2013). For this reason, the present assays were conducted on unextracted plasma. As with other methods of measuring neuropeptides in biological fluids, it is not at present possible to specify the degree to which OT is free versus bound.

The Experience in Close Relationships (ECR; Brennan, Clark, & Shaver, 1998) questionnaire is a dimensional measure of adult attachment. Although some versions of this measure assess attachment to romantic partners in particular, we inquired about attachment to

close relationship partners in general because we wanted to investigate adult attachment across multiple types of close relationships. This measure is composed of 36 items, which are rated from 1 (disagree strongly) to 7 (agree strongly). The anxiety scale is comprised of 18 items, in which higher scores represent a greater degree of anxious attachment. The avoidance scale is also comprised of 18 items, in which higher scores represent a higher degree of avoidant attachment. Studies of college students have found evidence for its internal consistency (.93 for anxiety, .94 for avoidance; Vogel & Wei, 2005) and for its 6-month test-retest reliability (.68 for anxiety, .71 for avoidance; Lopez & Gormley, 2002). Studies administering the ECR to college students have demonstrated the construct validity of this measure (Wei, Russell, Mallinckrodt, & Vogel, 2007), indicating that attachment anxiety and avoidance were linked with a range of psychosocial variables, including negative mood (Wei, Russell, Mallinckrodt, & Zakalik, 2004) and maladaptive perfectionism (Wei, Heppner, Russell, & Young, 2006). The ECR has also been administered to childbearing women in previous studies of OT (e.g. Weisman et al., 2013).

The Edinburgh Postnatal Depression Scale (EPDS; J. L. Cox et al., 1987) is a measure of depressive symptoms in the last 7 days. It consists of 10 items, each of which is rated from 0 to 3 where higher scores reflects greater symptomatology. The initial validation study of postpartum mothers reported adequate psychometric properties; 86% for sensitivity, 78% for specificity, and 73% for positive predictive value (J. L. Cox et al., 1987). A cut-off score of 13 or higher is recommended for English-speaking postpartum women (Matthey, Henshaw, Elliott, & Barnett, 2006). Studies indicate that the EPDS is also valid for women beyond one year postpartum (Thorpe, 2007), and this measure has been used with mothers between 2 and 3 years postpartum (e.g. Micali, Stahl, Treasure, & Simonoff, 2014).

The Measure of Parenting Style (MOPS; G. Parker et al., 1997) assesses parental over-control, indifference, and abuse experienced by 16 years of age. Only the abuse scale was administered in the present study. The scale is completed separately for mother and father. The abuse items inquire about whether each parent was unpredictable, verbally and physically abusive, and elicited feelings of being unsafe or endangered. This scale is composed of 5 items, each of which is rated from 0 (not true at all) to 3 (extremely true), where higher scores reflect greater abuse. There is evidence for concurrent validity between ratings from the MOPS abuse scale and psychiatric interviews of reported abuse (G. Parker et al., 1997). This measure has also demonstrated internal consistency, with alpha coefficients of .87 for maternal abuse and .92 for paternal abuse (G. Parker et al., 1997). Given that mothers tend to be the primary caregivers, analyses in the present study focus on maternal abuse.

Procedure

Upon arrival at the laboratory, a nurse drew blood from the participant, which was later assayed to measure endogenous OT. Participants then completed a background questionnaire to assess parity, age, and marital status, as well as whether they were currently taking psychotropic medication. Finally, they completed the ECR, EPDS, and MOPS.

Data Analysis

OT values were log-transformed consistent with other studies of OT in childbearing women (e.g. Feldman, Gordon, Influs, Gutbir, & Ebstein, 2013; Feldman et al., 2012; Gordon et al., 2010a). Log OT values were used in all analyses. On the background questionnaire, we

dummy coded partnered status (0 = unpartnered, 1 = partnered), and psychotropic medication (0 = none, 1 = any).

Relatively little abuse was reported in the present sample; out of a possible 15 on the MOPS, 54.87% of participants scored 0, 30.26% scored 1-3, and 14.87% scored 4-15. As such, we dichotomized MOPS scores according to whether participants reported any versus no maternal abuse (dummy coded as 0 = none, 1 = any).

An alpha level of .05 was used for each statistical analysis. Missing values on the EPDS (n = 1) and ECR (n = 7) were pro-rated; the participant's average score on the completed items was entered in the missing cell(s), keeping their average score the same. Nineteen (9.7%) participants scored above the cut-off of the EPDS. Because all participants in our pilot study were diagnosed with mood, anxiety, or adjustment disorders, we aimed to determine whether the results of the present study extended to non-depressed participants. As such, we dichotomized EPDS scores according to whether participants were above or below the cut-off of 13 (dummy coded as 0 = below, 1 = above) and examined whether the relationships remained unchanged when analyses were limited to participants scoring below the EPDS cut-off.

Pearson correlations, independent samples t-tests, and chi square tests were conducted to explore whether variables of interest (OT, ECR, MOPS) were related to demographic variables (parity, age, marital status) or to psychotropic medication (any versus none) and depression (above or below the EPDS cut-off). Next, independent samples t-tests were conducted to determine whether participants with and without a history of maternal abuse differed in terms of OT, attachment anxiety, or attachment avoidance. Pearson correlations were conducted to examine the associations between OT and attachment anxiety and avoidance in the sample as a whole, as well as in those with or without a history of ELS. Finally, a hierarchical linear

regression was performed to examine whether ELS moderated the relationship between OT and attachment insecurity.

Results

Descriptive Statistics

On the MOPS, 107 participants (54.9%) reported no maternal abuse during the first 16 years of life. Scores in the remaining 88 participants (45.1%) spanned the entire range of 1 to 15 (M = 3.76, SD = 3.77). In particular, these 88 participants indicated that the following items were slightly, moderately or extremely true of their mothers in their first 16 years of life: verbally abusive to them (n = 46), unpredictable towards them (n = 64), physically violent or abusive of them (n = 27), made them feel in danger (n = 19), or made them feel unsafe (n = 43).

Descriptive statistics for OT and ECR, in those with and without a history of ELS, are reported in Table 1. Consistent with other research using the ECR (Cameron, Finnegan, & Morry, 2012), attachment anxiety was positively associated with attachment avoidance; r = .385, p = .000. OT levels and avoidance ratings did not differ in those who reported any versus no maternal abuse. However, anxiety ratings were higher in participants who reported any (M = 58.42, SD = 18.64) versus no maternal abuse (M = 51.45, SD = 16.26); t (193) = -2.789, p = .006. These relationships remained unchanged when analyses were limited to participants scoring below the EPDS cut-off.

Those who reported any versus no abuse on MOPS did not differ in terms of parity, age, psychotropic medication, or EPDS group. There were more unpartnered participants in the group who reported any (n = 14, 15.91%) versus no (n = 5, 4.67%) abuse on MOPS (Chi Square = 6.932, df = 1, p = .01).

Log OT was not correlated with parity, and did not differ significantly by marital status, use of psychotropic medication, or depression. Log OT was positively associated with participant age (r = .210, p = .003), indicating that older participants had higher levels of OT.

Attachment anxiety was not correlated with parity, and did not differ significantly by marital status or use of psychotropic medication. Attachment anxiety was negatively associated with participant age (r = -.156, p = .030), indicating that younger participants were more anxiously attached. Levels of attachment anxiety were higher in those above (M = 68.58, SD = 12.36) versus below (M = 53.09, SD = 17.52) the EPDS cut-off, t (193) = -3.749, p = .000.

Attachment avoidance was not associated with parity and age, and it did not differ significantly by use of psychotropic medication. Levels of attachment avoidance were higher among unpartnered (M = 55.79, SD = 19.77) than partnered participants (M = 46.14, SD = 16.23); t (193) = 2.408, p = .017. Levels of attachment avoidance were also higher in those above (M = 60.53, SD = 19.11) versus below the EPDS cut-off (M = 45.63, SD = 15.92); t (193) = -3.798, p = .000.

Role of ELS in OT and Attachment

As shown in Figure 1, OT levels were negatively associated with avoidance ratings in participants who reported any maternal abuse on MOPS (r = -.242, p = .023). However, as depicted in Figure 2, OT levels and avoidance ratings were not associated in participants who did not report any maternal abuse. OT was not significantly associated with anxiety ratings in either group of participants. These relationships remained unchanged when analyses were limited to participants scoring below the EPDS cut-off.

Moderation Analysis

As presented in Table 2, a hierarchical linear regression was conducted to test our moderation hypothesis. Age was entered in the first block because it was positively correlated with log OT. This first block explained a small but significant portion of the variance in log OT; $R^{2 =}$ .044, F (1, 193) = 8.87, p = .003. MOPS group and ECR avoidance scores were standardized, and then entered in the second block. Given that attachment anxiety was associated with attachment avoidance, attachment anxiety was also entered in the second block in order to determine whether the relationship between attachment insecurity and endogenous OT was specific to attachment avoidance. This second block also explained a small but significant portion of the variance in log OT; $R^{2 =}$ .055, F (4, 190) = 2.754, p = .029. Finally, we computed the product of the standardized terms for MOPS group and ECR avoidance, and this interaction term was entered in the third block. This third block explained a significant portion of the variance in log OT; R^2 = .084, F (5, 189) = 3.463, p = .005. The interaction term was significant, indicating that ELS moderated the association between OT and attachment avoidance. In particular, greater attachment avoidance was associated with lower levels of OT, but only among participants with a history of ELS.

It is worth noting that the present sample included some women from our pilot study, who reported high rates of adversity and as such may have accounted for the results in the present study. To determine whether this was the case, we ran the hierarchical regression analysis excluding participants from the pilot study. Importantly, the pattern of results remained unaltered, indicating that the inverse relationship between OT and attachment avoidance extends to a community sample.

Discussion

Previous studies of OT and attachment have yielded discrepant results; whereas some have found positive associations between OT and attachment security, others have found inconsistent or inverse associations. This suggests that not all insecurely attached adults will have lower levels of OT. To clarify why OT is inversely related to attachment insecurity in some individuals but not others, the present study aimed to examine whether the relationship between OT and attachment differed in childbearing women with and without a history of ELS. We found that OT levels were not significantly associated with attachment anxiety or avoidance in the sample as a whole. ELS moderated the relationship between OT and attachment avoidance such that lower OT levels were associated with greater attachment avoidance, but only in participants with a history of ELS. These findings suggest that ELS may sensitize neuropeptide systems to later relationship information or attachment experiences. In particular, individuals exposed to ELS who were more avoidantly attached had lower levels of OT, whereas those exposed to ELS who were less avoidantly attached had higher levels of OT.

This finding replicates the results of our pilot study which found that, in pregnant women with high rates of cumulative psychosocial adversity and mood, anxiety or adjustment disorders, OT levels were lower in insecurely than securely attached participants (Samuel et al., 2015a). Importantly, the present study built upon our previous findings in multiple ways; in addition to demonstrating that the inverse association between OT and attachment insecurity extended to non-pregnant and non-depressed women, we found that this relationship was limited to women with a history of ELS.

Interestingly, we found that OT was inversely related to a specific dimension of attachment, namely, attachment avoidance. Why would OT be related to avoidant – but not

anxious – attachment? Attachment avoidance is characterized by a negative model of other, i.e. a tendency to be uncomfortable with closeness and to view others as untrustworthy and unreliable. OT appears to be a socially-oriented hormone; for instance, OT administration increases trust in others (for a meta-analysis, see van IJzendoorn & Bakermans-Kranenburg, 2012), decreases self-focus (Clarici et al., 2015), and increases an other-oriented, "communal" focus (Bartz et al., in press). Others have suggested that lower levels of OT may be linked with egocentric cognition (Crespi, 2015). As such, OT levels may be more strongly related to the "model-of-other" dimension of attachment, i.e. attachment avoidance. Consistent with this idea, intranasal OT was found to enhance cooperation and trust, but only among more avoidantly attached individuals, suggesting that OT may interact with avoidant attachment to impact one's model of others (De Dreu, 2012). In another experimental study, men who were administered OT viewed themselves as being more communal or oriented towards others, but this effect was strongest in avoidant participants; because avoidantly attached individuals prioritize self-reliance over interpersonal connectedness, OT may increase their other-orientation and as such may promote a more optimal balance between their concern with self and other (Bartz et al., in press). Indeed, OT administration has been shown to improve social cognition in more avoidantly attached (Hsih et al., 2015) and more alexithymic individuals (Luminet, Grynberg, Ruzette, & Mikolajczak, 2011), as well as in individuals with higher scores on the Autism Spectrum Quotient (Bartz, Zaki, Bolger, et al., 2010), suggesting that OT may exert social-cognitive benefits in those who are less socially oriented or skilled (see Bartz, Zaki, Bolger, et al., 2010; Shamay-Tsoory et al., 2009). In contrast, these effects of OT may be less evident in more secure or anxiously attached individuals, who already value interpersonal relationships and strongly desire closeness with others (also see Bartz et al., in press, for a discussion).

We also found that OT levels did not differ significantly between participants with or without a history of maternal abuse. Indeed, past studies on OT and ELS have yielded discrepant results; whereas some have found positive relationships (Bhandari, Bakermans-Kranenburg, et al., 2014; Crowley et al., 2015; Mizuki & Fujiwara, 2015; Pierrehumbert et al., 2010), others have found inverse associations (Bertsch et al., 2013; Heim et al., 2009; Mohiyeddini et al., 2014; Opacka-Juffry & Mohiyeddini, 2012). Most comparable to the present study, another investigation of childbearing women found no association between plasma OT and maternal abuse ratings on MOPS (Eapen et al., 2014). Researchers have posited that these conflicting findings may result in part from methodological differences across studies, including OT measurement, types of abuse, participant gender (Bhandari, Bakermans-Kranenburg, et al., 2014), or severity of abuse (Mizuki & Fujiwara, 2015). Indeed, previous studies from our group have shown that OT levels vary widely among participants with a history of adversity (Samuel et al., 2015a; Zelkowitz et al., 2014). Together, these findings suggest that not all individuals exposed to ELS will have lower levels of OT. It seems likely that experiences and events that occur later in life, including attachment relationships during adulthood, also contribute to individual differences in endogenous levels of OT. Consistent with this idea, Bartz, Simeon, et al. (2011) found that it was current attachment and not history of adverse life events that moderated the effects of OT, suggesting that what matters may be one's current experience and, specifically, whether and how one has reconciled past interpersonal experiences. The present study highlights the importance of examining both ELS and adult attachment in order to better understand individual differences in levels of endogenous OT. Averaging OT levels across participants with ELS without accounting for adult attachment, or vice versa, could yield the null

results reported in the present study or the inconsistent findings reported in the literature (also see Bartz, Zaki, et al., 2011).

Additional findings from this study are consistent with previous research. For instance, we found that those above the EPDS cut-off had greater attachment anxiety and avoidance, which is consistent with past research linking depression and insecure attachment in childbearing women (for a review, see Warfa, Harper, Nicolais, & Bhui, 2014). We also found that participants with a history of ELS were more anxiously attached than those without a history of ELS. This is consistent with past studies linking ELS to insecure attachment in adulthood (Bradley et al., 2011; Gwadz et al., 2004; Muller et al., 2000; Riggs & Jacobvitz, 2002; Twaite & Rodriguez-Srednicki, 2004).

Finally, we found that older participants had higher levels of OT. Similarly, a recent study of OT and ELS found that older participants had somewhat higher levels of OT than younger participants (Mizuki & Fujiwara, 2015). Some insight into this relationship may be derived from our finding that older participants had less attachment anxiety in the present study. Thus, older participants may have established more stable or satisfying relationships, which may in turn have contributed to their higher levels of OT. Future research is needed to explore this possibility.

Limitations

Consistent with previous studies of OT and attachment (Eapen et al., 2014; Feldman et al., 2011; Marazziti et al., 2006; Pierrehumbert et al., 2012; Weisman et al., 2013), we assessed plasma OT levels as an accessible index of central OT levels. Central OT is thought to modulate social processes but cannot be measured directly in human studies. Whether circulating OT

corresponds to brain OT remains an open question. Of note, human studies have found that plasma OT is associated with cerebrospinal fluid OT (D. S. Carson et al., 2014), and that intranasal OT administration prompts a rise in plasma OT (Burri et al., 2008).

In addition, controversy surrounds the use of sample extraction. Those who use extraction argue that unextracted samples may contain peptides other than OT, contributing to inaccurate measurement (Szeto et al., 2011). However, we used unextracted samples because extraction can discard a considerable amount of OT (Martin & Carter, 2013) and produce levels of OT below the detection level of available assays (Zhong et al., 2012). Moreover, because many studies of endogenous OT and adult attachment involved unextracted samples (e.g. Feldman et al., 2012; Weisman et al., 2013), our use of the same method enables us to build upon prior work.

As noted above, those who participated in our follow-up study had a higher degree of education than participants from our original sample. Other longitudinal studies of childbearing women and their children have also found a relationship between maternal education and retention (e.g. Constantine, Haynes, Spiker, Kendall-Tackett, & Constantine, 1993). This should be taken into account when considering the generalizability of our results.

Participants spanned the full range of scores on the MOPS but most did not have very high scores. Thus, it is possible that an association between OT and ELS would have been detected in the present study if our sample had included more participants with a history of severe ELS. On the other hand, the fact that an inverse relationship between OT and attachment avoidance was found only in women with relatively low levels of maternal abuse suggests that any childhood abuse, even if it is not very severe, may have a lasting impact on the OT system and may play a role in the relationship between OT and attachment.

Finally, research in animal models indicates that several neuropeptides not measured in the present study, including vasopressin (Cho, DeVries, Williams, & Carter, 1999), may also influence the formation of social attachments. For example, OT and vasopressin interact dynamically with each other's receptors (Grinevich, Knobloch-Bollmann, Eliava, Busnelli, & Chini, in press), with consequences that may be expressed as individual differences in attachment styles. Vasopressin and the vasopressin receptor are reactive to environmental challenges and stressors across the life cycle, and may become epigenetically sensitized in response to early adversity or neglect (Zhang et al., 2012). OT may be a component of a coping mechanism, which in turn modulates the vasopressin system. Thus, individuals exposed to high versus lower levels of ELS may use these peptides in different ways. However, testing this hypothesis in humans is not possible with current non-invasive methodologies.

Conclusions

In examining the relationship between OT and attachment, it is important to consider the moderating role of ELS. We found that OT levels were not associated with ELS or attachment in the sample as a whole. Rather, in the present study, OT was inversely related to attachment avoidance, but only in those with a history of ELS.

The present study contributes to a growing body of literature suggesting that the effects of OT are moderated by psychosocial factors such as ELS (Bartz, Zaki, et al., 2011). Together with the extant literature, our findings underscore the need for a deeper understanding of factors regulating individual differences in endogenous levels of OT, such as polymorphisms in - or epigenetic regulation of - the OTR gene, demographic factors such as gender, and psychosocial factors such as history of adversity, attachment insecurity, and mental health problems. Despite

the limitations of current methodologies and the complexity of these systems, the present findings support the potential usefulness of ELS and adult attachment styles in the prediction of endogenous OT, encouraging additional research on this important topic.

Table 1

Descriptive Statistics

M (*SD*)	No ELS (*n* = 107)	ELS (*n* = 88)
OT	591.50 (85.84)	606.21 (86.68)
Log OT	6.37 (.15)	6.40 (.15)
Attachment anxiety	51.45 (16.26)	58.42 (18.64)
Attachment avoidance	45.26 (15.74)	49.30 (17.83)

Note. OT = oxytocin.

Table 2

Hierarchical Linear Regression of Log OT

	B	SE	β	*t*	*p*
Block 1					
Age	.007	.002	.210	2.978	.003
Block 2					
MOPS group[a]	.010	.011	.071	.978	.329
ECR avoidance	-.009	.011	-.063	-.825	.410
ECR anxiety	.001	.001	.066	.842	.401
Block 3					
MOPS group[a] x ECR avoidance	-.025	.010	-.172	-2.452	.015

Note. OT = oxytocin; MOPS = Measure of Parenting Style
[a] No ELS group: 0 on MOPS; and any ELS group ≥ 1 on MOPS

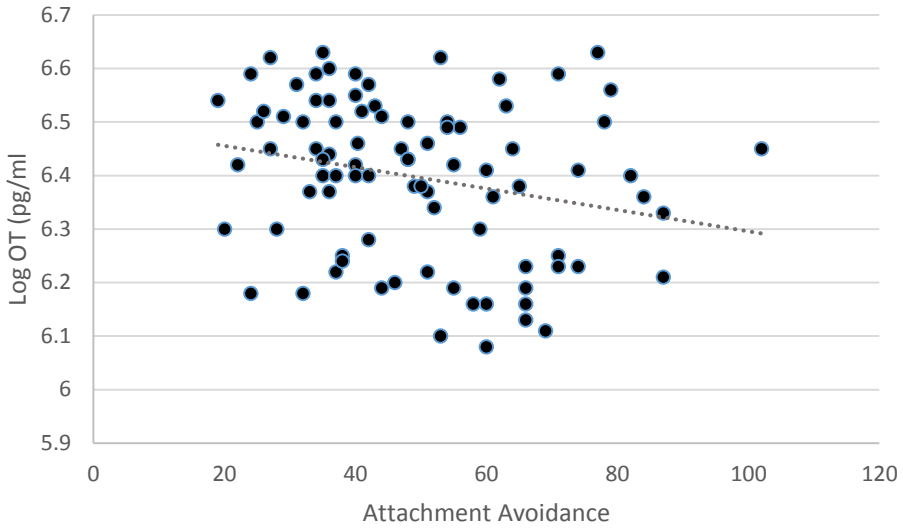

Figure 1. Scatterplot of Log OT levels (pg/ml) and Attachment Avoidance in Participants with a History of ELS. Higher scores on the avoidance scale reflect greater attachment avoidance. A significant, negative correlation is represented (r = -.242, p = .023).

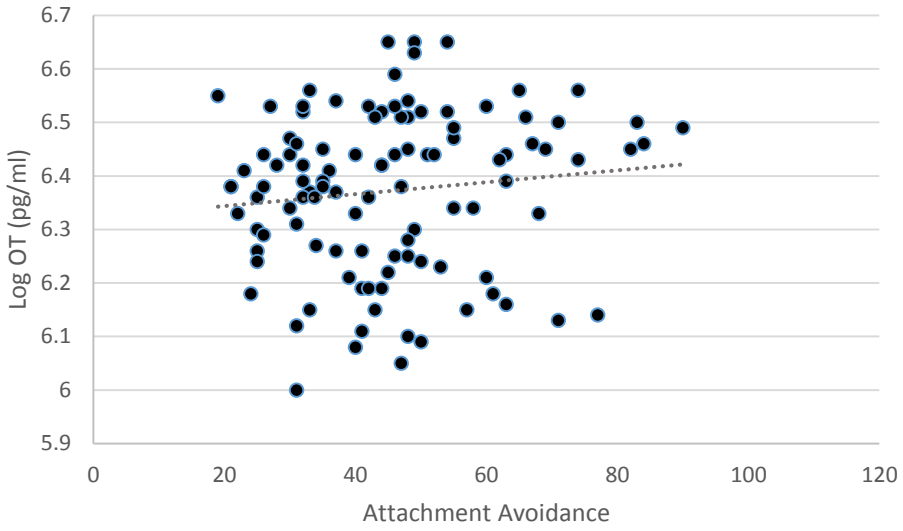

Figure 2. Scatterplot of Log OT levels (pg/ml) and Attachment Avoidance in Participants without a History of ELS. Higher scores on the avoidance scale reflect greater attachment avoidance. This correlation did not reach statistical significance ($r = .121$, $p > .05$).

General Discussion

The present thesis had two primary aims: The first was to identify maternal psychosocial characteristics linked with individual differences in circulating concentrations of oxytocin (OT), and the second was to investigate the role of OT in the interactive behaviors of mothers with and without mental health problems.

Studies examining the relationships between OT and psychosocial factors including adult attachment and mental health problems have yielded divergent findings. Thus, it is important to determine why OT is negatively related to attachment insecurity and mental health problems in certain adults but not others. We postulated that early adversity could moderate the association between OT and these psychosocial factors, that is, the association between OT and attachment insecurity or mental health problems may differ in adults with versus without a history of adversity. Consistent with this proposition, recent research indicated that OT was negatively associated with depressive symptoms and mood swings, but only among adults with a history of adversity (Crowley et al., 2015; Zelkowitz et al., 2014).

The present thesis found evidence that history of adversity also moderated the association between levels of OT and adult attachment insecurity. In Study 1, we found lower concentrations of OT in insecurely attached adults who experienced high degrees of cumulative adversity. Moreover, in Study 3, OT was not related to early life stress (ELS) or attachment insecurity in the overall sample - rather, ELS and greater attachment avoidance *interacted* to predict lower concentrations of circulating OT. Specifically, OT levels were negatively related to attachment avoidance, but only among adults with a history of ELS. These findings highlight the importance of investigating both ELS and adult attachment to capture a more complete picture of individual differences in OT concentrations. Together with the findings of Zelkowitz et al. (2014), our

results suggest that investigating the link between OT and attachment or mental health without considering the role of adversity may contribute to the inconsistent results found in the literature to date. Indeed, although ELS and attachment insecurity or mental illness are associated, they do not always go together; some individuals with a history of ELS become securely attached or mentally healthy adults, and others without a history of ELS become insecurely attached or develop mental health problems in adulthood.

Having examined certain psychosocial factors associated with individual differences in circulating concentrations of OT among childbearing women, the second goal of the present thesis was to investigate the role of OT in the interactive behavior of mothers with and without mental health problems. Specifically, we aimed to examine the moderating role of maternal mental health in the relationship between OT and interactive behavior. Although most studies on OT and interactive behavior have found a positive association (for a review, see Galbally et al., 2011), a small minority of studies have reported an inverse association (Elmadih et al., 2014; Feldman et al., 2011; Miura et al., 2014) and most have excluded mothers with mental health problems. However, mothers with mood or anxiety disorders have been found to interact less optimally with their children and some studies indicate that individuals with mental health problems have lower concentrations of OT. Because of its anti-stress, anxiolytic and antidepressant properties, OT may play an especially advantageous role in the interactive behavior of mothers with mood or anxiety disorders.

Study 2 was the first to compare the association between OT and interactive behavior in mothers with versus without mental health problems in the postpartum period. The results indicated that mental health moderated the association between OT and depressive interactive behaviors; higher OT concentrations were related to fewer self-absorbed, tense, and lethargic

behaviors, but only among mothers with mood, anxiety or adjustment disorders. Because OT has been shown to have anti-stress, anti-depressant and anxiolytic properties, higher levels of OT may have buffered the effects of mental health problems on interactive behaviors, enabling these mothers with mood, anxiety or adjustment disorders to interact with their infants in a more infant-focused, relaxed, and energetic manner. Indeed, meta-analytic evidence suggested that intranasal OT significantly reduced clinical symptoms, such as anxious and depressive symptomatology (Hofmann, Fang, & Brager, in press). These roles of OT may have been less needed or apparent among community sample mothers who had low levels of perinatal depressive and anxious symptoms as well as low levels of depressive interactive behavior. Higher OT concentrations were also associated with less intrusive interactive behaviors in the overall sample, suggesting that OT is related to more optimal caregiving behaviors in mothers with and without mental health problems, and that OT may have an added benefit for the interactive behavior of mothers with mood, anxiety or adjustment disorders.

It is important to note that the three studies that comprise the present thesis were cross-sectional in nature. Because OT and psychosocial variables were assessed concurrently, we were only able to assess associations and could not infer the directions of effects. However, experimental and longitudinal studies indicate that these relationships may be bidirectional. On one hand, exogenous OT has been found to exert anxiolytic effects (Heinrichs et al., 2003) and to promote attachment security (Buchheim et al., 2009; De Dreu, 2012) as well as more optimal caregiving behavior, such as touch and structuring (Mah et al., 2014; Naber et al., 2010; Weisman, Zagoory-Sharon, & Feldman, 2012). Moreover, longitudinal investigations have demonstrated that prenatal concentrations of OT predict postpartum maternal interactive behavior as well as depressive symptomatology (Feldman et al., 2007; Zelkowitz et al., 2014).

On the other hand, OT levels rise in response to interpersonal interactions (Strathearn et al., 2009). Thus, the poorer quality interpersonal relationships of individuals with greater attachment insecurity or mental health problems (Li & Chan, 2012; Whisman, Uebelacker, & Weinstock, 2004) may contribute to individual differences in their concentrations of OT.

Generalizability of results

As noted in previous investigations of OT (e.g. Bakermans-Kranenburg et al., 2012; Riem et al., 2011; Riem, van IJzendoorn, et al., 2013), findings from studies of mothers might not extend to non-childbearing women, and vice versa. This is partly due to hormonal changes that take place in the prenatal and postpartum periods (Levine et al., 2007; Prévost et al., 2014), and this should be kept in mind when assessing the generalizability of the present findings.

There is also reason to believe that our findings in samples of mothers might not generalize to fathers. Sex-divergent effects of OT have been reported in some animal and human studies (for a review, see K. S. Macdonald, 2012). Estrogen has been shown to stimulate OT gene promoters (Lee et al., 2009), and some have found that females have higher OT levels than males (Kramer et al., 2004; but see Weisman et al., 2013). The role that OT plays in the stress response is also theorized to be different in women; Taylor proposed that women may exhibit a "tend-and-befriend" response in which OT is released in reaction to distress, prompting them to seek social support from others (Taylor, 2006; Taylor et al., 2000). Perhaps most relevant to the present research, studies have shown distinct relationships between OT and interactive behaviors in fathers versus mothers; plasma OT was linked with affectionate touch and affect in mothers, but with stimulatory behaviors in fathers (Gordon et al., 2010a). Similarly, divergent effects of OT have been detected in experimental studies; following OT administration, fathers were better

able to structure interactions with their offspring (Naber et al., 2010), while mothers became more protective when a new adult initiated contact with their child (Mah et al., 2014). For these reasons, we would not necessarily expect that our findings of OT and maternal behavior would extend to paternal behavior.

Strengths

The studies that comprise the present thesis have a number of strengths. Some studies have used self-report measures to investigate the links between maternal bonding/behavior and OT (e.g. Levine et al., 2007; Mah et al., 2013) or mental health problems (Mason et al., 2011; Sockol et al., 2014; Tietz et al., 2014). Assessing both maternal bonding/behavior and mental health problems via self-report raises the issue of shared method variance. Moreover, mothers may not accurately perceive the quality of their interactive behaviors. Self-report measures are also subject to social desirability bias; mothers may not want to reveal that they do not feel connected or do not interact optimally with their children. On the other hand, mothers with mental health problems such as depression may be overly critical of their interactive behaviors. For these reasons, self-reports may not be representative of actual maternal behavior. To circumvent these potential shortcomings, maternal behavior in Study 2 was coded by objective raters using the Global Rating Scales (Murray et al., 1996).

Another strength is that we recruited a true clinical sample of mothers. In particular, childbearing women with mood, anxiety or adjustment disorders were recruited during pregnancy for Study 1, and in the postpartum period for Study 2. Most studies of OT and maternal behavior have focused on community samples of childbearing women without mental health problems. Those that examined mental health problems often employed self-report

measures of depressive or anxious symptomatology, where cut-off scores were used to identify childbearing women who were "symptomatic" (E. Q. Cox et al., 2015) or "at risk for postpartum depression" (Skrundz et al., 2011). However, the use of different cut-off scores may contribute to inconsistent results between studies (Matthey et al., 2006). Moreover, these questionnaires are not designed to be diagnostic tools, making it difficult to extend results based on these self-report measures to women diagnosed with mood or anxiety disorders. In recent years, several studies of postpartum OT and maternal behavior employed clinical interviews to diagnose psychiatric disorders. However, these studies were missing a control group of childbearing women without mental health problems (Mah et al., 2014; Mah et al., 2013), making it difficult to determine whether mental health played a role in their findings. Thus, Study 2 represented a step towards addressing this gap in the literature by investigating the association between OT and interactive behavior in mothers both with and without mental health problems.

Limitations

The studies that comprise the present thesis also have a number of limitations. The first limitation pertains to measurement of early adversity. We administered the Antenatal Risk Questionnaire in Study 1 to assess adversity endured across the lifespan, and the Measure of Parenting Style in Study 3 to evaluate early adversity operationalized as maternal abuse experienced by age 16. Studying early adversity was described as a "research challenge" due in part to a lack of consensus about how to define the term (Alves, Fielder, Ghabriel, Sawyer, & Buisman-Pijlman, 2015). Indeed, researchers studying OT have operationalized early adversity in multiple ways, ranging from childhood neglect or abuse (Heim et al., 2009) and early separation from parents (Meinlschmidt & Heim, 2007) to cancer (e.g. Pierrehumbert et al.,

2010). Studies of OT also vary in the timeframe for "early" adversity; for example, researchers have included events occurring until the age 13 (Meinlschmidt & Heim, 2007), 16 (Eapen et al., 2014), or 18 (Pierrehumbert et al., 2010). In addition to issues surrounding the conceptualization of early adversity, there are problems with the retrospective self-report measures that are employed to assess history of adversity. The degree of adversity reported on these measures may be influenced by participants' state of mind during the study; for instance, participants with mental health problems such as depression may be more likely to perceive past events as representing an instance of adversity. Of note, the findings in Study 3 remained unaltered when participants above the cut-off on a scale of depressive symptoms were excluded from analyses, suggesting that depressive symptoms were unlikely to account for the reported results. In addition, participants' OT concentrations and attachment styles may have interacted to impact their perceptions of past adversity; indeed, following OT administration, more anxiously attached participants were found to recall their mothers as less close and caring by age 16, while the reverse was found in less anxiously attached participants (Bartz, Zaki, Ochsner, et al., 2010).

In addition, we examined biological and psychosocial variables that may contribute to maternal behavior, but our investigation was limited to maternal characteristics and did not consider infant factors (e.g. temperament) which have been linked to maternal behavior (Kivijarvi, Raiha, Kaljonen, Tamminen, & Piha, 2005). Infant OT concentrations were associated with their behavior toward their mothers in both animal (Ross & Young, 2009) and human studies (Feldman, Gordon, & Zagoory-Sharon, 2010). In human studies, parental OT concentrations were associated with child OT levels and child social engagement (Apter-Levy et al., 2013; Clark et al., 2013). Thus, OT concentrations and interactive behaviors between

mothers and their children may be mutually reinforcing in a positive feedback cycle (see Rilling & Young, 2014).

Moreover, although mental health was assessed via diagnostic interview in the clinical sample, and via self-report measures in the community sample, we did not statistically control for the potential role of previous mental health problems. For instance, in the clinical sample, participants with mood, anxiety or adjustment disorders that arose in the perinatal period may have differed in their OT levels or in their interactive behaviors from those whose mental health problems preceded the perinatal period (and as such were more enduring and perhaps more severe).

Finally, controversy surrounds the measurement of OT in human studies. As a result of ethical and practical issues with sampling central OT in humans, plasma OT was used in the current thesis to estimate central OT, which is believed to impact social processes. However, it is not clear how closely peripheral levels of OT reflect central levels (see McCullough et al., 2013); some research suggests that central and endogenous OT secretion might be synchronized (Ross & Young, 2009), but others argue that distinct release patterns exist for central versus peripheral OT and that peripheral OT does not reflect actions specific to particular brain areas (see Neumann & Slattery, in press). Some have found a surge in plasma OT following intranasal administration (Burri et al., 2008; Domes et al., 2010). In addition, one study found a positive association between OT concentrations in plasma and CSF (D. S. Carson et al., 2014), though others have failed to find convergent results (Altemus et al., 2004; Jokinen et al., 2012; Kagerbauer et al., 2013). Thus, the extent to which findings of peripheral OT can be extended to central OT requires additional research and potentially the advent of novel methodologies.

In addition, we measured OT in unextracted samples. Some argue that extraction removes a sizeable amount of OT that may be bound to other molecules (Martin & Carter, 2013) and may result in undetectable amounts of OT (Zhong et al., 2012), while others note that unextracted samples could include molecules aside from OT (e.g. immunoreactive OT breakdown products, OT bound to carrier molecules such as albumin; McCullough et al., 2013; Szeto et al., 2011). There is some evidence of an association between levels of OT derived from unextracted and extracted samples (Michopoulos et al., 2011), though others have found a lack of correspondence (Szeto et al., 2011), putting into question whether studies using unextracted samples can be generalized to those using extracted samples.

We also quantified OT levels using an enzyme-linked immunosorbent assay (EIA) because radioimmunoassay (RIA) requires the use of radioactivity (McCullough et al., 2013), and often necessitates large sample quantities as well as extraction (Carter et al., 2007). In addition, RIA may have insufficient sensitivity as some have found OT values to fall below the detectable limit (Szeto et al., 2011). Some studies have found significant correlations among extracted levels of plasma OT using EIA and RIA (Christensen, Shiyanov, Estepp, & Schlager, 2014; Yasuda et al., 1989). However, OT measurement in humans is controversial, and results from studies using EIA may not be comparable to those using RIA. Accurate methodologies are crucial to the advancement of this field.

Implications

The research comprised in the present thesis has a number of important implications. A large body of literature indicates that - as a group - mothers with a history of adversity, insecure attachment, and mental health problems exhibit poorer caregiving behaviors with their children.

However, not all mothers with these psychosocial characteristics exhibit poorer interactive behaviors. For example, in a sample of depressed women, 36% were classified as withdrawn, 39% were intrusive, and 25% were "good" (neither withdrawn nor intrusive) with their infants (Field et al., 2003). The present thesis indicated that biological factors, and OT levels in particular, might help explain this variability. We reported that mothers with these psychosocial characteristics varied in their levels of OT; OT concentrations were not significantly dissimilar in participants with versus without mental health problems (Study 2), or in those with versus without a history of adversity (Study 3). Indeed, the association between OT and psychosocial factors was more complex; attachment insecurity was related to lower OT concentrations, but only in mothers with a history of adversity (Study 1, Study 3). In addition, although mothers with mental health problems interacted less optimally as a group, those with higher OT concentrations displayed less depressive behaviors than those with lower OT concentrations (Study 2). Similarly, another study by our group reported that higher OT concentrations were linked with more sensitive interactive behaviors among mothers who had experienced high degrees of cumulative adversity (Zelkowitz et al., 2014). Thus, mothers with these psychosocial characteristics may exhibit poorer interactive behavior as a group, but higher OT concentrations may buffer the impact of these psychosocial factors on their interactive behaviors. As such, those with higher concentrations of OT may exhibit interactive behaviors that are more comparable to mothers without these psychosocial characteristics.

These findings may represent a step towards developing a biopsychosocial profile of mothers who are more likely to display poorer interactive behaviors; although longitudinal studies are needed to delineate the directions of effects, the present thesis suggest that more avoidantly attached mothers with a history of adversity may have lower concentrations of OT,

which in turn may be related to more depressive interactive behavior among mothers with mood, anxiety or adjustment disorders. Mothers with these biopsychosocial characteristics may benefit from behavioral interventions aimed at ameliorating their interactions with their offspring.

Future studies should also investigate whether OT administration enhances the interactive behaviors of these mothers. Studies are just beginning to investigate this research question; following OT administration, mothers with postpartum depression referred to their connection with their infant in a more positive light (Mah et al., 2013), and became more protective once an unknown adult approached their infant (Mah et al., 2014). However, they were also sadder and described their infant as difficult (Mah et al., 2013). Together with research suggesting that individual differences and contextual variables moderate the effects of intranasal OT (Bartz, Zaki, et al., 2011), these results underline the importance of exploring the conditions under which OT is most likely to ameliorate maternal behavior.

Future research is required to examine the dynamic interplay between endogenous levels of OT, psychosocial factors of interest, and other biological factors that were not assessed in the present thesis. For instance, variants of the OT peptide and receptor genes have been associated with depression (Apter-Levy et al., 2013; B. Costa et al., 2009; Mileva-Seitz et al., 2013), adult attachment (B. Costa et al., 2009; but see Gillath, Shaver, Baek, & Chun, 2008), circulating OT levels (Apter-Levy et al., 2013; Feldman et al., 2013; Feldman et al., 2012), and interactive behavior including sensitivity, warmth, vocalizations and touch (Bakermans-Kranenburg & van IJzendoorn, 2008; Feldman et al., 2013; Feldman et al., 2012; Klahr et al., 2014; Michalska et al., 2014; Mileva-Seitz et al., 2013). Researchers have also noted interactions of these genetic variants with the psychosocial factors of interest in the present thesis (see Brune, 2012). For instance, variants of the OT peptide and OT receptor genes have been found to interact with

early adversity to predict anxious and depressive symptomatology (McQuaid, McInnis, Stead, Matheson, & Anisman, 2013; Myers et al., 2014; Thompson, Parker, Hallmayer, Waugh, & Gotlib, 2011), adult attachment (Bradley et al., 2011), and maternal instrumental care behaviors with their children (Mileva-Seitz et al., 2013). Indeed, investigators have suggested that interactions among endogenous OT levels and genetic variants of the OTR could help explain the inconsistent findings in the literature (Moons, Way, & Taylor, 2014).

In addition to genetic factors, endogenous levels of OT and psychosocial factors of interest are likely to interact with other neuropeptides and biological systems. In particular, OT and vasopressin can bind to one another's receptors (Carter, 2014), and researchers have suggested that these neuropeptides may have contrasting effects on mental health (Neumann & Landgraf, 2012). In addition, OT has been shown to interact in a bidirectional manner with the stress and dopaminergic systems, and connectivity between these systems may be altered following early adversity (for a review, see Buisman-Pijlman et al., 2014). In sum, future research should explore interactions among multiple biological systems to obtain a more complete understanding of the factors contributing to the quality of maternal behavior.

This line of work on maternal behavior has important implications for child development. Indeed, the quality of maternal behavior has been linked to various child outcomes, including academic achievement and social competence (Fraley, Roisman, & Haltigan, 2013), linguistic and cognitive development (Wang & Dix, 2013), verbal intelligence (Laucht et al., 2002), and attachment security (Dexter et al., 2013; Stacks et al., 2014), as well as fewer difficulties related to internalizing and externalizing (Brook, Zhang, Rosenberg, & Brook, 2006; Laucht et al., 2002; Mäntymaa et al., 2004). Findings from the present thesis suggest that mothers with lower concentrations of OT may display poorer interactive behaviors, which in turn could put their

children at risk for poorer developmental outcomes. Longitudinal studies are required to investigate this idea.

Conclusions

The present thesis indicates that OT levels are linked with more optimal interactive behavior in childbearing women both with and without mental health problems. The current results underline the importance of exploring the relationship between multiple psychosocial factors, including adult attachment and early adversity, to obtain a more complete understanding of individual differences in circulating OT. Finally, the present thesis adds to an emergent literature indicating that OT may represent a neurobiological substrate of maternal behavior, as well as a mechanism underlying the association between maternal psychosocial characteristics and the quality of their interactive behavior.

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