Oxytocin and Theory of Mind in Mothers and their Children:

A Longitudinal Investigation from Pregnancy to 3 Years Postpartum

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Table of Contents

Abstract

Given the ubiquity of social interactions in our daily lives and the importance of social relationships to our wellbeing, research has persistently investigated the processes that enable human sociality and affiliation. A growing body of neurobiological evidence has implicated the oxytocinergic system in promoting social cognition and behavior (for review see Carter, 2014), but the complex interplay of processes underlying this influence remains unclear. The present thesis aims to elucidate the role of the oxytocinergic system in relation to maternal caregiving and children's social cognitive development within the context of the mother–child relationship.

Article 1 is the first study to establish a link between circulating oxytocin and theory of mind (i.e., the ability to infer the mental states of others), demonstrating that increased levels of plasma oxytocin during the third trimester of pregnancy predicted better performance on an experimental theory of mind task in the early postpartum. This finding is consistent with the notion that endogenous oxytocin may represent a biomarker for sensitivity to social cues (Bartz,Zaki, Bolger, & Ochsner, 2011a). Theory of mind, in turn, was associated with less remote and less depressive maternal interactive behaviors (e.g., more engaged and relaxed; less focused on own experience). Moreover, plasma oxytocin was indirectly related to less depressive maternal behavior at 7–9 weeks postpartum via theory of mind ability. Article 2 confirmed and extended these findings by demonstrating that plasma oxytocin during late pregnancy was indirectly associated with more structuring and less intrusive maternal behavior at 2–3 years postpartum via mothers' theory of mind ability. Together the results of Articles 1 and 2 suggest that theory of mind may serve as a social cognitive mechanism through which oxytocin

promotes maternal caregiving by enhancing awareness of and ability to interpret social cues.

Article 3 demonstrated that another component of the oxytocinergic system—methylation of the oxytocin receptor (OXTR) gene—influences early emerging theory of mind abilities, which are an important aspect of children's social development. The findings revealed that higher levels of OXTR methylation, which down-regulates oxytocinergic system functioning by blocking receptor transcription and thus preventing oxytocin signalling, predicted worse performance on a battery of theory of mind tasks among 2- to 3-year-old children. This finding is suggestive of a functional impact of OXTR gene methylation on social cognitive processing. Moreover, exposure to more maternal structuring behavior buffered the impact of increased OXTR methylation on theory of mind performance. This pattern suggests that OXTR methylation may represent a biomarker of differential susceptibility to the influences of optimal and less optimal parenting on theory of mind development.

Overall the findings of the present thesis suggest that the oxytocinergic system plays an important and dynamic role in the reproductive-induced and developmental plasticity of the social brain that enables human sociality and affiliation in varying contexts. That is, the natural increase of peripheral oxytocin during late pregnancy may reflect a priming function of the oxytocinergic system on the social cognitive processes that facilitate long-lasting changes in the maternal caregiving that is required during infancy and early childhood. Further, during the early years methylation of the oxytocin receptor gene may confer differential susceptibility to maternal caregiving on social development. The findings also have important clinical implications, as they improve

identification of those at risk (e.g., women with low plasma oxytocin during the perinatal period and children with high OXTR methylation) and point to potential targets for prevention and early intervention (e.g., theory of mind and parent training).

Résumé

En raison de l'omniprésence des interactions sociales dans notre vie quotidienne ainsi que de l'importance des relations sociales pour notre bien-être, la recherche a continument étudié les processus permettant la socialité et l'affiliation humaines. Un nombre croissant de preuves neurobiologiques a lié le système ocytocinergique à la promotion de la cognition et du comportement social (pour une revue, voir Carter, 2014), mais l'interaction complexe des processus sous-jacents à cette influence reste incertaine. La présente thèse vise à élucider le rôle du système ocytocinergique en ce qui concerne les soins maternels et au développement social-cognitif des enfants dans le cadre de la relation mère–enfant.

L'Article 1 est la première étude à établir un lien entre l'ocytocine circulante et la théorie de l'esprit (i.e. la capacité à déduire les états mentaux des autres), démontrant que des taux accrus d'ocytocine plasmatique lors du troisième trimestre de la grossesse prédisent une meilleure performance à une tâche travaillant la théorie de l'esprit effectuée durant les premiers stades du postpartum. Cette découverte est en accord avec l'idée que l'ocytocine endogène pourrait représenter un biomarqueur de la sensibilité aux signaux sociaux (Bartz et al., 2011a). La théorie de l'esprit, à son tour, était associée à moins de comportements maternels désengagés et dépressifs (par exemple, plus engagés et détendus, moins centrés sur l'expérience personnelle). De plus, l'ocytocine plasmatique était indirectement liée à un comportement maternel moins dépressif à 7–9 semaines après l'accouchement, par l'intermédiaire de la théorie de l'esprit.

L'Article 2 a confirmé et élargi ces résultats en démontrant que l'ocytocine plasmatique en fin de grossesse était indirectement associée à un comportement maternel

plus structurant et moins intrusif à 2–3 ans postpartum, par l'intermédiaire des capacités de théorie de l'esprit des mères. Ensemble, les résultats des articles 1 et 2 suggèrent que la théorie de l'esprit sert potentiellement de mécanisme cognitif social par l'entremise duquel l'ocytocine optimise les soins maternels en améliorant la capacité à reconnaître ainsi qu'à interpréter les signaux sociaux.

L'Article 3 a démontré qu'une autre composante du système ocytocinergique—la méthylation du gène du récepteur de l'ocytocine (OXTR)—influence les capacités émergentes de la théorie de l'esprit, qui sont un aspect important du développement social des enfants. Les résultats ont révélé que des niveaux plus élevés de méthylation OXTR, qui régule négativement le fonctionnement du système ocytocinergique en bloquant la transcription des récepteurs et empêchant ainsi la signalisation de l'ocytocine, prédisent une performance plus faible à une batterie de tâches de théorie de l'esprit chez les enfants de 2–3 ans. Cette découverte suggère un impact fonctionnel de la méthylation du gène OXTR sur le fonctionnment cognitif social. De plus, l'exposition à un comportement maternel plus structurant attenue l'impact de l'augmentation de la méthylation de l'OXTR sur la performance en théorie de l'esprit. Ce modèle suggère que la méthylation de l'OXTR pourrait représenter un biomarqueur de la susceptibilité différentielle aux influences d'une parentalité plus ou moins optimale sur le développement de la théorie de l'esprit.

Dans l'ensemble, les résultats de la présente thèse suggèrent que le système ocytocinergique joue un rôle important et dynamique dans la plasticité liée à la reproduction et dans la plasticité développemental du cerveau social, ce qui permet la socialité et l'affiliation humaines au sein de contextes variés. Autrement dit,

l'augmentation naturelle de l'ocytocine périphérique en fin de grossesse pourrait refléter une fonction d'amorçage du système ocytocinergique sur les processus cognitifs sociaux facilitant des changements durables dans les soins maternels requis lors de la petite enfance. De plus, au cours des premières années, la méthylation du gène récepteur de l'ocytocine pourrait conférer une susceptibilité différentielle aux influences de soins maternels sur le développement social. Ces résultats ont également des implications cliniques importantes, car ils améliorent l'identification des personnes à risque (par exemple, les femmes avec un faible niveau d’ocytocine plasmatique pendant la période périnatale ou les enfants avec un niveau élevé de méthylation OXTR) et indiquent des cibles potentielles de prévention et d'intervention précoce (ex. formation parentale et formation sur la théorie de l'esprit).

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Contribution of Authors

The present thesis is comprised of three manuscripts which represent my doctoral work under the supervision of Dr. Phyllis Zelkowitz. The data reported in these manuscripts were collected as part of a larger program of research conducted by the CIHR Team in Perinatal Mental Health, whose investigators include Phyllis Zelkowitz, Ian Gold, Nancy Feeley, Barbara Hayton, C. Sue Carter, Togas Tulandi and Haim Abenhaim.

For the initial longitudinal study data reported in Articles 1 and 2, Phyllis Zelkowitz, Ian Gold, Nancy Feeley, and Barbara Hayton designed the study and wrote the protocol. C. Sue Carter supervised the hormonal assay analyses. Although I did not directly participate in data collection, I trained in and contributed to the coding of the observational data (e.g., maternal behavior and mind-mindedness).

For the follow-up study data reported in Articles 2 and 3, Phyllis Zelkowitz, Ian Gold, Nancy Feeley, and Barbara Hayton designed the study. Phyllis Zelkowitz and Ian Gold wrote the protocol. Stephanie Robins coordinated recruitment and data collection, Leonoara King and myself participated in recruitment and data collection, and I supervised and contributed to the coding of observational data (e.g., children's theory of mind tasks). Sangeetha Santhakumaran also contributed to coding and data entry. The processing of biological samples and methylation analyses were conducted by Leonora King and Corina Nagy under the supervision of Gustavo Turecki.

For each article, I managed the literature searches, generated the research questions, proposed a theoretical model, planned and conducted the statistical analyses and interpretation, and prepared the manuscripts for publication. All authors contributed

to and approved the final manuscripts. I also led the revise and resubmit process for Articles 1 and 2, which were subsequently published in *Psychoneuroendocrinology*. Article 3 is currently in preparation for submission to the journal *Development and Psychopathology*.

Contribution to Original Knowledge

The present thesis provides several novel contributions that improve our understanding of the complex interplay of processes that enable human sociality and affiliation. The present thesis utilized a biopsychosocial approach, employing multiple methods and advanced statistical techniques to investigate the role of the oxytocinergic system across two contexts—maternal caregiving and children's social development. More specifically, Articles 1 and 2 examined maternal caregiving following the important role transition from pregnancy to postpartum, while Article 3 examined emerging theory of mind abilities during the early years when children start learning to navigate the social world.

Article 1 is the first study, to my knowledge, to establish a link between circulating oxytocin and theory of mind (i.e., the ability to infer the mental states of others), and the first to do so during the perinatal period. The results demonstrated that increased levels of plasma oxytocin during the third trimester of pregnancy predicted better performance on an experimental theory of mind task in the early postpartum. Furthermore, Articles 1 and 2 demonstrated that theory of mind may serve as a social cognitive mechanism through which oxytocin promotes long-lasting changes to maternal caregiving.

Article 3 is the first study, to my knowledge, to provide empirical evidence that another component of the oxytocinergic system—methylation of the oxyticin receptor gene—influences early emerging theory of mind abilities, which are an important aspect of children's social development. Moreover, Article 3 is also the first to demonstrate that

OXTR methylation interacts with maternal behavior to predict individual differences in theory of mind development among young children.

Overall the findings of the present thesis suggest that the oxytocinergic system plays an important and dynamic role in the reproductive-induced and developmental plasticity of the social brain that enables human sociality and affiliation in varying contexts. The present thesis thus contributes to the extant literature exploring the role of the oxytocinergic system in promoting human sociality and affiliation, as one the most comprehensive longitudinal investigations from pregnancy through early childhood in a large, culturally diverse, non-clinical sample. The findings also have important clinical implications, by identifying novel biomarkers for risk and resiliency (e.g., women with low plasma oxytocin during the perinatal period and children with high OXTR methylation) and pointing to potential targets for prevention and early intervention (e.g., theory of mind and parent training), which could help to tailor and improve the effectiveness of mental health care in order to better meet the needs of mothers and their children.

General Introduction

"If we have no peace, it is because we have forgotten that we belong to each other."

- *Mother Teresa*

"Women are, in my view, natural peacemakers. As givers and nurturers of life, through their focus on human relationships and their engagement with the demanding work of raising children and protecting family life, they develop a deep sense of empathy that cuts through to underlying human realities."

- *Daisaku Ikeda*

As humans we are generally social creatures and much of our daily life involves interaction with others, be it in person or more recently through the use of technology. Moreover, we tend to form bonds with and care for others, which in turn are important for our wellbeing. For example, mother–child attachment is essential for survival and development (Bowlby, 1977; Cassidy, 2008). For decades researchers have been studying how we came to be this way, and more specifically what processes help us to navigate our complex social world and many social roles. From an evolutionary perspective, the social brain hypothesis (for review see Dunbar & Shultz, 2007) suggests that "the need to adapt behaviorally to increasing social complexity has substantially contributed to the development of brain mass, cognitive abilities, emotions, and language" (Neumann & Landgraf, 2012). That is, the evolution of brain size beyond what was necessary to maintain physiological functioning was driven by the cognitive and behavioral demands

of pair bonding, which serves as a mechanism through which to maintain cohesion for living in large social groups as well as a means to achieve mating and parenting. As research continues to explore the neurobiological underpinnings of human sociality and affiliation, a growing body of evidence points to the dynamic role of the oxytocinergic system (for review see Carter, 2014). Indeed, "the ubiquity of oxytocin-rich brain regions and oxytocin-responsive social behavior in diverse mammalian species highlights oxytocin's role in the evolution of central systems that privilege prosocial behavior" (MacDonald & MacDonald, 2010). According to the tend-and-befriend model (Taylor, 2006; Taylor et al., 2000), oxytocin facilitates the formation and maintenance of social relationships in order to protect from threat and manage stress. Despite mounting research, the interplay of processes underlying oxytocin's influences on human sociality and affiliation remain unclear.

In the present thesis I investigate the role of the oxytocinergic system in maternal caregiving and children's social development within the context of the mother–child relationship. I begin with a comprehensive, but selective, review of the extant literature. First, I provide a general overview of the oxytocinergic system including its components, relations to sociality and affiliation, as well as proposed mechanisms of action. Next, I examine the role of the oxytocinergic system in maternal caregiving among humans and introduce theory of mind as a potential social cognitive mechanism linking oxytocin to maternal caregiving behavior. Then, I explore the role of the oxytocinergic system in children's social development, highlighting both genetic and environmental influences on theory of mind in particular, and propose a potential interaction between DNA methylation of the oxytocin receptor gene and maternal caregiving behavior on children's

early emerging theory of mind abilities. Finally, I describe how the present thesis aims to build on and extend previous research.

The Oxytocinergic System

Components of the Oxytocinergic System

As research explores the neurobiological underpinnings of social affiliation, a growing body of evidence points to the modulatory role of the oxytocinergic system (Carter, 2014). This neurochemical system involves the production, binding, and signalling pathways of oxytocin, a nine amino acid neuropeptide that functions peripherally as a hormone and centrally as a neurotransmitter (Donaldson & Young, 2008). The oxytocin protein is encoded by and produced through transcription of the oxytocin gene (OXT). In humans, oxytocin is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus (Meyer-Lindenberg, Domes, Kirsch, & Heinrichs, 2011).

Oxytocin has long been known to be involved in reproduction (Donaldson & Young, 2008; MacDonald & MacDonald, 2010) including sexual function (i.e., stimulates arousal), labor and delivery (i.e., stimulates muscle contractions) and breastfeeding (i.e., stimulates milk release). This occurs via peripheral mechanisms through the transportation of oxytocin by magnocellular neurons to the pituitary gland and release into the bloodstream as well as synthesis of small quantities of oxytocin in tissues such as the testis, uterus, and placenta (Gimpl & Fahrenholz, 2001).

Oxytocin also acts in and on the brain. Oxytocin is released by parvocellular neurons via diffuse spread from dendrites and soma into extracellular fluid as well as directly through synapses from long-range axon projections to various regions in the

cortex, limbic system, and brainstem (Landgraf & Neumann, 2004; Meyer-Lindenberg et al., 2011; Sofroniew, 1983). Oxytocin exerts its signalling action by binding to oxytocin and vasopressin receptors on cell surfaces. The oxytocin receptor protein is encoded by and produced through transcription of the oxytocin receptor gene (OXTR). In humans, oxytocin receptors have been identified in several regions of the brain including areas in the brainstem, cortex, basal ganglia, thalamus, hypothalamus, and amygdala (Boccia, Petrusz, Suzuki, Marson, & Pedersen, 2013; Freeman, Smith, Goodman, & Bales, 2017; Loup, Tribollet, Dubois-Dauphin, & Dreifuss, 1991). It is through these neural mechanisms that oxytocin is thought to modulate region-associated social cognition and behavior.

Sociality, Affiliation and the Oxytocinergic System

Early research using animal models convincingly established the importance of the oxytocinergic system in facilitating social affiliation, particularly in the development and maintenance of pair bonding and offspring care (for review see Ross & Young, 2009). For example, in rats the onset of maternal behavior can be triggered by central administration of oxytocin or blocked by oxytocin receptor antagonists (e.g., Pedersen & Prange, 1979; van Leengoed, Kerker, &, Swanson, 1987). In sheep, oxytocin primes the formation of selective pair bonding with offspring via modulation of neurotransmitter activity within the olfactory system (Kendrick et al., 1997). Among the prairie vole, a monogamous mammal known to have a high density of oxytocin receptors in the brain (e.g., Shapiro & Insel, 1992), neonatal exposure to and central administration of oxytocin can enhance partner preference (e.g., Bales & Carter, 2003; Williams, Insel, Harbaugh, & Carter, 1994), and thus facilitate the formation of selective pair bonding between mates.

Subsequent research utilizing genetic modification revealed that both OXT and OXTR knockout mice, for whom production of the oxytocin hormone or receptor is inactivated, show impaired maternal nurturing and social memory as well as aggression and infanticide behaviors (e.g., Ferguson et al., 2000; Lee, Caldwell, Macbeth, Tolu, & Young, 2008; Pedersen, Vadlamudi, Boccia, & Amico, 2006; Ragnauth et al., 2005; Takayanagi et al., 2005). Moreover, elegantly designed cross-fostering studies suggested that the intergenerational transmission of maternal behavior is mediated by epigenetic changes in the oxytocinergic system (for review see Champagne & Meaney, 2001). With the advent of advanced, non-invasive pharmacological and neuroimaging techniques, this evidence base was parlayed into an abundant field of human research.

Interest in the role of the oxytocinergic system in promoting human sociality and affiliation appeared to peak following two seminal studies on trust and trustworthiness in social decision making (i.e., Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005; Zak, Kurzban, & Matzner, 2005). Using an experimental economic game, it was demonstrated that intranasal administration of synthetic oxytocin was associated with increased willingness to risk betrayal by making an investment without knowing who the receiver was or whether they would share the profit (i.e., trust). Moreover, higher levels of circulating oxytocin in blood plasma were observed among those who reciprocated intentional trust by sharing the profit (i.e., trustworthiness). A surge of studies then proceeded to investigate the prosocial effects, though sometimes subtle, of oxytocin administration on various aspects of social cognition that facilitate affiliation. These included the processing of and memory for social stimuli such as faces (e.g., Kirsch et al., 2005), speech (e.g., Hollander et al., 2007), and words (e.g., Unkelbach, Guastella, &

Forgas, 2008), as well as the perception of attractiveness (e.g., Theodoridou, Rowe, Penton-Voak, & Rogers, 2009) and the subjective experience of attachment security (e.g., Buchheim et al., 2009). Similar effects were also observed for social behaviors that facilitate affiliation including generosity (e.g., Zak, Stanton, & Ahmadi, 2007), eye contact (e.g., Guastella, Mitchell, & Dadds, 2008), and positive communication (e.g., Ditzen et al., 2009). Neuroimaging techniques indicated that inhibition or dampening of amygdala reactivity might modulate these effects of oxytocin (for review see MacDonald & MacDonald, 2010). However, most research conducted up to that point was limited to men. Interestingly, intranasal administration of synthetic oxytocin among women was related to enhanced neural activity in the amygdala when processing fearful faces, independent of eye gaze/fixation patterns and basal levels of plasma oxytocin, estradiol, and progesterone (Domes et al., 2010). The researchers suggested that this apparent sex difference may reflect the increased vigilance to threat stimuli observed in the luteal phase and increased oxytocin receptor affinity associated with female steroid hormones.

In a parallel line of inquiry, molecular genetics research revealed associations between several single nucleotide polymorphisms (SNPs) of the oxytocin receptor gene with social cognition and behavior including sensitive parenting (e.g., Bakermans-Kranenburg & van IJzendoorn, 2008), altruism (e.g., Israel et al., 2009), trait empathy (e.g., Rodrigues, Saslow, Garcia, John, & Keltner, 2009), loneliness (e.g., Lucht et al., 2009), sociability (e.g., Tost et al., 2010), and nonverbal cues such as eye gaze, smile, nod, and open arms (e.g., Kogan et al., 2011). Similarly, peripheral oxytocin has also been related to human sociality and affiliation. Lower levels of plasma oxytocin have been observed among individuals with autism spectrum disorder (e.g., Andari et al.,

2010) and borderline personality disorder (e.g., Bertsch, Schmidinger, Neumann, & Herpertz, 2013), which are both characterized by interpersonal difficulties. In contrast, higher levels of plasma and salivary oxytocin have been associated with perceived partner support, affectionate touch, and romantic behaviors (e.g., Gonzaga, Turner, Keltner, Campos, & Altemus, 2006; Grewen, Girdler, Amico, & Light, 2005; Holt-Lunstad, Birmingham, & Light, 2008; Light, Grewen, & Amico, 2005) as well as positive communication and parenting behaviors (e.g., Feldman, Gordon, & Zagoory-Sharon, 2011; Gouin et al., 2010). Higher plasma oxytocin is also associated with increased neural activity in areas implicated in social cognitive processing (e.g., Lancaster et al., 2015). However, in some studies higher plasma oxytocin was associated with negative outcomes such as relational distress and depression (e.g., Cyranowski et al., 2008; Parker et al., 2010; Taylor, Saphire-Bernstein, & Seeman, 2010).

Nuances and inconsistencies also began to emerge in the findings with regards to the prosocial effects of exogenous oxytocin, with some studies even suggesting negative or antisocial effects. For example, intranasal administration of synthetic oxytocin was associated with self-reported envy and gloating over winnings in an experimental game of chance (e.g., Shamay-Tsoory et al., 2009) as well as inclinations toward intimate partner violence, but only among individuals with high trait physical aggression (e.g., DeWall et al., 2014). Among individuals diagnosed with borderline personality disorder, oxytocin administration was observed to lower trust and cooperation, but only for those with an anxious attachment style or a history of trauma, both of which confer sensitivity to threat and rejection (e.g., Bartz et al., 2011b; Ebert et al., 2013). Similarly, oxytocin increased defensive aggression toward out-group (i.e., anonymous) competitors in

experimental economic games (e.g., Declerck, Boone, & Kiyonari, 2010; De Dreu et al., 2010). Moreover, oxytocin administration has been associated with lying, but only when beneficial to in-group (i.e., familiar) participants (Shalvi & De Dreu, 2014). In what would become a paradigm-shifting review of the state of the evidence, Bartz and colleagues (2011a) aptly suggested that the effects of exogenous oxytocin are not uniform or situation-invariant; rather they appear to be moderated by or dependent on contextual factors (e.g., task difficulty, in-group benefit vs. out-group threat) and stable individual differences (e.g., social proficiency, rejection sensitivity).

Theoretical Accounts and Proposed Mechanisms of the Oxytocinergic System

Given its role in the regulation of the central nervous system, early accounts in animal research proposed that oxytocin may promote prosocial behavior by reducing stress and anxiety to social threat (e.g., McCarthy, McDonald, Brooks, & Goldman, 1996). Indeed, oxytocin was observed to be released in response to perceived stress and has been shown to suppress hypothalamic pituitary adrenal (HPA) axis activation (for review see Neumann 2002). Subsequent evidence emerged supporting the anxiolytic effects of oxytocin in humans (for review see Heinrichs & Gaab, 2007). For example, oxytocin has been associated with decreased activation of the amygdala (e.g., Kirsch et al., 2005) and decreased release of adrenocorticotropic hormone (ACTH) and cortisol (e.g., Chiodera et al., 1991; Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Legros, 2001; Linnen, Ellenbogen, Cardoso, & Joober, 2012; Quirin, Kuhl, & Düsing, 2011). In addition, OXTR variants have been related to dispositional and physiological stress reactivity (e.g., Norman et al., 2012; Rodrigues et al., 2009). Together these findings suggest a general influence of oxytocin on reducing psychological and physiological

reactivity to stressors. However, in some studies oxytocin has also been related to increased stress among humans. For example, intranasal administration of synthetic oxytocin increased defensive anxiety responses to unpredictable threat (e.g., Grillon et al., 2013) and higher plasma oxytocin has been associated with social anxiety and relationship distress (Hoge, Pollack, Kaufman, Zak, & Simon, 2008). Moreover, Crockford and colleagues (2017) highlighted that oxytocin only appears to be released following stress when social support is available (e.g., Heinrichs et al., 2003; Seltzer, Ziegler, & Pollak, 2010). Thus, it may be the case that oxytocin facilitates the motivation and/or ability to mobilize social support, which in turn helps to manage and reduce stress. Consistent with the moderated effects of oxytocin on social cognition and behavior, the effects of oxytocin on buffering cortisol in response to stress also depend on contextual factors and individual differences such as early adversity, emotion regulation capacity, and psychiatric diagnosis (for reviews see Cardoso, Kingdon, & Ellenbogen, 2014; Weisman, Zagoory-Sharon, & Feldman, 2013). Therefore, the anxiolytic hypothesis alone cannot fully explain the role of the oxytocinergic system in human sociality and affiliation.

Alternatively, Kemp and Guastella (2011) proposed the social-approach/withdrawal hypothesis to explain the diverse effects of oxytocin. This theory suggests that oxytocin inhibits withdrawal-related social behaviors (e.g., fear, avoidance) by suppressing and/or decreasing judgments of displeasure or aversion (e.g., Evans, Shergill, & Averbeck, 2010), while enhancing approach-related social behaviors (e.g., trust, affection), by activating and/or intensifying judgments of pleasure or desire (e.g., Kosfeld et al., 2005). Correspondingly, neuroimaging data demonstrated that oxytocin is

differentially associated with amygdala activity depending on the emotional valence of social stimuli, with decreases for fearful faces and increases for happy faces (e.g., Gamer, Zurowski, Büchel, & 2010). Approach-related behaviors also include those construed as socially negative (e.g., jealousy, anger), which helps to make sense of the findings linking oxytocin to increased envy, gloating and aggression (e.g., Shamay-Tsoory et al., 2009; DeWall et al., 2014). Consistent with this theory, there is also evidence that oxytocin contributes to social motivation via interaction with the mesocorticolimbic dopaminergic reward system, which comprises a pathway from the ventral tegmental area (VTA) to several regions including the nucleus accumbens, amygdala and prefrontal cortex, many of which receive oxytocin neuron projections and are rich in oxytocin receptors (for reviews see Gordon, Martin, Feldman, & Leckman, 2011; Love, 2014). For example, among children with autism spectrum disorder, intranasal administration of oxytocin increased functional connectivity between reward areas (e.g., nucleus accumbens and amygdala) and those implicated in social-emotional perception (e.g., prefrontral cortex and fusiform gyrus) preferentially for social stimuli (Gordon et al., 2016). However, it is not clear how the social-approach/withdrawal hypothesis explains the oxytocin-induced increases in lying and decreases in trust and cooperation. Further, this theory does not explain the observed context- and individual-dependent effects of oxytocin.

Intriguingly, the social saliency hypothesis previously put forth to account for oxytocin findings in animal research (e.g., Ross & Young, 2009) may point to an underlying mechanism explaining the differential effects of oxytocin observed in humans (Bartz et al., 2011a; Olff et al., 2013; Shamay-Tsoory et al., 2009), whereby oxytocin signaling alters the perceptual salience of or sensitivity to social stimuli, thus enhancing

attention to and processing of social information, for better or for worse (i.e., leading to prosocial or antisocial responses). Shamay-Tsoory and Abu-Akel (2016) elaborated the potential processes and neural systems that lead to social saliency, wherein oxytocin increases the orienting of attention (e.g., gaze, pupil dilation) toward social cues such as eyes and emotional face expressions (e.g., Guastella et al., 2008; Leknes et al., 2013), for which saliency is reinforced through oxytocin's modulation of the mesocorticolimbic dopamineregic reward system (e.g., Groppe et al., 2013; Scheele et al., 2013). Interestingly, Gamer and colleagues' (2010) study provided evidence consistent with this model of social saliency: intranasal administration of oxytocin was associated with increased gaze to the eye region during processing of faces as well as enhanced functional connectivity between the amygdala (a region involved in the appraisal of stimuli as salient) and the superior colliculus (a region involved in controlling eye movement and attention). Once social stimuli have been attended to and deemed salient, the oxytocinergic system may further enhance its processing. For example, oxytocin administration increased neural activation in the fusiform gyrus, a region involved in facial recognition (e.g., Petrovic, Kalisch, Singer, & Dolan, 2008). Although the social saliency hypothesis appears to resolve the paradox of the observed conflicting prosocial and antisocial effects of oxytocin, it is not clear how it explains some findings where oxytocin had a prosocial effect regardless of valence (e.g., De Dreu et al., 2010) or the possibility that reduced anxiety could decrease attention to social cues (Ebitz & Platt, 2014).

Subsequently, Bethlehem and colleagues (2014) suggested that the three previously described theoretical accounts and their mechanisms are not necessarily

mutually exclusive. They proposed an integrated model wherein oxytocin leads to anxiety reduction and/or social motivation/reward sensitivity which together influence the saliency and processing of social stimuli to promote or impede social interaction depending on feedback from the environment (e.g., indicating whether it is safe/pleasurable or threatening/aversive). Moreover, they suggested that individual differences in social anxiety and reward processing may account for the moderated effects of oxytocin. Bernard Crespi (2016) further elaborated an integrated social-evolutionary model to explain the adaptive significance of the oxytocinergic system in human sociality and affiliation. According to this model, oxytocin is released in response to social events that are expected to negatively or positively influence one's social relationships and therefore evolutionary fitness, which functions to increase the sensitivity of and/or activate relevant brain regions involved in social cognition and behavior in order to protect from the perceived threat (e.g., mobilizing social support) or take advantage of the opportunity (e.g., bond formation). This theoretical account is supported by evidence that oxytocin's effects are dependent on the availability of social information (e.g., Declerck et al., 2010) and that oxytocin increases functional connectivity between the amygdala and brain regions involved in social cognition (e.g., Riem et al., 2012; Sripada et al., 2013). Further, it suggests that the previously confusing link observed between oxytocin and increased anxiety or relationship distress may be adaptive in that it serves to facilitate the mobilization of social support and protection of relationships. This theory is also broadly consistent with the tend-and-befriend model (Taylor, 2006; Taylor et al., 2000), which stipulates that oxytocin promotes the motivation to nurture and bond with others in order to promote safety and reduce stress.

Also from an evolutionary perspective, Selective Investment Theory (Brown & Brown, 2006; Brown, Brown, & Preston, 2012), posits a "caregiving system" wherein oxytocin is selectively released under conditions when fitness interdependence (i.e., mutual dependence for reproduction and/or survival) is cued (e.g., sex or birth), which may increase the chances of suppressing one's own needs to support the wellbeing of a partner or child, possibly by interacting with other neurobiological systems to inhibit fight-or-flight self-preservation responses and enhance motivation for species-preservation behaviors. Correspondingly, Rilling and Young (2014) delineated a set of mechanisms that may underlie how oxytocin promotes maternal caregiving in particular. First, oxytocin has been shown to interact with the mesocorticolimbic dopaminergic pathway to increase the reward value of infant stimuli (e.g., Atzil, Hendler, & Feldman, 2011; Gregory, Cheng, Rupp, Sengelaub, & Heiman, 2015; Strathearn, Fonagy, Amico, & Monatgue, 2009), and thus may enhance approach-motivation. Indeed, higher levels and/or reactivity of plasma oxytocin among mothers have been related to increased gaze toward their infants during the postpartum period (e.g., Feldman, Weller, Zagoory-Sharon, & Levine, 2007; Kim, Fonagy, Koos, Dorsett, & Strathearn, 2014). Oxytocin has also been associated with dampened amygdala activation and increased recruitment of the prefrontal cortex in response to infant crying (e.g., Kim et al., 2011; Riem et al., 2011; Riem, Bakermans-Kranenburg, & van IJzendoorn, 2016), and thus may function to attenuate aversive emotional responses thereby inhibiting avoidance-motivation. Moreover, oxytocin has been related to augmented anterior insula responses to infant crying and sad faces (e.g., Riem et al., 2011; Strathearn et al., 2009), an area implicated in empathy (e.g., ability to represent others' feelings), which would in turn facilitate

sensitive and responsive caregiving. In addition, Rilling and Young also highlighted research among rodents indicating that oxytocin indirectly activates the ventral pallidum in response to rewarding stimuli (i.e., offspring), which modulates motor output (i.e., behavior). Together these mechanisms are consistent with an integrated model wherein oxytocin influences the motivation and coordination of maternal caregiving via the attenuation of anxiety/aversion and strengthening of salience/reward value toward infant stimuli.

Maternal Caregiving

Individual Differences and Outcomes of Maternal Caregiving

Maternal caregiving plays a crucial role in the development of adaptive social and emotional functioning in children (Cassidy, 2008). Indeed, responsive, sensitive, emotionally engaged, and cooperative maternal interactive behavior promotes the development of secure attachment (Ainsworth, 1979; Barnas & Cummings, 1994; Sroufe, 2005). Maternal sensitivity and responsiveness are related to the development of social competence, social skills, language and communication, academic achievement, and overall cognitive ability (e.g., Egeland, Pianta, & O'Brian, 1993; Landry, Smith, & Swank, 2006; McElwain & Volling, 2004; NICHD, 2002). However, women vary in the extent to which they engage in optimal caregiving behaviors (Galbally, Lewis, van IJzendoorn, & Permezel, 2011). Some mothers may experience difficulty interpreting their infants' cues and responding appropriately to their needs, as well as trouble interacting and emotionally engaging with their infants. Research in non-clinical populations suggests that such parenting difficulties negatively impact various child development outcomes. For example, impaired skills in providing scaffolding and

supporting engagement with the environment may hinder cognitive functioning, whereas lack of parental sensitivity and responsiveness can lead to insecure attachment and risk for depression, while the use of coercive or harsh discipline increases the likelihood of conduct problems (for reviews see Murray, 2014; Murray, Cooper, & Fearon, 2014). There is thus a clear need to improve our understanding of the factors that influence maternal caregiving.

The Oxytocinergic System and Maternal Caregiving

It is widely contended that "the transition to parenthood also involves a degree of maternal brain plasticity around the time of childbirth" (Swain et al., 2012), and that the oxytocinergic system plays a central role in these processes (Kim & Strathearn, 2016). As reviewed above, research using animal models has established that oxytocin plays an important role in triggering maternal caregiving behavior (for review see Lim & Young, 2006). A growing body of research also implicates the oxytocinergic system in the onset and maintenance of maternal caregiving among humans (for reviews see Bakermans-Kranenburg & van IJzendoorn, 2017; Galbally et al., 2011; Rilling, 2013).

In terms of peripheral oxytocin, higher plasma oxytocin levels during the perinatal period predicted more sensitive maternal caregiving behaviors including gaze, motherese vocalizations, affectionate touch, and positive affect directed toward infants (e.g., Apter-Levi, Zagoory-Sharon, & Feldman, 2014; Feldman et al., 2007; Gordon, Zagoory-Sharon, Leckman, & Feldman, 2010a). Mothers' plasma and salivary oxytocin levels have also been associated with social engagement, synchrony of affect, and positive communication during interaction with their infant (e.g., Feldman et al., 2011; Gordon, Zagoory-Sharon, Leckman, & Feldman, 2010b). Neuroimaging data indicated that higher

plasma oxytocin was associated with greater activation in the nucleus accumbens and amygdala among mothers observed to engage in more synchronous interaction with their infants (Atzil et al., 2011). An increased maternal plasma oxytocin response has also been observed following mother–infant interaction, which is related to activation in oxytocin-associated brain regions (Strathearn et al., 2009) as well as to trait sensitivity and responsiveness to others' emotions, moods, and sensory cues (Strathearn, Iyengar, Fonagy, & Kim, 2012).

The intranasal administration of synthetic oxytocin has been associated with caregiving. For example, decreased neural activation and aversion to infant crying was observed among nulliparous women (e.g., Bakermans-Kranenburg, van Ijzendoorn, Riem, Tops, & Alink, 2012; Riem et al., 2011; Rupp et al., 2014), while increased protective responses and perceptions of a positive relationship with their infant have been observed among mothers with postpartum depression (e.g., Mah, Bakermans-Kranenburg, van IJzendoorn, & Smith, 2014; Mah, van IJzendoorn, Smith, & Bakermans-Kranenburg, 2013). Moreover, intranasal oxytocin was associated with increased functional connectivity between the amygdala and several brain regions involved in social processing and emotion regulation in response to infant laughter (Riem et al., 2012).

Molecular genetic research has linked oxytocin receptor gene variants to caregiving. For example, both OXT rs2740210 and rs4813637 SNPs have been associated with increased infant directed vocalizations and provision of instrumental care, depending on mothers' own history of received care (Mileva-Seitz et al., 2013). Mothers with the homozygous GG genotype for the OXTR rs53576 SNP display more maternal

sensitivity including responsiveness, warmth and emotional engagement during interaction with their toddlers (e.g., Bakermans-Kranenburg & van IJzendoorn, 2008; Sturge-Apple, Cicchetti, Davies, & Suor, 2012), whereas mothers with the homozygous AA genotype display less warmth towards their children (Klahr, Klump, & Burt, 2014). The TT genotype for the OXTR rs1042778 SNPs has also been associated with less parental touch toward infants than among carriers of the G allele (Feldman et al., 2012). In contrast, a neuroimaging study demonstrated that mothers with A alleles for the OXTR rs53576 SNP and T alleles for the OXTR rs1042778 SNP displayed more positive parenting behaviors such as praise and positive affect as well as greater neural activation when viewing images of their own child (Michalska et al., 2014). This differential pattern of findings may reflect moderation by contextual (e.g., partner conflict) and/or personal (e.g., early life experiences) factors.

Together these findings provide support for the role of oxytocinergic system in maternal caregiving behavior. However, further research is needed to elucidate the complex interplay of processes through which oxytocin influences maternal interactive behavior.

Theory of Mind as a Link between the Oxytocinergic System and Maternal Caregiving

Given that oxytocin has been implicated in various social cognitive processes, as reviewed above, I propose that theory of mind may serve as a potential social cognitive mechanism linking oxytocin to maternal caregiving behavior. Theory of mind is an important component of social cognition, which encompasses the ability to infer or understand the mental states of others, such as thoughts, beliefs, feelings, and desires, and how they influence behavior (Frith and Frith, 2005; Goldman, 2006). Responding

effectively to an infant's needs requires the ability to interpret those needs based on subtle cues such as facial or non-verbal signals (Ainsworth et al., 1978; Sroufe, Egeland, Carlson, & Collins, 2005). Thus, theory of mind may be implicated in a mother's ability to recognize her infant's social cues and may facilitate the provision of caregiving and interaction with her infant.

This hypothesis is strengthened by a line of research demonstrating that maternal mind-mindedness, a construct theoretically related to theory of mind, is closely tied with maternal sensitivity (Meins, Fernyhough, Fradley, & Tuckey, 2001). Maternal mind-mindedness is defined as mothers' ability to attribute mental states specifically to their young children (Meins, 1997). Maternal mind-mindedness has been operationalized and assessed two ways: using an interactional measure of a mother's tendency to comment appropriately on her infant's putative mental states during the first year of life, and thereafter with a representational measure of a mother's use of mental state terms when asked to describe her child (Meins & Fernyhough, 2015). Mothers who are higher in mind-mindedness, that is those whose attributions accurately reflect their infant's mental states (e.g., saying "You're such a happy boy" while the infant is laughing and smiling) and/or who are more likely to characterize their child as having mental states (e.g., "She's a very curious child"), should be better able to respond appropriately to social cues (Meins, 1999). Indeed, maternal mind-mindedness has been associated with concurrent measures of maternal sensitivity at 6 months and 12 months postpartum (e.g., Laranjo, Bernier, & Meins, 2008; Meins et al., 2001).

There is some evidence to suggest that oxytocin is associated with theory of mind ability and specifically to performance on an experimental measure called the Reading

the Mind in the Eyes Test (RMET; Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001), which involves identifying complex mental states depicted in photographs of the eye region of adults, though results have been inconsistent. In some studies, intranasal administration of synthetic oxytocin has been observed to enhance neural activation during, and improve accuracy on, the RMET among healthy males (e.g., Domes, Heinrichs, Michel, Berger, & Herpertz, 2007), males with autism spectrum disorders (e.g., Guastella et al., 2010), and less socially proficient males (e.g., Feeser et al., 2015). Intranasal oxytocin also selectively improved empathic accuracy (e.g., ability to understand the thoughts and feelings experienced by others) for less socially proficient males (e.g., Bartz et al., 2010). Neuroimaging studies (e.g., Baron-Cohen et al., 1999; Gallagher et al., 2000) have also demonstrated that performance on theory of mind tasks is associated with activation in oxytocin-sensitive areas such as the amygdala and prefrontal cortex. In addition, several oxytocin receptor gene polymorphisms have also been linked to RMET performance (e.g., Lucht et al., 2013; Rodrigues et al., 2009).

Despite the rising number of studies examining endogenous oxytocin in relation to maternal caregiving, little research has examined how endogenous oxytocin is implicated in theory of mind ability, nor specifically in mothers or during the perinatal period. To my knowledge, only one study (Lancaster et al., 2015) has demonstrated a link between higher plasma oxytocin levels, among males, and increased neural activation in several brain regions involved in social cognition including mentalizinga synonym for theory of mind ability). Consistent with Bartz and colleagues (2011a), the authors suggested that their findings support the proposal that natural variations in endogenous oxytocin may represent a biomarker for individual sensitivity to social cues. Interestingly,

plasma oxytocin levels have been observed to rise across pregnancy (e.g., Dawood, Ylikorkala, Trivedi, & Fuchs, 1979; De Geest, Thiery, Piron-Possuyt, & Vanden Driessche, 1985; Kumaresan, Anandarangam, Dianzon, & Vasicka, 1974), which is known to stimulate labor and delivery, but has also been related to maternal-fetus bonding during the third trimester as well as postpartum maternal interactive behavior (e.g., Feldman et al., 2007; Levine, Zagoory-Sharon, Feldman, & Weller, 2007). This natural increase in oxytocin has been suggested to serve a priming function in preparation for motherhood (Strathearn, 2011). Animal research has also demonstrated increased oxytocin binding and receptor expression in late pregnancy (e.g., Pedersen, 1997; Young, Muns, Wang, & Insel, 1997). Thus, I propose that the pregnancy-related changes in the oxytocinergic system, such as the increase in plasma oxytocin, may enhance the social cognitive processes, such as theory of mind, that in turn facilitate maternal caregiving and bonding after childbirth.

Children's Social Development

Individual Differences and Outcomes of Theory of Mind Development

Theory of mind is an important aspect of social cognition that contributes to the development of social competence (Astington & Edward, 2010). As described above, theory of mind involves the ability to infer or attribute mental states such as thoughts, feelings, and desires to the self and others, and understand how they influence behavior (Premack and Woodruff, 1978; Sodian and Kristen, 2010). Research has established age level precursors and milestones, such as visual perspective taking and false belief understanding, in the development of theory of mind from infancy through 5 years of age (Astington & Edward, 2010). The initial stages of theory of mind development involve

implicit understanding, as demonstrated through behavior, whereas later stages become reflective and comprise explicit understanding through verbal descriptions and explanations of others' motivations and intentions (Hughes & Leekam, 2004). At age 2, children display understanding that thoughts and objects in the world are different (Astington & Edward, 2010), an awareness of their own and others' desires (Meltzoff, Gopnik, & Repacholi, 1999), and comprehension of how someone else will feel when they do or do not get what they want (Wellman & Banerjee, 1991). These early developing aspects are less well studied, as much of the research on theory of mind focuses on the preschool period. Importantly, it has been suggested that "early differences in performance provide an index of more lasting variation in reasoning about mental states and social development" (Hughes & Devine, 2015).

Indeed, theory of mind is not uniformly acquired and/or applied. Although most children can pass false-belief tasks by middle childhood, they do vary in the extent to which they are able to use theory of mind skills across social situations and on more advanced tasks. Stable individual differences in theory of mind performance have been observed from early childhood through adolescence (for a review see Hughes & Devine, 2015). These individual differences predict negative social outcomes such as poor social skills, aggression, and peer rejection (e.g., Banerjee, Walting, & Caputi, 2011; Devine, White, Ensor, & Hughes, 2016; Holl, Kirsch, Rohlf, Krahé, & Elsner, 2017). Moreover, theory of mind deficits underpin many of the difficulties experienced by individuals with autism spectrum disorder (ASD; Baron-Cohen, 1995; Yirmiya, Erel, Shaked, & Solomonica-Levi, 1998) and schizophrenia (Corcoran, Mercer, & Frith, 1995; Sprong, Schothorst, Vos, Hox, & Van Engeland, 2007). Interestingly, well-developed theory of

mind abilities can also be used for antisocial purposes such as manipulation and deception. As such, individuals with conduct disorder, callous-unemotional traits, and psychopathy demonstrate intact performance on and typical neural activation during completion of theory of mind tasks, though they exhibit a lack of affective empathy (e.g., Dolan & Fullam, 2004; Jones, Happé, Gilbert, Burnett, & Viding 2011; O'Nions et al., 2014). While both environmental and biological influences have been proposed, there is a need for more integrated research on the complex interplay of processes contributing to individual differences in theory of mind development.

Nature versus Nurture in Theory of Mind Development

It is thought that "environmental factors have their greatest influence in early childhood" (Hughes & Plomin, 2000), as this is a critical period of remarkable development and neural plasticity. In terms of environmental influences (i.e., nurture), theory of mind is thought to develop in part through social experiences (Carpendale & Lewis, 2004; Meltzoff & Gopnik, 2013). The family setting is important as the first context involving interpersonal interaction. Correspondingly, parenting practices, particularly maternal, have been implicated in children's early theory of mind development (for reviews see Miller, 2016; Pavarini, de Hollanda Souza, & Hawk, 2013). Caregiving behavior that is sensitive and responsive (e.g., Cahill, Deater-Deckard, Pike, & Hughes, 2007) and comprises structure and discussion (e.g., Ruffman, Perner, & Parkin, 1999) provides opportunities for reasoning and encourages reflecting on other perspectives, which facilitates learning about mental states and thus promotes the development of children's theory of mind abilities (Miller, 2016). Mothers' own theory of mind skills (Sabbagh & Seamans, 2008) and trait level empathy (Farrant, Devine,

Maybery, & Fletcher , 2012)—an overarching construct encompassing theory of mind—are considered to influence children's theory of mind abilities through maternal behavior (e.g., Lundy, 2013) and mental state talk (e.g., Tompkins, Benigno, Kiger Lee, & Wright, 2018) exposure. However, social influences only account for part of the variability in children's theory of mind development, as biological influences are also involved.

In terms of biological influences (i.e., nature), the oxytocinergic system has received increasing attention for its role in the development of the social brain (for reviews see Carter, 2014; Donaldson & Young, 2008; Feldman, Monakhov, Pratt, & Ebstein, 2016). As reviewed above, oxytocin is released centrally and binds to receptors in brain regions involved in social and emotion processing (Meyer-Lindenber et al., 2011). Several lines of investigation have implicated the oxytocinergic system in children's theory of mind abilities. For example, the intranasal administration of synthetic oxytocin has been associated with improved performance on, and increased neural activation during, completion of a theory of mind task among children and adolescents with ASD (Gordon et al., 2013; Guastella et al., 2010). Levels of and changes in children's plasma and salivary oxytocin concentrations have also been associated with improved performance on, and increased neural activation during, theory of mind tasks (Gordon et al., 2013; Parker et al., 2014), as well as greater observed social reciprocity behavior (Feldman, Gordon, Influs, Gutbir, & Ebstein, 2013). Higher oxytocin levels in newborns' cerebral spinal fluid (CSF) was associated with increased interest in social engagement (Clark et al., 2013), a potential precursor to theory of mind development. Single nucleotide polymorphisms in the oxytocin receptor gene have been related to performance on theory of mind tasks among preschool (Wu & Su, 2015) and school-aged

(Slane et al., 2014) children, as well as to a range of other social cognition tasks (e.g., joint attention, empathy, cooperation and self-recognition) among toddlers (Wade, Hoffmann, Wigg, & Jenkins, 2014). Furthermore, alterations in the oxytocinergic system have been implicated in the etiology of autism spectrum disorders (for a review see Green, Taylor, & Hollander, 2013), which are characterized by theory of mind deficits. For example, there is some evidence for deficiencies in plasma oxytocin levels (e.g., Andari et al., 2010; Husarova et al., 2016; Modahl et al., 1998) as well as alterations of the oxytocin and oxytocin receptor genes (e.g., Campbell et al., 2011; Francis et al., 2016; Lerer et al., 2008; Wu et al., 2005) among individuals with autism spectrum disorder and related phenotypes. In addition, children exposed prenatally to an oxytocin receptor antagonist, to delay preterm labor, demonstrated more autism-related impairments (Friedlander et al., 2017).

Interplay of Genetic and Environmental Influences on Theory of Mind Development

Despite calls for the importance of investigating gene–environment interactions in child development and psychopathology (e.g., Caspi & Moffit, 2006; Meaney, 2010), few studies have examined the interplay between the environmental and biological influences underlying individual differences in children's theory of mind development. One study (Wade, Hoffmann, & Jenkins, 2015) demonstrated a gene–environment interaction between variation in OXTR SNP genotypes and maternal behavior, whereby more maternal cognitive sensitivity predicted better theory of mind performance among preschool-aged children with the major allele of the rs11131149 variant. A second study (McDonald, Baker, & Messinger, 2016) observed a similar gene–environment interaction, such that better parent–child interaction quality predicted more empathic

behavior among preschool-aged children with the minor allele of a different OXTR variant, rs53576. In both studies, no independent effect of the SNPs emerged, suggesting that it is crucial to consider gene–environment interactions in order to improve our understanding of theory of mind development. However, less is known about the potential influence of DNA methylation, a stable genetic biomarker (How Kit, Nielsen, & Tost, 2012), of the oxytocin receptor gene on children's theory of mind development.

Research has recently begun to investigate functional outcomes of oxytocin receptor gene methylation. DNA methylation is a dynamic process whereby methyl groups attach to individual cytosine-phosphate-guanine (CpG) sites thus impeding the recruitment and binding of transcription factors that allow for gene expression. DNA methylation within the OXTR CpG island has been associated with decreased messenger RNA (mRNA) transcription and suppressed gene expression (Kusui et al., 2001). That is, OXTR methylation and concomitant reduction in mRNA may impede the production of oxytocin receptors, which would impact functioning of the oxytocinergic system and in turn lead to different behavioral phenotypes (for a review see Kumsta, Hummel, Chen, & Heinrichs, 2013). Indeed, OXTR methylation has been associated with decreased mRNA levels in temporal cortex tissue (Gregory et al., 2009) and decreased levels of circulating oxytocin in blood plasma (Dadds et al., 2013). Interestingly, some studies involving children and adolescents have linked increased OXTR methylation to theory of mind-related impairments such as poor social communication (Rijlaarsdam et al., 2017), callous-unemotional traits (Cecil et al., 2014; Dadds et al., 2013), and ASD diagnosis (Gregory et al., 2009), while others have found decreased methylation to be associated with social problems (e.g., Milaniak et al., 2017; Yuksel, Yuceturk, Karatas, Ozen, &

Dogangun, 2016). In addition, two neuroimaging studies (Jack, Connelly, & Morris, 2012; Puglia, Lillard, Morris, & Connelly, 2015) found increased OXTR methylation to be associated with greater neural activity in brain areas involved in social perception and emotional processing. However, the researchers suggested that this pattern is actually indicative of poor functioning or risk of psychopathology as increased activity may reflect more effortful processing. Examining the moderating role of social influences may help to elucidate these differential effects of oxytocin receptor gene methylation.

The Present Thesis

The purpose of the present thesis is to improve our understanding of the complex interplay of processes underlying human sociality and affiliation using a biopsychosocial model. More specifically, I aim to elucidate the role of the oxytocinergic system in relation to maternal caregiving and children's social development within the context of the mother–child relationship. My research objectives are twofold: First, I will investigate whether maternal theory of mind represents a social cognitive mechanism linking the hormone oxytocin to maternal interactive behavior during the perinatal period and into early childhood (Articles 1 and 2). Second, I will examine the interplay between OXTR methylation and maternal behavior on children's theory of mind development (Article 3).

In Article 1, I seek to test the social saliency hypothesis of the oxytocinergic system as it applies to maternal caregiving. To this end I explore whether theory of mind may represent a social cognitive mechanism through which the oxytocinergic system promotes maternal caregiving during the transition from pregnancy to the early postpartum period. In a community sample of women, I examine plasma oxytocin levels measured longitudinally across the perinatal period in relation to postpartum performance

on an experimental theory of mind task (i.e., the RMET) and maternal behavior observed during mother–infant interaction. To account for the competing anxiolytic hypothesis, self-reported symptoms of both general anxiety and pregnancy-related worry were included as controls in the statistical analyses. Given that the effects of oxytocin may be moderated by contextual factors and individual differences, social demographic information and psychosocial risk factors (e.g., history of psychological and social problems such as depression or abuse) were also included as controls.

In Article 2, I seek to build on and extend the findings from Article 1 through a follow-up study in three important ways. First, the follow-up study provided a unique opportunity for a more robust test of my model with temporal separation in the measurement of the main variables, by assessing maternal behavior again when participating children were approximately 2–3 years old. Second, this also allowed me to investigate whether pregnancy-related changes in the oxytocinergic system impart long-lasting changes in maternal caregiving. Lastly, given that the RMET comprises adult stimuli, I also assessed mothers' ability to attribute mental states specifically to their young children using an observational measure of maternal mind-mindedness (Meins, 1997).

In Article 3, I seek to explore the role of the oxytocinergic system in theory of mind development. To accomplish this, I examine DNA methylation of the oxytocin receptor gene in conjunction with maternal caregiving on children's early emerging theory of mind abilities. Given the suspected functional impact of gene suppression, I test whether increased OXTR methylation is associated with poorer performance on theory of mind tasks, and whether exposure to more optimal maternal behavior buffers this effect.

The present thesis and all data reported herein form part of a larger program of research involving a longitudinal study on hormonal, genetic, and psychosocial factors in perinatal mental health and the developing mother–child relationship, of which other data are reported elsewhere (e.g., King et al., 2017; Zelkowitz et al., 2014).

Article 1

The Role of Oxytocin in Mothers' Theory of Mind and Interactive Behavior during the Perinatal Period

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Summary The present longitudinal study examined the relations between plasma oxytocin, theory of mind, and maternal interactive behavior during the perinatal period. A community sample of women was assessed at 12–14 weeks gestation, 32–34 weeks gestation, and 7–9 weeks postpartum. Oxytocin during late pregnancy was significantly positively correlated with a measure of theory of mind, and predicted theory of mind ability after controlling for parity, maternal education, prenatal psychosocial risk, and general anxiety, measured during the first trimester. Theory of mind was associated with less remote and less depressive maternal interactive behavior. Oxytocin, across all time points, was not directly related to maternal interactive behavior. However, there was a significant indirect effect of oxytocin during late pregnancy on depressive maternal behavior via theory of mind ability. These preliminary findings suggest that changes in the oxytocinergic system during the perinatal period may contribute to the awareness of social cues, which in turn plays a role in maternal interactive behavior.

Oxytocin is a neuropeptide implicated in both social cognition and social behavior (Carter, 2014). Oxytocin has been associated with maternal caregiving behavior (Strathearn, 2011), which in turn is crucial for infant social and emotional development (for review see Cassidy, 2008). However, the processes whereby oxytocin influences maternal behavior remain unclear. The present study examines whether theory of mind ability may represent a social cognitive mechanism linking oxytocin and maternal interactive behavior.

Oxytocin is a nine amino acid neuropeptide that functions as a hormone and a neuromodulator. Oxytocin is made in and acts on the brain, especially in regions involved in emotion and social interaction (Meyer-Lindenberg et al., 2011). Specifically, in humans oxytocin is synthesized in the supraoptic and paraventricular nuclei of the hypothalamus and released into the brain, where it binds to receptors in several regions including areas in the cortex, basal ganglia, thalamus, and hypothalamus (Loup et al., 1991), as well as in the amygdala (Boccia et al., 2013). Oxytocin also is transported to the pituitary gland where it is released peripherally via the bloodstream.

As research explores the neurobiological underpinnings of social behavior, a growing body of evidence points to the role of oxytocin in prosocial and affiliative behavior (Carter, 2014). While animal models consistently implicate oxytocin in parenting behavior, few studies explore the link between oxytocin and maternal caregiving behaviors and attachment relationships in humans. Plasma oxytocin levels during the perinatal period have been associated with maternal interactive behaviors (Feldman, 2012). There is an increased maternal plasma oxytocin response following mother–infant interaction, which is related to activation in oxytocin-associated brain

regions (Strathearn et al., 2009) and to trait sensitivity and responsiveness to others' emotions, moods, and sensory cues (Strathearn et al., 2012). Molecular genetic research has linked oxytocin receptor gene variants to sensitive parenting (Bakermans-Kranenburgand van IJzendoorn, 2008; Feldman, 2012). These findings provide support for the role of oxytocin in maternal behavior. However, further research is needed to elucidate the mechanisms through which oxytocin influences maternal interactive behavior. We propose here that the capacity for theory of mind may be a social cognitive mechanism with implications for understanding maternal behavior.

Theory of mind is a component of social information processing which involves the understanding of mental states such as thoughts, beliefs, feelings, and desires, and how they influence behavior (Wellman et al., 2000). Theory of mind requires the cognitive ability to attribute mental states to oneself, and to infer the mental states of others (Baron-Cohen, 1989; Sodian and Kristen, 2010). The ability to interpret social cues is of particular importance to respond effectively to an infant's needs, as a mother must be able to determine those needs based on subtle cues such as facial or non-verbal signals (Ainsworth et al., 1978; Sroufe et al., 2005).

A few studies have investigated the relationship between oxytocin and theory of mind ability. The intranasal administration of synthetic oxytocin improved theory of mind, as measured by the Reading the Mind in the Eyes Test (RMET; Baron-Cohen et al., 2001), among both healthy males (Domes et al., 2007) and males with autism spectrum disorders (Guastella et al., 2010). Intranasal oxytocin also selectively improved empathic accuracy (e.g., ability to understand the thoughts and feelings experienced by others) for less socially proficient males (Bartz et al., 2010). In addition, several oxytocin

receptor gene polymorphisms are linked to theory of mind performance on the RMET (Rodrigues et al., 2009; Lucht et al., 2012). To our knowledge, research has yet to examine the influence of endogenous oxytocin on theory of mind, nor specifically in mothers.

Theory of mind may serve as a potential mechanism linking oxytocin with maternal behavior. Endogenous oxytocin may be a biomarker of social motivation and of individual sensitivity to social cues (Bartz et al., 2011). In the present investigation we examined whether plasma oxytocin levels would be related to social motivation, as manifested by positive maternal interactive behaviors, and to sensitivity to social cues, as measured by theory of mind ability. Given the importance of accurately interpreting social cues in the ability to respond appropriately to an infant's needs, we also examined whether theory of mind ability would be related to maternal interactive behavior. The present study aimed to test whether peripheral oxytocin influences maternal behavior indirectly through theory of mind ability, during the perinatal period.[1] Consistent with previous research examining plasma oxytocin during the perinatal period (e.g., Strathearn et al., 2012) we controlled for potential confounding variables related to child-bearing including parity, breastfeeding status, and birth control use, as oxytocin is involved in parturition and lactation.

Oxytocin also is proposed to influence social cognition and behavior via its anxiety reducing effects (Bartz et al., 2011). Oxytocin suppresses HPA axis stress hormones (e.g., Heinrichs et al., 2006), indicating a more general influence of reducing

[1] The present investigation forms part of a larger longitudinal study on perinatal mental health, of which other data are not reported here.

psychological and physiological reactivity to stressors. Anxiety in turn may influence RMET performance by increasing reluctance to look at others' eyes (Churchland and Winkielman, 2012) or the capacity to use information gained by eye gaze. Maternal anxiety also is related to less sensitive and more intrusive maternal interactive behavior (Kaitz and Maytal, 2005). In order to test whether theory of mind represents a unique mechanism, we controlled for anxiety, including both general anxiety and pregnancy related worry.

The effects of oxytocin on social cognition and behavior may be modulated by contextual factors and stable individual characteristics (Bartz et al., 2011). Given that oxytocin may be dysregulated by childhood trauma (e.g., Heim et al., 2009), early adversity may represent a potential moderator. In the present study, we used psychosocial risk factors (e.g., history of psychological and social problems such as depression or abuse) to control for contextual factors, and socio-demographic information to control for individual characteristics.

The current study proposes that theory of mind ability represents a social cognitive mechanism mediating the link between peripheral oxytocin and maternal interactive behavior during the perinatal period. We hypothesized a mediational model wherein (a) oxytocin is related to theory of mind and to maternal interactive behavior; (b) theory of mind is related to maternal interactive behavior; and (c) theory of mind mediates the link between oxytocin and maternal interactive behavior.

1. Methods

1.1. Participants

Pregnant women were recruited from prenatal clinics during their first routine prenatal

examination, and from a freestanding birthing center during their first information session. Eligibility criteria included being within 12–14 weeks of gestation, expecting to deliver a single infant, and the ability to respond to questionnaires in either English or French. A total of 665 women were approached, and 394 met eligibility requirements, of which 53 declined to participate. Thus, a total sample of 341 participants was enrolled in the study between September 2009 and January 2011. Of the 341 women enrolled in the study, 7.3% (n = 25) were withdrawn due to miscarriage, preterm birth, giving birth to twins, poor comprehension, neonatal death, non-Canadian residency, or if they were no longer followed at the hospital or the birthing center by the third trimester of pregnancy. As a result, the final sample comprised 316 participants (M_{age} = 31.40 years, SD = 4.60). Of these participants 58.5% were born in Canada; 78.8% had Canadian citizenship; 38.3% of participants' main language spoken at home was French, 38.3% English, 2.8% reported equal French and English, and 20.6% another language. On average women had 16.46 years of education (SD = 3.07), ranging from completion of high school to a doctoral level degree. The majority of women (93.7%) reported they were married or living with their partner. In terms of parity, 46.8% of women were having their first child, 37.0% their second, and 16.2% their third or more. At 7-9 weeks postpartum, 87.8% of participants were breastfeeding and 13.9% reported they were using oral contraceptives.

1.2. Materials

1.2.1. Background information

The socio-demographic data collected included age, marital status, years living with partner, who lives in household, employment status, level of education, citizenship, ethnicity, religion, and languages spoken. Health data included obstetrical history

information such as number of previous pregnancies, deliveries, and abortions, the use of in vitro fertilization (IVF) to conceive, and use of medication. Post birth questions inquired about infant feeding, infant sleep, and maternal use of birth control.

1.2.2. Psychosocial risk

Maternal prenatal psychosocial risk (i.e., history of physical/sexual abuse, history of depression, marital quality, availability of support, and stressful life events) was assessed using the 10-item self-report Antenatal Risk Questionnaire[2] (ANRQ; Priest et al., 2008), a short form of the Pregnancy Risk Questionnaire (Austin et al., 2005). Total scores can range from 7 to 67, where scores above 23 indicate the presence of significant risk factors for perinatal depression. The ANRQ demonstrates high acceptability among pregnant women and is a valid screener for postnatal depression (Austin et al., 2011).

1.2.3. Anxiety and worry

Level of maternal anxiety was measured with the 7-item Generalized Anxiety Disorder scale[2] (GAD-7; Kroenke et al., 2007). Total scores can range from 0 to 21, where higher scores indicate more symptoms of anxiety. The GAD-7 is validated for use in primary care patients, with good internal consistency, test–retest reliability, and convergent validity with clinical diagnoses (Kroenke et al., 2007). The content and degree of maternal worry during pregnancy was assessed using the 16-item Cambridge Worry Scale[2] (CWS; Green et al., 2003), which includes items on finances, relationships with partners, family, and friends, and health of the baby. The CWS is well validated for use with pregnant women, demonstrating adequate internal consistency and temporal stability

[2] All self-report measures were translated into French by two independent French–English bilingual research assistants, who then met to reach consensus on final versions.

across trimesters, and correlates with measures of state and trait anxiety (Green et al., 2003).

1.2.4. Oxytocin

Participants provided a 10ml blood sample, in which circulating plasma oxytocin levels were measured. Registered nurses drew blood from antecubital veins into heparinized vacutainer tubes, which were then placed on ice. Within 6h the blood samples were cold centrifuged at 4°C at 1600 × g for 15min to separate plasma, and then stored in an −80°C freezer until analysis in the Carter lab at the University of Illinois. Oxytocin concentrations were determined using a commercial enzyme-linked immunosorbent assay kit (EIA; Enzo Life Sciences Inc., NY, USA) from unextracted plasma, and followed methods validated in previous research (Carter et al., 2007). Unextracted samples were used in the current study given that extraction may remove the majority of plasma oxytocin, including oxytocin that is bound to other molecules in plasma such as albumin, glutathione, and cysteine (Martin and Carter, 2013). Measurements were conducted in duplicate or triplicate, and the lower detectable limit was 15.6pg/ml. Intra-assay and inter-assay coefficients of variation were both below 8.7%.

1.2.5. Theory of mind

Theory of mind was evaluated using the revised version of the Reading the Mind in the Eyes Test[3] (RMET-R; Baron-Cohen et al., 2001). The RMET is the most widely used experimental task to measure theory of mind in adults, as it assesses the ability to infer a variety of complex mental states (e.g., reflective, ashamed). For this task, participants are presented 36 photographs of the eye region and asked to choose one of four words (one

[3] The RMET was translated into French and validated (Prevost et al., 2014).

correct target, three incorrect foils) that they feel ‘‘best describes what the person in the picture is thinking or feeling’’. To ensure that comprehension of the words does not impact task performance, participants are encouraged to refer to the standardized glossary of word definitions if they do not understand the meaning of a word (Baron-Cohen et al., 2001). Participants are asked to make their choice as quickly as possible, however the task is not timed. Scores range from 0 to 36, where higher scores indicate better theory of mind and scores below 26 suggest a subtle impairment in social intelligence. The RMET comprises positive, neutral, and negative stimuli, and items range in difficulty to avoid ceiling effects. Evidence supports the convergent validity of the RMET with other tasks measuring theory of mind, as well as discriminant validity in identifying social cognitive impairments (Baron-Cohen et al., 1997, 2001). The RMET is also sensitive to intranasal administration of oxytocin (e.g., Domes et al., 2007) and genetic variation in the oxytocin receptor gene (e.g., Rodrigues et al., 2009).

1.2.6. Maternal behavior

The Global Rating Scales (GRS; Fiori-Cowley et al., 2000) was used to code filmed 5min, face-to-face interactions between mothers and their two-month-old infants. Trained coders, blind to all other data obtained from the mother, rated maternal behavior on four dimensions: sensitivity (5 items; warmth, acceptance, responsiveness, demanding, sensitivity), intrusiveness (2 items; intrusive behavior and speech), remoteness (2 items; withdrawal, silence), and overt behaviors reflecting depression (4 items; happiness, energy, engagement, relaxed). Items are rated on 5-point scales, where high scores indicate optimal maternal behaviors. The GRS demonstrates good inter-rater reliability, as well as discriminant and predictive validity (Murray et al., 1996a, 1996b; Gunning et

al., 2004). Mean intraclass correlation coefficients (ICC's; single measure, absolute agreement) were calculated to assess inter-rater reliability between two coders for a random sample of videos (N = 10). Satisfactory inter-rater reliability was established for each maternal dimension: sensitivity (ICC = .52, p = .06), intrusive (ICC = .44, p = .09), remote (ICC = .69, p = .01), depressive (r = .78, p = .003). The two coders achieved the required inter-rater reliability established by the developers from the Winnicott Research Unit at the University of Reading (e.g., Costa and Figueiredo, 2011), as 51.5% of cross-rated items had identical ratings and 90.8% of items were rated within one point of each other.

1.3. Procedure

This study was approved by the Research Ethics Committee at the Jewish General Hospital and was carried out in accordance with the Declaration of Helsinki. After providing written informed consent, participants were assessed at three time points: 12–14 weeks gestation (T1) and 32–34weeks gestation (T2) in conjunction with their scheduled prenatal appointments, and then were visited at 7–9 weeks postpartum (T3) in their homes. At each time point a 10ml blood sample was collected (between 1000h and 1600h, at least 30min before/after breastfeeding), and participants were asked to provide demographic and health information and to complete questionnaires assessing symptoms of anxiety. Participants were also asked to complete self-report measures of psychosocial risk factors at T1 and maternal prenatal worry at T1 and T2. At T3, an experimental task evaluating theory of mind was administered and 5min of mother–infant interaction in a free play situation was filmed. Participant retention was high: 316 participants completed T1, 301 participants (95.3%) completed T2, and 287 participants (90.8%) completed T3.

Participant attrition (n = 29) reflected loss of interest, not wanting another blood draw, partner disagreement regarding participation, missed appointments, or unavailability. Participants who were withdrawn or dropped out (n = 54) did not significantly differ from those who completed all time points (n = 287) on any of the socio-demographic characteristics or main study variables measured at T1.

1.4. Data analysis

Descriptive statistics were computed to examine the characteristics of each measure. Bivariate Pearson's *r* correlations were calculated to examine relationships among variables. Descriptive statistics and correlation analyses were performed using SPSS Statistics 19.0 (IBM, USA). Path analysis was conducted to determine whether oxytocin is a unique predictor of theory of mind (a-path), and whether theory of mind is a unique predictor of maternal interactive behavior (b-path), beyond control variables. Acceptable model fit is indicated by a comparative fit index (CFI) and Tucker-Lewis (TLI) in the range .90-.95 or above, as well as a root mean square error of approximation (RMSEA), with 90% confidence interval (90% CI), in the range .05-.08 or less (T.D. Little, 2013). The mediational hypotheses were evaluated using bootstrap analyses with 20,000 resamples to test the significance of the indirect effects (i.e., multiplication of the a- and b-paths), where bias-corrected 95% confidence intervals (95% CI) that do not include zero indicate a significant indirect effect (Hayes, 2009). The bootstrapping method has high power and does not require the assumption of a normal sampling distribution (Hayes, 2009). Path analysis and bootstrapping were performed with Mplus 7.11 software. Missing values analysis indicated 8.4% of the data to be missing, and covariance coverage ranged from 0.77 to 1.00. A non-significant Little's MCAR test

suggests that data are likely missing completely at random ($\chi^2 = 142.41$, $p = .91$). Listwise deletion was used for descriptive statistics and correlation analyses, and missing data were handled with the Full Information Maximum Likelihood (FIML) for path analysis and bootstrapping, as this method produces unbiased parameter estimates and standard errors (Enders, 2010).

2. Results

2.1. Descriptive statistics

Means and standard deviations for the main study variables are presented in Table 1. The distribution of scores on the ANRQ is consistent with previous research examining pregnant women in primary care settings (e.g., Priest et al., 2008). The means for the GAD-7 and CWS self-report questionnaires fell within one standard deviation of means reported in past studies with similar samples of pregnant women (e.g., Pop et al., 2011; Trillingsgaard et al., 2011). The mean theory of mind score for the women in the current study fell within one standard deviation of the mean reported for healthy females from the general population control group of Baron-Cohen et al.'s (2001) study. The mean ratings of maternal behavior were within one standard deviation of previous observations of mother–infant interaction at 6-8 weeks postpartum (e.g., Zelkowitz et al., 2011).

Although standard ranges of peripheral oxytocin levels in humans during the perinatal period are not yet established, the mean level of plasma oxytocin in early pregnancy (12–14 weeks gestation) and during the postpartum period (7–9 weeks after delivery) were both within one standard deviation of values found in other reports (e.g., Feldman et al., 2007; Levine et al., 2007). The mean level of plasma oxytocin during the third trimester (32–34 weeks gestation) was higher than the values reported in studies

cited above. However, in the longitudinal study reported by Feldman et al. (2007) and Levine et al. (2007), blood samples were taken earlier in the third trimester, at approximately 22–32 weeks gestation. In the current investigation, an overall pattern emerged where there was a significant increase (M = 78.78, SD = 225.40) in plasma oxytocin from T1 to T2 (t = 6.02, p < .001), and then a decrease (M = −109.83, SD = 237.69) from T2 to T3 (t = −7.63, p < .001), to below the level observed at T1 (t = −2.20, p = .028). Given oxytocin levels were not normally distributed within each time point, log-transformed values were used for all subsequent analyses.

2.2. Bivariate correlations

Bivariate correlations for the main study variables are presented in Table 2. As expected plasma oxytocin was related to theory of mind. However, only oxytocin at T2, where the highest levels were reported (see Table 1), was significantly positively correlated with performance on the RMET. Also as expected, theory of mind was significantly related to maternal interactive behaviors, such that higher scores on the RMET were associated with less remote and less depressive behaviors. However, theory of mind ability was unrelated to the sensitive and intrusive dimensions of observed maternal interactive behavior. Contrary to expectations, oxytocin, across all time points, was not significantly related to maternal interactive behaviors.

Given the unexpected lack of relationship of overall maternal sensitivity with oxytocin and theory of mind, we explored the associations between oxytocin with each item of the GRS sensitivity subscale (i.e., warmth, acceptance, responsiveness, demanding, sensitivity). Results indicated that oxytocin, across all time points, was not significantly correlated with any of the GRS sensitivity subscale items. However, theory

of mind was significantly positively correlated with responsiveness (r = .13, p = .036) and acceptance (r = .13, p = .050).

We also examined the associations between the potential control variables and the main study variables. Across all time points, neither general anxiety nor prenatal worry was significantly related to theory of mind. However, general anxiety at T1 and T2 were significantly positively correlated to oxytocin at T3 (see Table 2). There was also a significant negative correlation between general anxiety at T1 and maternal sensitivity. Given that oxytocin at T3 was not correlated with theory of mind or maternal interactive behaviors and will not be included in the path analyses, only general anxiety at T1 was entered as a control variable.

Correlations with contextual variables indicated that psychosocial risk factors were significantly positively related to oxytocin at T2 and to theory of mind ability, but not with maternal interactive behaviors. These findings support the possibility that context may modulate the influence of perinatal oxytocin on maternal theory of mind. That is, oxytocin may have differential effects on theory of mind performance depending on women's background history of distress (as measured here by psychosocial risk factors). In terms of individual characteristics, maternal years of education was related to oxytocin at T2 (r = −.15, p = .022), theory of mind ability (r = .36, p < .001), as well as sensitivity (r = .13, p = .045), (non)remote (r = .19, p = .003) and (non)depressive (r = .21, p = .001) maternal interactive behavior. Consequently, we controlled for psychosocial risk and maternal education in all subsequent analyses.

Further analyses were carried out with variables related to childbearing to test for potential confounding factors. Oxytocin, theory of mind, and maternal behaviors did not

significantly differ between women who are breastfeeding or not, or between women who were using birth control or not. However, bivariate correlations indicated that parity was significantly negatively related to oxytocin at T2 ($r = -.12$, $p = .047$) and theory of mind ability ($r = -.32$, $p < .001$), but not with maternal interactive behaviors. In other words, the more children a mother has borne, the lower her levels of oxytocin during the third trimester and the poorer her theory of mind performance will be. Thus, parity was included as a control variable in all subsequent analyses.

2.3. Path analyses

Building on the bivariate correlation findings, path analyses were conducted to examine the role of oxytocin in predicting theory of mind as well as the role of theory of mind in predicting maternal behaviors. General anxiety (GAD-7) at T1, prenatal psychosocial risk (ANRQ), years of education, and parity were included as control variables via correlations with the predictor variable (e.g., T2 oxytocin) and by including pathways to the mediator (e.g., theory of mind) and outcome (e.g., maternal remote or depressive behavior) variables. As both the model for remote and the model for depressive (see Fig. 1) maternal behaviors are saturated (e.g., all possible parameters are estimated, degrees of freedom equals zero), model fit cannot be evaluated. However, model parameters can be interpreted.

In both models the direct path from T2 oxytocin to theory of mind, beyond control variables, was statistically significant: $\beta = .107$, $p = .048$ for the remote behavior model, and $\beta = 0.107$, $p = .043$ for the depressive behavior model.[4] This pattern of

[4] Competing models for each T1 and T3 oxytocin were also tested but no significant paths or indirect effects emerged.

findings suggests that endogenous oxytocin maybe involved in promoting understanding of social cues.

Neither the direct path from theory of mind to remote maternal behavior (β = 0.068, p = .439), nor the direct path from theory of mind to depressive maternal behavior (β = 0.124, p = .102) were statistically significant. Maternal years of education was the only predictor to approach significance for both (non)remote (β = .153, p = .063) and (non)depressive (β = .150, p = .059) maternal behavior.

Consistent with bivariate correlations, the direct paths from T2 oxytocin to maternal (non)remote (β = .085, p = .175) and to (non)depressive (β = −.01, p = .873) behavior were not statistically significant. The mediational hypotheses cannot be tested given the lack of a direct effect between oxytocin and maternal behavior. However, an indirect effect can be interpreted regardless of whether its constituent paths are statistically significant (Hayes, 2013).

2.4. Indirect effects

Bootstrap estimates indicated that the indirect effect of T2 oxytocin on remote maternal behavior (β = .007, B = 0.019) was not significant (95% CI: −.004–.035). However, the indirect effect of T2 oxytocin on depressive maternal behavior (β = .013, B = 0.030) was statistically significant (95% CI: .001–.040).[4] These results indicate that endogenous oxytocin levels during the third trimester of pregnancy are associated with (non)depressive maternal interactive behavior through theory of mind ability.

3. Discussion

This study examined the relationship between oxytocin, social cognition, and maternal behavior during the perinatal period. Oxytocin during late pregnancy, when hormone

levels were at their highest, was significantly positively correlated with theory of mind, and predicted theory of mind ability after controlling for parity, maternal education, prenatal psychosocial risk, and general anxiety. Theory of mind was associated with less maternal remote and depressive interactive behaviors. Oxytocin, across all time points, was not directly related to maternal interactive behavior. However, oxytocin during late pregnancy was indirectly related to depressive maternal behavior through theory of mind ability.

Our results indicate that oxytocin is related to and predictive of theory of mind ability, which suggests that higher levels of endogenous oxytocin may promote awareness of social cues. This finding also supports the hypothesis that endogenous oxytocin may be a biomarker for sensitivity to social cues (Bartz et al., 2011). Furthermore, there is now evidence using three different methodologies – intranasal administration (e.g., Domes et al., 2007; Guastella et al., 2010), receptor gene polymorphisms (e.g., Rodrigues et al., 2009; Lucht et al., 2012), and now circulating plasma – that oxytocin is related to or predicts theory of mind ability as measured by the RMET. The present study thus adds to the growing literature demonstrating that oxytocin modulates social cognition.

Concurrent oxytocin level was not related with performance on the theory of mind task. Research examining endogenous oxytocin, particularly during the perinatal period, has not consistently found that concurrent levels of oxytocin are related to maternal cognitive or behavioral outcomes. For example, Skrundz et al. (2011) found that plasma oxytocin during late pregnancy was related to postpartum depression but not to concurrent levels of depressive symptomatology. Our results are also in line with Levine

et al.'s (2007) findings demonstrating that an increase in plasma oxytocin from first to third trimester, but not concurrent oxytocin levels, was associated with maternal bonding to fetus during the third trimester. More specifically, women whose oxytocin levels increased across pregnancy scored higher on the subscales assessing differentiation of fetus from self and attribution of characteristics and intentions to the fetus, thus tapping maternal theory of mind toward the unborn child. These findings suggest that changes in oxytocinergic system functioning during pregnancy are associated with maternal social cognition. Correspondingly, in the current study, only oxytocin during the third trimester of pregnancy (32–34 weeks gestation), where the highest levels were measured, was a significant predictor of theory of mind ability (assessed at 7–9 weeks postpartum). This may indicate that the natural increase of peripheral oxytocin during late pregnancy may reflect a priming function of the oxytocinergic system on social cognitive processes that facilitate maternal bonding behavior after childbirth (Feldman et al., 2007; Strathearn, 2011). That is, changes in the oxytocinergic system during pregnancy may prepare a mother to respond appropriately to her new infant by enhancing her sensitivity toward, and ability to interpret, social cues. Similarly, there is evidence that ability to encode emotions, as assessed with an emotion recognition task using adult faces, improves from early (before 14 weeks gestation) to late (after 34 weeks gestation) pregnancy (Pearson et al., 2009). This is suggested to be an evolutionary adaptation whereby the increased sensitivity to emotional stimuli of threat or support during pregnancy helps prepare women for motherhood, in order to protect and provide adequate care for their newborn. Although our results reveal a temporal association between oxytocin during pregnancy and postpartum maternal social cognition, experimental studies are required to determine

potential causal mechanisms.

Our findings also correspond with animal research suggesting that oxytocin activates the onset of maternal behavior. For example, Pedersen et al. (1982) demonstrated that central administration of oxytocin induced immediate and long-lasting maternal behavior in estrogen primed virgin female rats. Oxytocin binding in the medial preoptic area (MPOA) and the ventral tegmental area (VTA) is increased during late pregnancy and parturition among rats (Pedersen, 1997) and blocking oxytocin receptors during parturition results in inhibition of maternal behavior after birth (Pedersen et al., 1994). Additionally, a stress induced decrease in oxytocin receptor expression during late pregnancy lowered levels of maternal responsiveness in rat mothers who were previously high in pup licking-grooming (Champagne and Meaney, 2006). Research with sheep has also demonstrated increased oxytocin concentration in the paraventricular nucleus of the hypothalamus at birth, and central administration of oxytocin increased release of plasma oxytocin and induced maternal behavior (Da Costa et al., 1996). The authors proposed that prolonged stimulation of postpartum maternal behavior occurs through a positive feedback mechanism whereby oxytocin released in the paraventricular nucleus activates parvocellular oxytocin neurons, which leads to further oxytocin release in oxytocin terminal regions. Da Costa and colleagues also suggested that activation of different sites might stimulate different components of maternal behavior. Thus, oxytocin may be associated with theory of mind ability by activating brain regions associated with social and emotion processing. Accordingly, the RMET is associated with activation in the amygdala and prefrontal cortex (e.g., Baron-Cohen et al., 1999), which are oxytocin binding areas (e.g., Boccia et al., 2013; Loup et al., 1991). Moreover, Kinsley et al.

(2006) suggested that the neuroendocrine changes during pregnancy associated with the onset of maternal behavior might lead to permanent alterations in neuronal structure and brain functioning. Finally, oxytocin knock out mice, with decreased central oxytocin availability, demonstrate a longer latency and lower frequency of maternal behavior (Pedersen et al., 2006). Thus, the increase in peripheral oxytocin during late pregnancy observed in the current study may reflect increased central oxytocin availability (Levine et al., 2007), which facilitates the onset of postpartum maternal behavior. Although research has yet to investigate the role of oxytocin during the peripartum period on maternal social cognitive processes, we can infer from animal research on maternal behavior that the changes which the oxytocinergic system undergoes during late pregnancy, such as increased binding and increased receptor expression (e.g., Pedersen, 1997; Young et al., 1997), may underlie the improved emotion processing observed during late pregnancy (Pearson et al., 2009) and theory of mind ability assessed in the current study during the early postpartum period.

Animal research suggests that sex hormones stimulate postpartum maternal behavior by promoting oxytocin synthesis, transport, release, and binding in brain areas associated with maternal behavior (for review see Pedersen, 1997). Similarly, the relationship between oxytocin and maternal social cognition may reflect an interaction with the changes in sex hormones during pregnancy. Estrogen and progesterone have been associated with altered emotion processing of visual stimuli across the estrous cycle and during pregnancy (for review see A.C. Little, 2013). It has also been suggested that changes in the oxytocinergic system during pregnancy may interact with dopamine reward circuitry to prime maternal behavior (e.g., Galbally et al., 2011; Numan, 2006).

For example, central administration of oxytocin in the paraventricular nucleus in sheep also led to an increased concentration of dopamine (Da Costa et al., 1996). An increased peripheral oxytocin response to infant contact among human mothers was also associated with brain activation in dopamine brain reward processing regions (Strathearn et al., 2009).

Given that oxytocin is released in response to social stimuli, measuring maternal oxytocin response by taking samples of plasma oxytocin before and after mother—infant interaction may have provided a better measure of oxytocinergic system functioning in relation to maternal social cognition and behavior. For instance, an increased peripheral oxytocin response to mother—infant interaction was observed among mothers who engage in high levels of affectionate contact (Feldman et al., 2010). Thus, it is possible that a relation between postpartum oxytocin levels and theory of mind ability was not detected because a single baseline sample was used in the current study. While oxytocin has been implicated in triggering the onset of maternal behavior, it is not necessary for the maintenance of established maternal behavior, rather offspring or infant stimuli has been found to play an important role (for reviews see Numan, 2006; Numan and Insel, 2003). This may explain why postpartum levels of oxytocin were not related to theory of mind ability.

Theory of mind was associated with less remote and less depressive maternal interactive behaviors. That is, mothers with better theory of mind abilities appear to be more attentive, less self-absorbed and less withdrawn when interacting with their infant, and their affective states reflect enjoyment in interacting. Individuals with clinical depression are significantly impaired in their ability to identify the mental states of others

(Wolkenstein et al., 2011). This deficit may contribute to the flat affect, lower levels of activity and playfulness, and less affectionate contact that is characteristic of depressed mothers (Cohn et al., 1990; Field, 2010; Field et al., 1985). Although the depressive behavior subscale of the GRS does not assess symptoms of depression, it is an observational measure of overt behaviors that may reflect depression including: lack of expression of positive affect and enjoyment in interacting (e.g., smiling, laughing), nervous tension or anxiety (e.g., jumpy movements, high pitched voice), self-consciousness (e.g., looking in mirror, talking about unrelated events), and energy (e.g., amount of effort and vitality). Our results suggest the ability to interpret social cues may be related to mothers' ability to actively engage with their infants, where mothers with poorer theory of mind appear less relaxed in interaction and more focused on their own experience.

Bootstrap analyses indicated there was an indirect effect of plasma oxytocin levels during the third trimester of pregnancy on (non)depressive maternal interactive behavior, through theory of mind ability. These findings thus provide preliminary evidence that theory of mind may represent a social cognitive mechanism explaining how oxytocin influences maternal behavior. However, these results should be interpreted with caution, as causality cannot be established in the current study due to the correlational nature of the data. The small effect size also suggests this finding requires replication.

The indirect effect of plasma oxytocin on depressive maternal behavior also sheds light on the association between oxytocin and postpartum depression. Accumulating research suggests oxytocin is involved in the development of mood disorders. For example, lower peripheral levels of oxytocin during late pregnancy have been associated

with an increased occurrence of postpartum depression (Skrundz et al., 2011). The indirect effect points to theory of mind as a social cognitive mechanism through which oxytocin is linked to depressive maternal interactive behavior. Our findings add to the extant research by integrating the underlying biological and cognitive processes involved in postpartum depression. Theory of mind was not related to sensitivity or (non)intrusive maternal interactive behavior. The social cognitive processes involved in understanding others' mental states may not play a role in influencing whether mothers tend to be overbearing or over-stimulating with their infant (i.e., intrusive). Theory of mind ability may be unrelated to sensitivity in the current study in part due to the diversity of behaviors rated within this dimension. Mothers were assessed on a range of behaviors including whether they expressed love and affection rather than criticism, were accepting of their infant's experience rather than being frustrated or rejecting, responded promptly to their infant's behaviors, required the infant to behave according to their expectations, and their ability to empathize and identify with the infant. These behaviors are not necessarily mutually inclusive. For example, a mother may interact in a warm and positive manner, but may fail to respond to many of her infant's cues (Fiori-Cowley et al., 2000). Conversely, a mother may respond promptly to her infant's cues, but do so in a manner that is inappropriate or does not match the infant's needs. Thus, theory of mind may only be related to more specific behaviors. Indeed, our item analysis indicated that theory of mind was related to responsiveness, which rated a mother's awareness of and responsiveness to her infant's cues, and to acceptance, which rated ability to follow infants' interests and respond at the same level of affect as their infant. It is also possible that a relationship was not detected between theory of mind ability and maternal

sensitivity as this scale assesses behavior in response to and dependent on the infant. Two-month-old infants do not yet engage in a wide variety of interactive behaviors, thus there may be fewer cues for mothers to respond to. Theory of mind may have been related to the depressive and remote scales as these behaviors may be more reflective of internal maternal states. Further research should continue to investigate the role of oxytocin with other maternal behaviors and with infants of different ages.

Oxytocin levels across the perinatal period were not directly related to maternal interactive behavior. These findings differ from reports from previous research linking perinatal oxytocin to maternal bonding behaviors across all mothers (Feldman et al., 2007; Levine et al., 2007). Our results also may reflect a lack of variability in ratings of maternal behavior. Overall mothers were rated relatively high, reflecting optimal behavior, in all dimensions. Similarly, given that 87.8% of the sample reported they were still breastfeeding at T3, the small group size of women who did not report breastfeeding, and the potential lack of variance therein, may have prevented the statistical detection of differences by breastfeeding status (i.e., Type II error). However, some previous studies have found that breastfeeding status was unrelated to postpartum levels of oxytocin (e.g., Gordon et al., 2010; Strathearn et al., 2012).

Our findings suggest that, contrary to other reports (e.g., Heinrichs et al., 2003), endogenous oxytocin may not influence maternal social cognition or behavior by reducing anxiety or psychological reactivity to stressors. General anxiety and pregnancy related worry were not related to third trimester oxytocin levels, and anxiety was not a significant predictor of theory of mind or maternal behavior. Further, anxiety during pregnancy was positively associated with postpartum levels of oxytocin. This finding is

consistent with research suggesting that oxytocin is released in response to stress (e.g., Grippo et al., 2007). It also corresponds with evidence indicating that oxytocin is associated with higher levels of attachment anxiety among women (e.g., Weisman et al., 2013). There may also be differential consequences of acute as compared to chronic oxytocin release which might explain the discrepant findings. Acute stress could trigger the oxytocin system which then suppresses the HPA axis response. However, chronic stress may prevent the down regulation of oxytocin. The current study employed well-validated self-report measures of symptoms of anxiety, however our community sample displayed relatively low rates of anxiety, and the measures may reflect more trait-like or general levels of anxiety. It may be more beneficial to experimentally investigate the role of oxytocin in real-time anxiety reduction, where anxiolytic effects can be more reliably assessed using direct physiological measurements of central and peripheral mechanisms associated with stress such as amygdala activity, HPA axis stress hormones, and cardiovascular reactivity (Churchland and Winkielman, 2012). Furthermore, research in animals has found that the actions of oxytocin are most apparent under conditions of duress, such as social isolation (Grippo et al., 2007). Thus, the comparatively optimal conditions of the mothers in the present study, in which most women were well supported and breastfeeding, may have reduced the relative importance of oxytocin.

3.1. Limitations

The current study was limited by the use of circulating blood plasma to measure endogenous levels of oxytocin. Peripheral oxytocin is thought to correspond to, or have coordinated release with, central or brain levels (e.g., Burri et al., 2008). However, research has yet to firmly establish this relationship, especially in humans (Churchland

and Winkielman, 2012). Future research may benefit from examining peripheral oxytocin levels in conjunction with oxytocin gene receptor variants or methylation of the oxytocin receptor gene, in order to better understand the role of endogenous oxytocin. Additionally, the impending development of methods to study central oxytocin in humans, such as nonpeptide oxytocin antagonists and agonists (Ring et al., 2010) as well as a PET tracer for oxytocin receptors, will offer promising lines of new research (Insel, 2010).

The time of day of the blood draw at T3 varied across women, ranging from 1004h to 1600h (M = 1213h). Other than breastfeeding, physical interaction between mothers and their infants was not standardized. This may have impacted the findings given that oxytocin increases after mother–infant interaction (e.g., Feldman et al., 2010). These procedural factors may have led to variance in the plasma oxytocin measurements, which in turn may have contributed to the lack of an association between T3 oxytocin levels and theory of mind or maternal behavior. Some researchers have questioned the specificity of the RMET to assess theory of mind. It has been suggested that the RMET measures the performance of both lower- and higher-order social cognitive processes (Guastella et al., 2010), as the task involves the recognition and semantic comprehension of the mental state terms, decoding of thoughts and feelings based on facial/eye expressions, and then matching terms to expressions. Thus, in future research it may be important to use tasks that assess these processes separately. The RMET is also restricted by its forced choice response option, limited to perception of the eye region of faces, and lacks diversity in target face ethnicity. Although theory of mind is a social cognitive ability, the RMET does not assess on-line processing in a social context. Future research

may benefit from using an ecologically valid measure such as an empathic accuracy task (Zaki et al., 2008). Finally, we assessed the mothers' general theory of mind ability, using a task that required them to look at the eye region of unknown adults. Given social information processing is situation specific, future research may build on the current findings by measuring theory of mind ability within the interpersonal context of the mother–child relationship (e.g., a mother's ability to attribute mental states to her child).

4. Conclusions

The present study is the first to investigate the connection between peripheral levels of plasma oxytocin, theory of mind ability, and maternal behavior, during the perinatal period. Higher levels of endogenous oxytocin during late pregnancy were related to better performance on a theory of mind task, suggesting that changes in the oxytocinergic system in the immediate prenatal period may promote awareness of social cues. The ability to interpret and understand mental states of others was associated with less maternal behavior reflecting remoteness and depression. Theory of mind may represent a social cognitive mechanism linking endogenous oxytocin and maternal behavior, as suggested by the indirect effect of oxytocin during late pregnancy on (non)depressive maternal behavior through theory of mind performance. Further research is required to replicate these findings and to clarify the processes through which oxytocin influences maternal behavior.

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Table 1

Descriptive Data.

	M	*SD*	*Range*	*α*
ANRQ (T1)	19.25	10.31	5–50	.65
CWS (T1)	14.71	10.02	0–57	.82
CWS (T2)	13.55	10.33	0–50	.85
GAD-7 (T1)	3.97	3.34	0–17	.83
GAD-7 (T2)	3.69	3.21	0–27	.85
GAD-7 (T3)	2.81	2.79	0–14	.81
OT pg/ml (T1)	311.02	287.60	58.45–1913.26	--
OT pg/ml (T2)	387.99	286.84	32.32–2297.64	--
OT pg/ml (T3)	296.76	288.69	32.30–2029.61	--
RMET (T3)	24.80	4.72	10–33	.69
Maternal Behavior (T3)				
Sensitivity	3.54	.63	1.80–5.00	--
(Non)Intrusive	4.00	.70	1.50–5.00	--
(Non)Remote	4.54	.70	1.50–5.00	--
(Non)Depressive	4.20	.62	2.25–5.00	--

Note. T1 = Time 1, 12 to 14 weeks gestation; T2 = Time 2, 32 to 34 weeks gestation; T3 = Time 3, 7 to 9 weeks postpartum; ANRQ = Antenatal Risk Questionnaire; CWS = Cambridge Worry Scale; GAD-7 = Generalized Anxiety Disorder scale; OT = oxytocin; RMET = Reading the Mind in the Eyes Test.

Table 2

Bivariate Correlations

	Time 1				Time 2			Time 3						
Variable	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Time 1														
1. logOT	--													
2. GAD-7	.06	--												
3. CWS	.07	.61**	--											
4. ANRQ	.09	.32**	.40**	--										
Time 2														
5. logOT	.61**	.10	.07	.12*	--									
6. GAD-7	.08	.50**	.52**	.35**	.06	--								
7. CWS	.03	.45**	.73**	.35**	.03	.68**	--							
Time 3														
8. logOT	.70**	.12*	.10	.08	.56**	.13*	.05	--						
9. GAD-7	.01	.44**	.45**	.28**	.03	.48**	.50**	-.07	--					
10. RMET	.05	-.01	.02	.25**	.13**	-.04	.07	.05	.04	--				
11. Sensitivity	.08	-.14*	-.08	.03	-.02	-.10	-.04	-.03	-.04	.12	--			
12. Intrusive	.06	-.04	.06	-.02	.004	-.05	.01	.02	.01	-.03	.35**	--		
13. Remote	.06	-.05	-.07	.05	.08	.03	-.06	-.05	.04	.16*	.21**	-.10	--	
14. Depressive	-.002	-.10	-.09	.04	-.02	-.08	-.07	-.08	-.03	.18**	.48**	.06	.65**	--

Note. Time 1 = 12 to 14 weeks gestation; Time 2 = 32 to 34 weeks gestation; Time 3 = 7 to 9 weeks postpartum; OT = oxytocin; GAD-7 = Generalized Anxiety Disorder scale; CWS = Cambridge Worry Scale; ANRQ = Antenatal Risk Questionnaire; RMET = Reading the Mind in the Eyes Test.

* correlations significant at the $p < 0.05$ level.

** correlations significant at the $p < 0.01$ level.

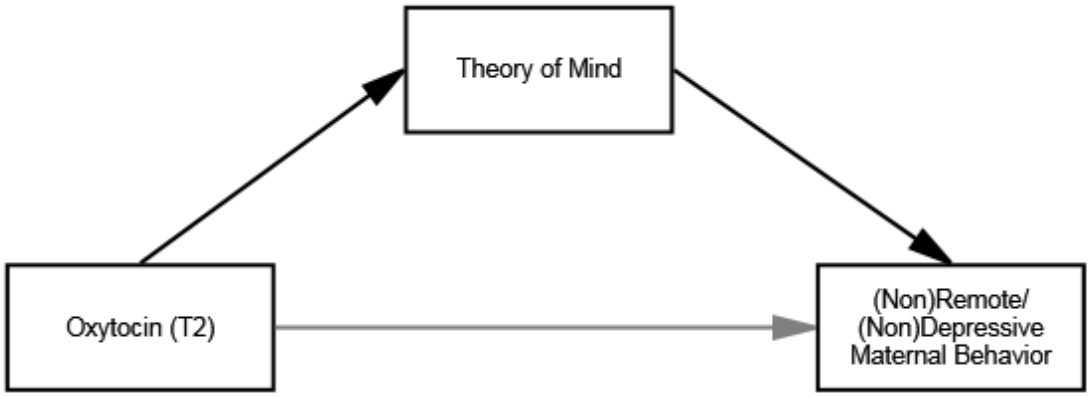

Figure 1 Mediational path model for (non)remote/(non)depressive maternal behavior. T2 = Time 2, 32 to 34 weeks gestation. Black arrows represent hypothesized direct effects. The grey arrow between oxytocin and (non)remote/(non)depressive maternal behavior represents the hypothesized indirect effect. Control variables are not shown for the purpose of clarity.

Bridge to Article 2

Article 1 demonstrated that increased levels of plasma oxytocin during the third trimester of pregnancy indirectly promoted maternal behaviour (i.e., less depressive interaction style) in the early postpartum period through enhanced performance on an experimental theory of mind task (i.e., Reading the Mind in the Eyes Test; RMET). This finding suggests that theory of mind may serve as a social cognitive mechanism through which oxytocin promotes maternal caregiving. The purpose of Article 2 is to test whether this indirect effect will hold longitudinally. More specifically, Article 2 aims to build on, and extend, the findings from Article 1 in three important ways: First, a follow-up study provided a unique opportunity for a more robust test of the proposed model with temporal separation in the measurement of the main variables, by assessing maternal behavior again when participating children were approximately 2- to 3-years-old. Second, this also allowed for the investigation of whether pregnancy-related changes in the oxytocinergic system impart long-lasting changes in maternal caregiving. Lastly, given that the RMET comprises adult stimuli, mothers' ability to attribute mental states specifically to their young children was also assessed using an observational measure of maternal mind-mindedness.

Article 2

Theory of Mind as a Link between Oxytocin and Maternal Behavior

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Abstract

Background: Oxytocin is a neuropeptide associated with maternal behavior. However the mechanisms underlying this link remain unclear. In a previous study we observed an indirect effect of increased plasma oxytocin during late pregnancy on early postpartum maternal interactive behavior via theory of mind, as assessed by the Reading the Mind in the Eyes Test (RMET). The current study aimed to extend these findings by testing whether this indirect effect would hold longitudinally for maternal behavior at 2–3 years postpartum, as well as for an additional observational measure of maternal mind-mindedness.

Method: The original sample of 316 pregnant women (M_{age}=31.92 years) was assessed at 12–14 weeks gestation (T1), 32–34 weeks gestation (T2), and 7–9 weeks postpartum (T3). Follow-up measures were taken at 2–3 years postpartum (T4).

Results: Mothers' RMET performance (T3) was associated with more structuring and less intrusive maternal behavior at 2–3 years (T4), while their tendency to use mind-related comments (T3) was associated with greater sensitivity (T4). Bootstrap estimates also revealed a significant indirect effect of plasma oxytocin levels during late pregnancy (T2) on maternal structuring and non-intrusive behavior at 2–3 years postpartum (T4) through RMET performance (T3).

Conclusions: Results of the current study confirm and extend the previous findings, demonstrating that theory of mind may represent a social cognitive mechanism linking endogenous oxytocin and maternal behavior. Important changes in the oxytocinergic system during late pregnancy may help prepare for motherhood by promoting the awareness of social cues, which in turn promote maternal behavior from the early

postpartum to the early childhood years.

Keywords: Oxytocin; Theory of mind; Maternal behavior; Mind-mindedness; Perinatal; Social cognition

1. Introduction

Maternal caregiving plays a crucial role in the development of adaptive social and emotional functioning in children (Cassidy, 2008). However, women vary in the extent to which they engage in optimal caregiving behaviors (Galbally et al., 2011). There is thus a clear need to improve our understanding of both psychosocial and biological factors that influence maternal interactive behavior. Oxytocin has been implicated as a neurobiological factor underlying prosocial and affiliative behavior (Carter, 2014). Research has recently begun to clarify the processes through which oxytocin promotes maternal behavior among humans. The present investigation is a follow-up to a previous study examining theory of mind—the ability to mentally represent the states of mind of others—as a social cognitive mechanism linking oxytocin and maternal interactive behavior.

Oxytocin is a neuropeptide that functions centrally as a neurotransmitter and peripherally as a hormone. When released into the brain, oxytocin binds to receptors in several regions including those involved in emotion and social interaction (Meyer-Lindenberg et al., 2011). Oxytocin is also transported to the pituitary gland where it is released through the bloodstream. Oxytocin has been implicated in triggering and maintaining maternal caregiving (e.g., Strathearn, 2011). For example, levels of circulating plasma oxytocin during the perinatal period have been associated with mothers' interactive behaviors and oxytocin receptor gene variants have been linked to sensitive parenting (for review see Feldman, 2012). Oxytocin has also been implicated in various social cognitive processes, including emotional empathy (e.g., Hurlemann et al., 2010) and social perception (e.g., De Dreu et al., 2010), as well as theory of mind. We

proposed a possible social cognitive mechanism whereby oxytocin enhances theory of mind ability, which in turn promotes maternal behavior.

Theory of mind encompasses the ability to infer or understand the mental states of others, such as thoughts, beliefs, feelings, and desires, and how they influence behavior (Frith and Frith, 2005; Goldman, 2006). Responding effectively to an infant's needs requires the ability to interpret those needs based on subtle cues (Ainsworth et al., 1978; Sroufe et al., 2005). Thus, theory of mind may be implicated in a mother's ability to recognize her infant's social cues and may in turn affect her interaction with her infant. There is some evidence to suggest that oxytocin is associated with theory of mind ability and to performance on an experimental measure called the Reading the Mind in the Eyes Test (RMET; Baron-Cohen et al., 2001), which involves identifying complex mental states depicted in photographs of the eye region of adults, though results have been inconsistent. In some studies, intranasal administration of synthetic oxytocin has been observed to enhance neural activation during, and improve accuracy on, the RMET among less socially proficient individuals (e.g., Feeser et al., 2015). Several oxytocin receptor gene polymorphisms have also been linked to RMET performance (e.g., Lucht et al., 2012).

Few reports have investigated the interplay between oxytocin and social cognition in relation to maternal behavior. A study by our team (MacKinnon et al., 2014) began to elucidate these processes by examining theory of mind as a social cognitive mechanism through which endogenous oxytocin influences maternal behavior during the perinatal period. The findings revealed a significant indirect effect whereby increased levels of plasma oxytocin during the third trimester of pregnancy (32–34 weeks gestation)

predicted higher theory of mind scores on the RMET at 7–9 weeks postpartum, which in turn predicted a less depressive maternal interaction style (e.g., more engaged and relaxed; less focused on own experience) also assessed at 7–9 weeks postpartum using the Global Rating Scales (GRS; Fiori-Cowley et al., 2000), an observational measure of mother–child interaction. To our knowledge, this was the first study to show a link between circulating plasma oxytocin and theory of mind ability, and thus provided further support to the social saliency hypothesis according to which endogenous oxytocin may represent a biomarker for sensitivity to social cues (Bartz et al., 2011). The results also suggested that changes in the oxytocinergic system during late pregnancy may facilitate early maternal behavior by enhancing awareness of social cues and the ability to interpret them.

The present follow-up study aimed to build on, and extend, these findings in three important ways. First, it provided a unique opportunity for a more robust test of our model with temporal separation in the measurement of the main variables, by assessing maternal behavior again when participating children were approximately 2–3 years old. Second, this also allowed us to investigate whether there are long-lasting changes in maternal behavior following the neurobiological changes that occur during pregnancy. Lastly, given that the RMET uses adult stimuli, we also assessed mothers' ability to attribute mental states specifically their young children using an observational measure of maternal mind-mindedness (Meins, 1997).

Maternal mind-mindedness has been operationalized and assessed two ways: using an interactional measure of a mother's tendency to comment appropriately on her infant's putative mental states during the first year of life, and thereafter with a

representational measure of a mother's use of mental state terms when asked to describe her child (Meins and Fernyhough, 2015). Mothers who are higher in mind-mindedness, that is those whose attributions accurately reflect their infant's mental states and/or who are more likely to characterize their child as having mental states, should be better able to respond appropriately to social cues (Meins, 1999). Indeed, maternal mind-mindedness has been associated with concurrent measures of maternal sensitivity at 6 months and 12 months postpartum (e.g., Laranjo et al., 2008; Meins et al., 2001).

In the present study we investigated processes suggestive of a possible social cognitive mechanism linking endogenous oxytocin to maternal behavior. More specifically, we hypothesized an indirect effect of plasma oxytocin levels (from 32 to 34 weeks gestation) on maternal behavior (at 2–3 years postpartum) through theory of mind, as measured by both the RMET performance and mind-mindedness (at 7–9 weeks postpartum).

2. Method

Participants were originally assessed at 12–14 weeks gestation (T1), 32–34 weeks gestation (T2), and 7–9 weeks postpartum (T3). Follow-up measures were taken at 2–3 years postpartum (T4). The present investigation forms part of a larger program of research on hormonal, genetic, and psychosocial factors in the developing mother–child relationship, from which other data are reported elsewhere (e.g., Zelkowitz et al., 2014).

2.1. Summary of methods from initial study

At each time point, participants provided 10 ml blood samples, which were used to measure unextracted plasma oxytocin levels with a commercial enzyme-linked immunosorbent assay kit (EIA; Enzo Life Sciences Inc., NY, USA). Consistent with

previous research, log-transformed oxytocin values were used for analyses. Theory of mind was assessed at T3 by administering the revised version of the Reading the Mind in the Eyes Test (RMET-R; Baron-Cohen et al., 2001). Maternal behavior was also assessed at T3 with the Global Rating Scales (GRS; Fiori-Cowley et al., 2000), which was designed and validated for use from 2 to 6 months postpartum. Control variables included prenatal psychosocial risk factors measured using the Antenatal Risk Questionnaire (ANRQ; Priest et al., 2008) and symptoms of anxiety measured using the Generalized Anxiety Disorder Scale (GAD-7; Kroenke et al., 2007), both administered at T1. More details regarding these methods were published in the initial study (see MacKinnon et al., 2014).

2.2. Follow-up study methods

2.2.1. Participants

Of the 316 women who participated in the initial study, 29 were lost to follow up at earlier timepoints and 29 indicated they did not want to be re-contacted. Therefore, 258 women were approached for recruitment in the follow-up study approximately 2.5 years later. Of these women, 189 (M_{age} = 35.56 years, SD = 4.36) agreed to participate again with their child (M_{age} = 2.89 years, SD = 0.38), 46 declined, and 23 were unreachable. Data were collected between November 2012 and January 2015. Participant characteristics for the original sample have been reported previously (MacKinnon et al., 2014). Of the 189 women who returned for the T4 follow-up, 91.0% reported being married or living with their partner, 3.7% became single, divorced, or widowed since participation in the original study, 32.8% gave birth to another child, 9.5% were currently pregnant, 8.9% were using contraception, and 10.1% were still breastfeeding the

participating child. In terms of parity, 26.5% had given birth to only one child, 50.8% to two children, and 22.2% to three or more. Compared to the women who did not return, those who participated in the follow-up study had, on average, more schooling (ΔM = 1.30 years, $p < 0.001$), higher plasma oxytocin at 32–34 weeks gestation (ΔM = 64.45 pg/mL, $p = 0.05$), and slightly better RMET scores (ΔM = 1.47 points, $p = 0.013$). There were no significant differences in maternal age, parity, and marital status at 12–14 weeks gestation, or interactive behavior, as measured by the GRS, at 7–9 weeks postpartum.

2.2.2. Materials

2.2.2.1. Background information. Updated socio-demographic, health, and obstetrical information was collected including maternal and child age, marital status, employment status, parity, pregnancies, contraception, and breastfeeding.

2.2.2.2. Maternal mind-mindedness. A five-minute face-to-face mother–infant interaction video without toys was filmed during home visits at 7–9 weeks postpartum (T3). It was recoded using Meins and Fernyhough's (2015) procedure for interactional measures of mind-mindedness in the first year of life. Maternal speech was transcribed verbatim then trained coders blind to other measures identified mind-related comments (i.e., explicit internal or mental state terms used to describe the infant or speech on the infant's behalf) and classified whether they were appropriate (i.e., consonant with the child's behavior or current state) or non-attuned. For example, saying "You're such a happy boy" while the infant is laughing and smiling, or saying "You're fascinated by the dog" after the infant has been focused intently on a dog, would be coded as appropriate. This measure of maternal mind-mindedness demonstrates good construct and predictive validity (Meins et al., 2003) and reliability (Laranjo et al., 2008). The number of mind-related comments,

and the subsets of appropriate and non-attuned comments were each summed to create three frequency total scores. Frequency counts are considered valid indicators of mind-mindedness (Laranjo et al., 2014). A randomly selected sample of interactions (n = 22) was double-coded by three raters. Intraclass correlation coefficients (*ICC*s; single measure, absolute agreement) indicated good inter-rater reliability for mind-related (*ICC* = 0.88), appropriate (*ICC* = 0.75) and non-attuned comments (*ICC* = 0.63).

2.2.2.3. Maternal behavior. Five minutes of free play with toys was filmed at follow-up (T4) and coded using the Emotional Availability Scales (EAS; Biringen et al., 2000). Mothers were given an open instruction to "do whatever you'd like" with their child during the interaction. Physical contact and movement was allowed. The EAS assesses four dimensions of maternal interactive behavior: sensitivity (e.g., contingent responsiveness to the child's communications, acceptance, and affect regulation); structuring (e.g., supportive and appropriate organization of child's play, allowing exploration, and providing assistance when needed); non-intrusiveness (e.g., avoidance of over-stimulating or interfering with child's play); and non-hostility (e.g., warmth, not being harsh or rejecting). Sensitivity was rated on a 9-point scale and the other dimensions on a 5-point scale, where higher scores indicate better behavior. The EAS has been validated for use from birth to 14 years and has well-established reliability over time as well as construct validity (for review see Biringen et al., 2014). Mean intraclass correlation coefficients (*ICC*s; single measure, absolute agreement) were calculated to assess inter-rater reliability between two coders for a random sample of videos (n = 59). Satisfactory interrater reliability was established for all scales (*ICC*s = 0.51–0.71), except for non-hostility (*ICC* = 0.38), which likely reflects limited variance in scores and thus is

not included in the path analyses.

2.2.3. Procedure

The follow-up study was approved by the Research Ethics Committee at the study site and was carried out in accordance with the Declaration of Helsinki. The participating women provided written informed consent for themselves as well as assent for their child. Participant dyads were invited to the laboratory where mothers completed the background information questionnaire and five minutes of mother–child free play was filmed.

2.2.4. Data Analysis

Descriptive statistics and bivariate Pearson's r correlations were computed using SPSS Statistics 24 (IBM, USA). As in the initial study, Mplus 7.11 software was used to conduct path analysis and bootstrapping (with 20,000 resamples) in order to test the indirect effect of oxytocin on maternal interactive behavior via theory of mind. A significant indirect effect is indicated by bias-corrected 95% confidence intervals (95% CI) that do not include zero (Hayes, 2009). Acceptable model fit is indicated by a comparative fit index (CFI) and Tucker-Lewis (TLI) in the range of 0.90–0.95 or above, as well as a root mean square error of approximation (RMSEA), with 90% confidence interval (90% CI), in the range of 0.05–0.08 or less (Little, 2013).

Since we used data from the time-points of the initial study, all 316 participants from the original sample were included in the current analyses. Overall, 20.21% of the data was missing and covariance coverage ranged from 0.53 to 1.00, which mainly reflects attrition in the follow-up study. Listwise deletion was used for descriptive statistics and correlation analyses, and Full Information Maximum Likelihood (FIML)

was used for path analysis and bootstrapping. FIML is recommended for handling missing data due to attrition in longitudinal research as it estimates values based on all available data, and thus produces unbiased model parameters (Enders, 2010). It is also recommended that variables associated with missingness be included in the model (Little, 2013). Given that attrition in longitudinal research is often related to socioeconomic status (SES; Little, 2013), we controlled for years of education, an indicator of SES, which differed among participants who returned at T4 by including it as an auxiliary variable. In addition, we controlled for previous maternal behavior (GRS), as well as the control variables from the initial study, including T1 measures of anxiety symptoms (GAD-7), prenatal psychosocial risk (ANRQ), and parity.

3. Results

3.1. Descriptive statistics

Means and standard deviations for the mind-mindedness scores and the EAS subscales are reported in Table 1. The frequency counts for appropriate and total mind-related comments fell within one standard deviation below the mean reported in previous studies that measured maternal mind-mindedness during 10 min free-play sessions at 12 months (Laranjo et al., 2010) and 18 months (Demers et al., 2010) postpartum. The mean ratings for maternal behavior were within one standard deviation of previous research reports using observations of mothers and their 24-month-old children (e.g., Biringen et al., 2010).

3.2. Bivariate correlations

Bivariate correlations between the main study variables are reported in Table 2. Contrary to expectations, none of the maternal mind-mindedness scores (T3) were related

to RMET performance (T3). However, the frequency of mind-related comments (T3) was significantly correlated with maternal sensitivity at follow-up (T4). Since mind-mindedness scores (T3) were not related to plasma oxytocin (T2), they were not included in the subsequent path analysis.

Consistent with the previous findings, plasma oxytocin levels during late pregnancy (T2) were not directly related to any of the dimensions of maternal behavior at follow-up (T4). Mothers' theory of mind performance on the RMET at 7–9 weeks postpartum (T3) was not correlated with maternal sensitivity, but was significantly related to more structuring and less intrusive interactive behavior at follow-up (T4).

Maternal sensitivity, as measured by the GRS during the early postpartum period (T3), was correlated with the EAS structuring ($r = 0.16$, $p = 0.039$) and non-intrusive ($r = 0.18$, $p = 0.021$) subscales (T4), and was therefore entered in the path analysis as a control for previous behavior on follow-up ratings of maternal behavior.[1]

3.3. Path analysis

The tested model, depicted in Fig. 1, fit the data well: CFI = 0.99; TLI = 0.88; RMSEA = 0.04 (90% CI: 0.00, 0.16). Consistent with the bivariate correlation findings, the path analysis indicated significant direct paths from RMET performance to maternal structuring ($\beta = 0.178$, $p = 0.036$) and non-intrusive ($\beta = 0.177$, $p = 0.029$) behavior measured at 2–3 years postpartum. The direct paths from oxytocin to maternal structuring ($\beta = 0.076$, $p = 0.291$) and non-intrusive behavior ($\beta = -0.014$, $p = 0.837$) were not significant. The significant path from oxytocin to RMET performance ($\beta = 0.105$, $p = 0.043$) reflects data reported in the initial study.

[1] Results of the path analysis remained significant when controlling for GRS intrusive, remote, and depressive subscales.

3.4 Indirect effects

Indirect effects can be interpreted regardless of whether their constituent paths are statistically significant (Hayes, 2013). Bias-corrected bootstrap confidence intervals revealed an indirect effect of oxytocin on maternal structuring (β = 0.019, B = 0.056) through RMET performance that was statistically significant (95% CI: .002, .167). The indirect effect of oxytocin on maternal non-intrusive behavior (β = 0.019, B = 0.063) through RMET performance was also statistically significant (95% CI: .006, .192).

4. Discussion

This follow-up study examined the relationship between oxytocin, social cognition and maternal behavior. Oxytocin during late pregnancy was indirectly associated with more structuring and less intrusive maternal behavior at approximately 2–3 years postpartum via mothers' theory of mind ability, as measured by the RMET. The results of the follow-up study confirm and extend the previous findings, demonstrating that theory of mind may represent a social cognitive mechanism linking endogenous oxytocin and maternal behavior.

Overall, our findings are in line with the social saliency hypothesis that endogenous oxytocin represents a biomarker for awareness of social cues (Bartz et al., 2011), which in turn helps promote more adaptive social behavior (Carpendale and Lewis, 2004). In the initial study, we demonstrated that only oxytocin measured during the third trimester of pregnancy, but not concurrent levels, predicted enhanced RMET performance at 7–9 weeks postpartum, which in turn was associated with better maternal behavior at that time. The follow-up study results revealed that this indirect effect holds for maternal behavior observed at 2–3 years postpartum, further supporting the notion

that the neuroendocrine adaptations of pregnancy may impart long-lasting effects on postpartum maternal caregiving behavior (Kinsley et al., 2015), via a social cognitive mechanism. In particular, the changes in the oxytocinergic system during pregnancy, may lead to permanent changes in neuronal structure and brain functioning (e.g., Kinsley et al., 2006), possibly including areas associated with theory of mind ability, such as the amygdala and prefrontal cortex (e.g., Baron-Cohen et al., 1999). Theoretically, such modifications would function to enhance the saliency of social stimuli, particularly infant cues, which would in turn facilitate more adaptive maternal behavior throughout the postpartum period. A positive feedback loop may also be involved, wherein children's responses to such maternal behavior may stimulate further oxytocin release in the mother (e.g., Strathearn et al., 2009). These processes may be reinforced by oxytocin's activation of the dopamine reward circuitry (Love, 2014; Strathearn et al., 2009). Thus, oxytocin may help to kick start the maternal brain and support the ongoing caregiving that is required during infancy and early childhood development. Future research exploring epigenetic mechanisms may help to further elucidate the role of oxytocin in the long-term maintenance of maternal behavior. Indeed, methylation of the oxytocin receptor gene has been associated with social functioning (for review see Kumsta et al., 2013).

The initial study revealed that mothers' RMET performance was related to concurrent interactive behavior with their infant in the early postpartum period. The follow-up study provides evidence that this association remains significant into early childhood, suggesting that theory of mind is also implicated in the long-term maintenance of maternal behavior. In this case, theory of mind facilitates mothers' ability to engage in supportive organization of their child's play (i.e., structuring) as well as the ability to

avoid over-stimulating or interfering with their child's play (i.e., intrusiveness). This pattern of findings suggests that good theory of mind skills may be particularly important for mothers' ability to respond with an appropriate balance between providing assistance and allowing exploration. That is, awareness and interpretation of mental states may allow mothers to better match their responses with their child's needs for support or autonomy during play. One aspect of theory of mind is perspective-taking (Frith and Frith, 2005), which allows one to look at a situation from another person's point of view. Given that intrusiveness tends to serve the needs (e.g., for control or attention) of the parent (Biringen et al., 1998), the capacity of a mother to take the perspective of her child may improve her awareness of her child's needs and subsequent ability to set aside her own. Similarly, structuring would also require perspective-taking in order to break down steps of activities in a way that the child can understand. Moreover, these two dimensions of maternal behavior are important for infant attachment security as well as children's social and cognitive development (for review see Biringen et al., 2014).

Interestingly, mothers' tendency to use mind-related comments when interacting with their infants during the early postpartum period, and not whether these comments were deemed appropriate, was associated with greater sensitivity 2–3 years later. These results are in line with one previous study that reported the frequency of mind-related, but not appropriate, comments at 18 months postpartum to be concurrently correlated with observed maternal sensitivity, as measured by the Maternal Behavior Q-Sort (Demers et al., 2010). Research using the representational measure of mind-mindedness has consistently produced similar findings. For example, mothers' use of mental attributes when asked to describe their 6-month-old infants during a single-question interview was

associated with greater observed sensitivity during play when their children were 1 year old (Farrow and Blissett, 2014). Taken together, these findings suggest that the general "proclivity to treat one's infant as an individual with a mind, rather than merely an entity with needs" (Meins, 1997) may play an important role in sensitive maternal behavior regardless of the ability to accurately interpret mental states during early infancy. That is, mothers who are inclined to be aware of and attend to their infants' mental life may be more likely and better able to provide sensitive responses to their children. However, it is possible that our results reflect some degree of measurement error. Inter-rater reliability was higher for mind-related than for appropriate comments, suggesting that identifying mind-related comments may be clearer, but determining whether they are appropriate may be a more subjective judgment. To our knowledge, this is the first study to apply the interactional coding scheme of mind-mindedness with infants as young as 2 months old and without toys. Given the developmentally limited range of interactive and purposeful behaviors at this age, there may have been fewer cues and thus more difficulty accurately interpreting infants' mental states, which may have led to limited variability in appropriate comments. This is not likely, however, because Meins et al. (2011) demonstrated that there is temporal stability in both appropriate and non-attuned indices of maternal mind-mindedness between 3 and 7 months postpartum, although the overall frequency of mothers' comments is lower when infants were younger. Furthermore, maternal representations of infants' sentience can begin to form before childbirth. Indeed, the number of comments made even by pregnant women to describe "their future child" was related to appropriate interpretations of their infants' mental states at 6 months postpartum (Arnott and Meins, 2008).

In contrast, the current study did not uncover a statistically significant association between RMET performance at 7–9 weeks postpartum and maternal sensitivity measured at 2–3 years postpartum. Other research (Licata et al., 2016) did find maternal theory of mind, measured as the ability to attribute mental states to characters in vignettes, to be correlated with concurrent sensitivity rated on the EAS at 3–6 years postpartum. However, this study was limited by a smaller sample size, cross-sectional design, and lacked covariates of emotional availability such as perceived social support and maternal history of trauma, which were controlled for in the current study using the Antenatal Risk Questionnaire. The results of the current longitudinal study are also consistent with our previous study where RMET performance was not correlated with concurrent maternal sensitivity rated on the GRS at 7–9 weeks postpartum. Although accuracy in reading social cues was expected to support maternal sensitivity, the non-significant findings may reflect the diversity of factors rated within the construct of maternal sensitivity. Indeed several qualities are taken into account in determining the single-item rating for sensitivity on the EAS, including the ability to be warm, emotionally connected, responsive, accurate in reading communications and to smoothly resolve conflicts. The EAS sensitivity scale also places more of an emphasis on the affective quality of interactions, as opposed to solely on behaviors. For example, a mother who engages in responsive behavior but does not demonstrate affect that is authentic (i.e., spontaneous positive emotion) or congruent (i.e., reflecting acceptance of her child's emotional signaling) would not receive a high rating. Maternal theory of mind may be differentially related to the underlying components of sensitivity, and perhaps less so to the affective aspects captured by the EAS.

The fact that a different pattern of results emerged for RMET performance compared to maternal mind-mindedness suggests that these measures may capture different abilities, given that they were not significantly correlated. Similarly, one recent study (Barreto et al., 2016) found no association between parents' mentalizing (e.g., the capacity think about and take the mental states of others), a construct which overlaps theory of mind, and mind-mindedness after controlling for education, psychopathology, and child temperament. While the RMET is widely used to assess general theory of mind ability, it has been suggested that mind-mindedness represents a phenomenon specific to interpersonal relationships rather than a general cognitive-behavioral trait (Meins et al., 2014). For example, these researchers found that levels of mind-mindedness in adults' descriptions of persons with whom they were close (e.g., child, friend, romantic partner) were correlated with each other, but not with levels of mind-mindedness in their descriptions of someone with whom they had no relationship (e.g., famous person, works of art). Meins et al. (2014) also highlighted a potential competence-performance gap, wherein having the general ability to impute the mental states of others may not translate to the spontaneous use of this capacity. This could explain why in the present study performance on the RMET, an experimental measure explicitly requiring participants to identify mental states using static, unknown adult stimuli, was not related to observed maternal mind-mindedness using a measure based on coding of real-time mother–infant interaction.

This follow-up study contributes to the extant research on the processes linking oxytocin and maternal behavior as the most comprehensive longitudinal investigation across the perinatal period in a large, culturally diverse non-clinical sample of women.

Further, we utilized two different methods to assess maternal social cognition. Nevertheless, the results must be understood in the light of several methodological issues. In terms of statistical analyses, despite having temporal separation between our main variables, we could not test a full longitudinal mediation model as we did not have equally spaced time points and we were not able to assess each variable, using the same measure, at every time point (e.g., it is not possible to measure maternal behavior before the child is born). Second, the possible effects of attrition and differences between the original sample and those who returned for follow-up were mitigated by entering years of schooling as a control variable and by including all of the data available for oxytocin, the RMET, and mind-mindedness from the 316 participants of the previous study. As noted above, using FIML to handle missing data produces unbiased parameter estimates (Enders, 2010), thus providing better generalizability of the findings. Lastly, only the bivariate correlations at the $p < 0.001$ level would remain significant after Bonferroni correction for multiple comparisons. However, some argue that correction may not be necessary, particularly "if a small number of hypotheses have been stated a priori" (Streiner and Norman, 2011). Although the observed effects between constructs are small ($r \leq 0.20$), they are in line with previous work, as discussed above, and thus warrant further investigation.

In terms of materials, the RMET is the most commonly used experimental measure of theory of mind, but has been criticized for its lack of specificity in measuring theory of mind. The associations between the RMET and other tests are mixed, perhaps because they tap different underlying components of theory of mind (for review see Vellante et al., 2013). However, the RMET can distinguish between individuals with

theory of mind deficits such as those with autism spectrum disorder (for review see Olderbak et al., 2015). In addition, while we used the same protocol as previous studies examining plasma oxytocin in the perinatal period in relation to maternal behavior (e.g., Feldman et al., 2007) and found comparable concentration levels, the use of unextracted samples has been criticized for producing higher estimates than methods using extraction (e.g., Leng and Sabatier, 2016). However, evidence across species suggests that this discrepancy reflects the removal of oxytocin that is bound to other molecules (e.g., albumin) during the extraction step (Brandtzaeg et al., 2016; MacLean et al., 2018; Martin and Carter, 2013). Newly established procedures to separate protein-bound oxytocin prior to measurement, involving reduction and alkylation paired with nano liquid chromatography, provide estimates of total plasma oxytocin levels consistent with those using unextracted samples (Brandtzaeg et al., 2016), indicating that unextracted samples are not measuring other compounds, but rather are capturing bound oxytocin. Further, Brandtzaeg and colleagues suggested that measurement of total oxytocin may be a better biomarker than the free fraction, which shows large variations and can be confounded by several factors including age, morbidity, or drugs. We also cannot make clear inferences about plasma levels reflecting oxytocin activity in the brain. Although peripheral and central oxytocin release is thought to be coordinated, the research findings are inconsistent (e.g., Lefevre et al., 2017). Some studies have found a correlation between oxytocin concentrations in plasma and cerebral spinal fluid among humans, particularly under stress conditions (e.g., Carson et al., 2015; Valstad et al., 2017), while others have not (e.g., Kagerbauer et al., 2013). Finally, it would have been interesting to look at concurrent plasma oxytocin levels in relation to maternal behavior at 2–3 years

postpartum. Unfortunately, the oxytocin assay was not available at follow-up. However, in the original study the concurrent measure of oxytocin was not related to maternal behavior at the 7–9 weeks postpartum assessment, which is consistent with other research during the perinatal period (e.g., Levine et al., 2007). The current investigation focused on the 32–34 weeks gestation measurement, where oxytocin levels significantly increased (see MacKinnon et al., 2014), as we were interested in pregnancy-related changes in the oxytocinergic system.

5. Conclusions

Theory of mind may represent a social cognitive mechanism through which oxytocin influences maternal behavior. Important changes in the oxytocinergic system during late pregnancy may help prepare for motherhood by promoting the awareness of social cues, which in turn enhances maternal behavior and lays the foundation for building the mother–infant relationship.

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Table 1

Descriptive Data for New Measures.

	n	*M*	*SD*	*Range*
Maternal Mind-Mindedness (T3)	240			
Mind-related comments		6.18	4.94	0-27
Appropriate comments		3.76	3.68	0-24
Non-attuned comments		2.40	2.95	0-24
Emotional Availability Scales (T4)	185			
Sensitivity		6.68	.84	3-8
Structuring		3.90	.80	2-5
Non-Intrusive		4.05	.89	2-5
Non-Hostility		4.97	.19	3-5

Note. T3 = 7–9 weeks postpartum; T4 = 2–3 years postpartum

Table 2

Bivariate Correlations.

	T2	T3				T4			
Variable	1	2	3	4	5	6	7	8	9
T2									
1. logOT	--								
T3									
2. RMET	.13*	--							
3. Mind-related	.06	.06	--						
4. Appropriate	.07	.06	.80***	--					
5. Non-attuned	.001	.02	.67***	.11	--				
T4									
6. Sensitivity	.01	.14	.15*	.14	.07	--			
7. Structuring	.07	.17*	.02	-.02	.03	.50***	--		
8. Non-intrusive	.03	.20**	-.13	-.11	-.11	.16*	.24***	--	
9. Non-hostility	.04	.05	.03	-.02	.07	.15*	.09	.04	--

Note. T2 = 32–34 weeks gestation; T3 = 7–9 weeks postpartum; T4 = 2–3 years postpartum; OT = oxytocin; RMET = Reading the Mind in the Eyes Test.

* correlations significant at the $p < 0.05$ level.

** correlations significant at the $p < 0.01$ level.

***correlations significant at the $p < .001$ level.

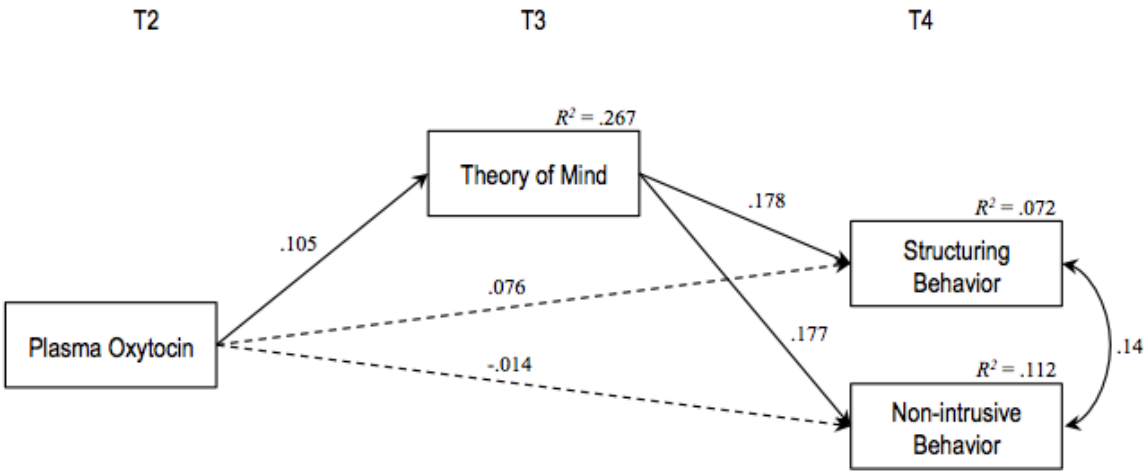

Fig. 1. Tested path model for indirect effects of plasma oxytocin on maternal structuring and non-intrusive behavior via theory of mind as measured by the Reading the Mind in the Eyes Test. Rectangles represent manifest (measured) variables. Single-headed solid arrows represent statistically significant paths ($p < 0.05$). Single-headed dashed arrows represent non-significant paths ($p > 0.05$). The double-headed arrow between structuring and non-intrusive behavior represents a significant correlation ($p < 0.05$). Numbers above paths represent standardized path coefficients. Control variables are not shown for the purpose of clarity. R^2 = proportion of variance accounted for by exogenous (predictor) variables. T2 = 32–34 weeks gestation; T3 = 7–9 weeks postpartum; T4 = 2–3 years postpartum.

Bridge to Article 3

Articles 1 and 2 explored the role of the oxytocinergic system in relation to maternal caregiving, by examining circulating levels of oxytocin in blood plasma across the perinatal period. Together the findings from Articles 1 and 2 demonstrated that theory of mind may serve as a social cognitive mechanism through which endogenous oxytocin facilitates maternal caregiving. The natural increase of peripheral oxytocin during pregnancy may reflect a priming function of the oxytocinergic system to prepare for motherhood by promoting the awareness of and ability to interpret social cues. Maternal caregiving, in turn, is crucial for children's social development (Cassidy, 2008). Indeed, Rilling & Young (2014) pointed out that "from the offspring's perspective, the nurturing relationship between parent and infant profoundly affects the development of the brain systems regulating social behavior." Thus, Article 3 explores the role of a different component of the oxytocinergic system—methylation of the oxyticin receptor gene—in conjuction with maternal caregiving in another important context: children's early social cognitive development. More specifically, Article 3 aims to examine the influence of OXTR methylation, and its interplay with maternal behavior, on emerging theory of mind abilities among 2- to 3-year-old children.

Article 3

The Interaction between Oxytocin Receptor Gene Methylation and Maternal Behavior on Children's Early Developing Theory of Mind Abilities

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Abstract

Theory of mind—the ability to represent the mental states of others—is an important social cognitive process, which contributes to the development of social competence. Recent research suggests that gene–environment interactions, between oxytocin receptor gene (OXTR) polymorphisms and maternal parenting behavior, may underlie individual differences in children's theory of mind development. However, the potential influence of DNA methylation of OXTR remains unclear. The current study investigated the roles of OXTR methylation, maternal behavior, and their statistical interaction on toddlers' early emerging theory of mind abilities. Participants included a community sample of 189 dyads of mothers and their 2- to 3-year-old children, whose salivary DNA was analysed. Results indicated that more maternal structuring behavior was associated with better performance on a battery of three theory of mind tasks, while higher OXTR methylation within exon 3 was associated with poorer performance. A significant interaction also emerged, such that OXTR methylation was related to theory of mind among children whose mothers displayed less structuring, when controlling for children's age, sex, ethnicity, number of child-aged siblings, verbal ability and maternal education. Maternal structuring behavior may buffer the potential negative impact of hypermethylation on OXTR gene expression and function.

Keywords: theory of mind, oxytocin, methylation, maternal behavior, OXTR

The Interaction between Oxytocin Receptor Gene Methylation and Maternal Behavior on Children's Early Developing Theory of Mind Abilities

Theory of mind, which involves the ability to infer or attribute mental states such as thoughts, feelings, and desires to the self and others, and understand how they influence behavior (Premack and Woodruff, 1978; Sodian and Kristen, 2010), is an important aspect of social cognition that contributes to the development of social competence (Astington & Edward, 2010). However, theory of mind is not uniformly acquired. Indeed, stable individual differences in theory of mind performance have been observed across early childhood through adolescence (for review see Hughes & Devine, 2015a) and predict negative social outcomes such as poor social skills, aggression, and peer rejection (e.g., Banerjee, Walting, & Caputi, 2011; Devine, White, Ensor, & Hughes, 2016; Holl, Kirsch, Rohlf, Krahé, & Elsner, 2017). Moreover, theory of mind deficits underlie the difficulties experienced in several forms of psychopathology including autism spectrum disorder (ASD; Baron-Cohen, 1995; Yirmiya, Erel, Shaked, & Solomonica-Levi, 1998) and schizophrenia (Corcoran, Mercer, & Frith, 1995; Sprong, Schothorst, Vos, Hox, & Van Engeland, 2007). While both social and biological influences have been proposed, there is a call for more integrated research on their complex interplay in contributing to individual differences in theory of mind development. The current study investigated the roles of maternal behavior, oxytocin receptor (OXTR) gene methylation, and their interaction on toddlers' early emerging theory of mind abilities.

In terms of social or environmental influences, theory of mind is thought to develop in part through social experiences (Carpendale & Lewis, 2004; Meltzoff &

Gopnik, 2013). The family setting is important as the first context involving interpersonal interaction. Correspondingly, parenting practices, particularly maternal, have been implicated in children's early theory of mind development (for reviews see Miller, 2016; Pavarini, de Hollanda Souza, & Hawk, 2013). Caregiving behavior that is sensitive and responsive (e.g., Cahill, Deater-Deckard, Pike, & Hughes, 2007) and comprises structure and discussion (e.g., Ruffman, Perner, & Parkin, 1999) provides opportunities for reasoning and encourages reflection on other perspectives, which facilitates learning about mental states and thus promotes the development of children's theory of mind abilities (Miller, 2016). However, social influences only account for part of the variability in children's theory of mind development, as biological influences such as hormones and genes are also involved.

One biological factor that has received increasing attention for its role in the development of the social brain is the oxytocinergic system (for reviews see Carter, 2014; Donaldson & Young, 2008; Feldman, Monakhov, Pratt, & Ebstein, 2016), which involves the production, binding, and signalling action of oxytocin. Oxytocin is a neuropeptide that functions peripherally as a hormone via bloodstream release and centrally as a neurotransmitter where it binds to receptors in brain regions involved in social and emotion processing (Meyer-Lindenber, Domes, Kirsch, & Heinrichs, 2011). Several lines of investigation have implicated the oxytocinergic system in children's theory of mind abilities. For example, the intranasal administration of synthetic oxytocin has been associated with improved performance on, and increased neural activation during, completion of a theory of mind task among children and adolescents with ASD (Gordon et al., 2013; Guastella et al., 2010). Levels of and changes in children's plasma

and salivary oxytocin concentrations have also been associated with improved performance on, and increased neural activation during, theory of mind tasks (Gordon et al., 2013; Parker et al., 2014), as well as greater observed social reciprocity behavior (Feldman, Gordon, Influs, Gutbir, & Ebstein, 2013). Single nucleotide polymorphisms (SNPs) in the oxytocin receptor gene have been related to performance on theory of mind tasks among preschool (Wu & Su, 2015) and school-aged (Slane et al., 2014) children, as well as to a range of social cognition tasks (e.g., joint attention, empathy, cooperation and self-recognition) among toddlers (Wade, Hoffmann, Wigg, & Jenkins, 2014). Furthermore, alterations in the oxytocinergic system have been implicated in the etiology of autism spectrum disorders (for review see Green, Taylor, & Hollander, 2011), which are characterized by theory of mind deficits.

To date, few studies have examined the interplay between the social and biological influences underlying individual differences in children's theory of mind development. One study (Wade, Hoffmann, & Jenkins, 2015) demonstrated a gene–environment interaction between variation in OXTR SNP genotypes and maternal behavior, whereby more maternal cognitive sensitivity (e.g., identifying and responding to the child's cognitive needs and abilities) predicted better theory of mind performance among preschool-aged children with the major allele of the rs11131149 variant. A second study (McDonald, Baker, & Messinger, 2016) observed a similar gene–environment interaction, such that better parent–child interaction quality predicted more empathic behavior among preschool-aged children with the minor allele of a different OXTR variant, rs53576. In both studies, no independent effect of the SNPs emerged, suggesting that it is crucial to consider gene–environment interactions in order to improve our

understanding of theory of mind development. However, less is known about the potential influence of DNA methylation, a relatively stable genetic biomarker (e.g., How Kit, Nielsen, & Tost, 2012), of the oxytocin receptor gene on children's theory of mind development.

Research has recently begun to investigate functional outcomes of oxytocin receptor gene methylation. DNA methylation is a dynamic process whereby methyl groups attach to the 5-carbon of a cytosine ring typically in the cytosine-phosphate-guanine (CpG) context which can block the recruitment and binding of transcription factors that allow for gene expression. Indeed, methylation in a promoter region of a gene, typically a CpG island (i.e., area with a high density of CpG sites, >200bp; UCSC Genome Bioinromatics, 2009a), proximal to the transcription start site is generally associated with reduced gene expression (for review see Jones, 2012). DNA methylation within the OXTR CpG island, which has been classified as a promoter (ENCODE Project Consortium, 2012), can suppress gene transcription (Kusui et al., 2001). In other words, OXTR methylation and concomitant reduction in mRNA decrease the production of oxytocin receptors, which would impact functioning of the oxytocinergic system and in turn lead to different behavioral phenotypes (for review see Kumsta, Hummel, Chen, & Heinrichs, 2013). Indeed, OXTR methylation has been associated with decreased mRNA levels in temporal cortex tissue (Gregory et al., 2009) and decreased levels of circulating oxytocin in blood plasma (Dadds et al., 2013). Interestingly, some studies involving children and adolescents have linked increased OXTR methylation to theory of mind-related impairments such as poor social communication (Rijlaarsdam et al., 2016), callous-unemotional traits (Cecil et al., 2014; Dadds et al., 2013) and ASD diagnosis

(Gregory et al., 2009), while others have found decreased methylation to be associated with social problems (e.g., Milaniak et al., 2017; Yuksel, Yuceturk, Karatas, Ozen, & Dogangun, 2016). Examining the moderating role of social influences may help to elucidate these differential effects of oxytocin receptor gene methylation.

The current study aimed to investigate the social influences of maternal behavior as well as the biological influences of children's oxytocin receptor gene methylation, and their interaction, on children's early emerging theory of mind abilities. Given its potential regulatory role, we expected that increased methylation on a region within the OXTR CpG island would be associated with poorer performance on theory of mind tasks, whereas more optimal maternal behavior would be associated with better performance. We also hypothesized an interaction such that exposure to more optimal maternal behavior would buffer the impact of OXTR methylation on children's theory of mind performance.

Method

The present investigation forms part of a larger follow-up study on hormonal, genetic, and psychosocial factors in the developing mother–child relationship, of which other data are reported elsewhere (e.g., King et al., 2017; MacKinnon et al., 2018).

Participants

A community sample of mothers and their 2- to 3-year-old children agreed to participate in the follow-up study (n = 189 dyads). The assessment protocol was approved by the Research Ethics Committee at the hospital where the research took place and was carried out in accordance with the Declaration of Helsinki. The participating women provided written informed consent for themselves and assent for their child. Inclusion

criteria for the original study included: a singleton pregnancy, minimum 18 years of age, and ability to understand the procedures and respond to questionnaires in English or French. The follow-up study data were collected between November 2012 and January 2015. At follow-up, the average age of mothers was 35.56 years (*SD* = 4.36), 91.0% reported being married or living with a partner, 63.8% were employed (48.4% full-time and 15.4% part-time), 32.8% reported an average household income within $65,000-$104,999 and 29.5% within $25,000-$64,999. The average age of children was 2.89 years (*SD* = .38) and there was an equal number of males (49.7%) and females (50.3%). Compared to the women who did not return, those who participated in the follow-up study included fewer immigrants (52.8% vs. 33.9%; $\chi^2 = 11.17$, $p = 0.001$) and had more schooling (15.69 vs. 16.99 years average; $t = -3{,}76$, $p < .001$).

Measures

Background information. Socio-demographic information was collected including maternal age, marital status, employment status, as well as child sex and age.

Maternal behavior. Five minutes of free play with toys was filmed and coded using the Emotional Availability Scales (EAS; Biringen, Robinson, & Emde, 2000), which assesses four dimensions of maternal interactive behavior: sensitivity (e.g., contingent responsiveness to the child's communications, acceptance, and affect regulation); structuring (e.g., supportive and appropriate organization of child's play, allowing exploration, and providing assistance when needed); non-intrusiveness (e.g., avoid over-stimulating or interfering with child's play); and non-hostility (e.g., warmth, not being harsh or rejecting). Sensitivity was rated on a 9-point scale and the other dimensions on a 5-point scale, where higher scores indicate optimal behavior. The EAS

has well-established test–retest reliability and construct validity (for review see Biringen Derscheid, Vliegen, Closson, & Easterbrooks, 2014). For this study, a random sample of videos (*n* = 59; 23.7%) was double coded and mean intraclass correlation coefficients (ICC; single measure, absolute agreement) indicated satisfactory inter-rater reliability for all scales (*ICCs* = .51 - .71) except non-hostility (*ICC* = .38), which likely reflects limited variance in scores and thus is not included in the analyses.

OXTR methylation. Saliva samples were collected using the Oragene™ OG-250 kit (DNA Genotek Inc., Ottawa, Canada). Mothers were asked to refrain from allowing children to eat or drink 30 minutes prior to collection in order to reduce the possibility of contamination from bacterial DNA. In accordance with the manufacturers' instructions, DNA was extracted using the Oragene™ prepIT-CD2 kit (DNA Genotek Inc., Ottawa, Canada) and then 20µl per participant underwent sodium bisulfite conversion using the EZ DNA Methylation-Gold Kit™ (Zymo Research, Irvine, CA, USA).

DNA primers for the OXTR gene were designed using MethPrimer software (Li & Dahiya, 2002) and the OligoAnalyzer tool 3.1 (Integrated DNA Technologies, 2015), as detailed in a previous report (King et al., 2017). Optimal annealing temperatures were established using the gradient ProFlex™ 96-well PCR System (Thermo Fisher Scientific, Waltham, MA, USA) and target amplicons were visualized on 1.5% agarose gel to validate lengths. Subsequently, bisulfite converted DNA was amplified using Kapa HiFi Uracil + ™ (Kapa Biosystems, Wilmington, MA, USA**)**, following the manufacturer's instructions for PCR amplification and thermo-cycling. After the first round of amplification comprising 25 cycles with the target sequences, amplicons underwent an additional 15 cycles to bind Fluidigm™ common sequence primers (CS1-forward and

CS2-reverse primers) which attach adaptor tags compatible with Illumina® universal indexes, and finally were pooled for each participant. Samples were subsequently purified using AmPure™ (Agencourt, Beverly, MA, USA) magnetic bead technology, quantified using Tape Station™ (Agilent Technologies, Santa Clara, CA, USA), diluted to 2nmol for optimal cluster density, and sequenced using Illumina® MiSeq (Illumina, San Diego, CA, USA), in duplicate for quality control. Adaptor sequences were trimmed following Illumina® Fluidigm parameters and reads with a Phred quality score less than 20 were discarded. Bismark v0.14.4 and Bowtie 2.1.0 were used to align remaining reads with target regions. Only CpG sites with more than 20 reads were retained (Ziller, Hansen, Meissner, & Aryee, 2015). The percentage of methylation was calculated for each CpG site by dividing the unconverted read counts by the total read counts. PhiX was used as a calibration control to provide an estimation of error rates. The data generated from MiSeq runs were batch-corrected using the limma package v.3.32.10 (Smyth et al., 2002) in R, then merged to create an average percent methylation score for each CpG site per participant.

We aimed to capture DNA methylation on the OXTR gene CpG island located on chromosome 3 between coordinates 8809306 and 8811279, corresponding to the Human GRCh37/hg19 assembly of the UCSC Genome Browser (UCSC Genome Bioinformatics, 2009b). We were able to extract data for 22 CpG sites (between 8809306 and 8809501) within a protein-coding region on exon 3 (Gimpl & Fahrenholz, 2001; UCSC Genome Bioinformatics, 2013). According to the publically available data from the Encyclopedia of DNA Elements (ENCODE Project Consortium, 2012) and WashU Epigenome Browser (Zhou et al., 2011; Zhou, Li, Lowdon, Costello, & Wang, 2014), OXTR's 2.3kb

intergenic CpG island, which overlaps exon 3 and consequently the 22 CpG sites captured, displays moderate to strong promoter activity, specifically in cells found in saliva. For example, evidence suggests that the area captured on exon 3 may have important regulatory functions as indicated by the proximity of active histone marks such as H3K4Me3, transcription factor binding sites such as those for CTCF, and a 5' untranslated region or leader sequence where micro RNA can bind (Zhou et al., 2011, 2014). We also captured DNA methylation on several other CpG sites between intron 2 and exon 1, however coverage was not sufficient (e.g., less than 80% of sample data available) to include these in the analyses. The percent methylation scores for each of the 22 CpG sites captured on exon 3 were averaged to obtain children's overall mean percent of methylation for the 22-site region.

Theory of Mind. Early developing aspects of theory of mind were assessed by administering a battery of three tasks, which are demonstrated to be at the appropriate developmental level for use with 2-year-old children (Carlson, Mandell, & Williams, 2004; Hughes & Esnor, 2005, 2007; Müller, Liebermann-Finestone, Carpendale, Hammond, & Bibok, 2012).

Visual perspective. This task assesses whether children understand that people cannot see when vision is obstructed, and is modeled after Müller and colleagues' (2012) adaptation of other blocked visual access tasks (Carlson et al., 2004; Lempers, Flavell, & Flavell, 1977). The child is asked to show a toy to the mother, who is instructed to block her vision in a different way (e.g., closing eyes, turning around) on each of four trials. Children's responses are scored for attempts at correction (e.g., adjusting themselves, their mothers, or the toy) on a 5-point scale: 1 (no show or dropped toy in parent's lap

and walked away), 2 (held toy near parent but no attempt at correction), 3 (partial correction), 4 (full correction but did not show the toy), and 5 (full correction and showed the toy). For this task, the possible range of total scores is from 4 to 20 points.

Pretend play. The pretend play task is modeled after Hughes and Esnor's (2005) adaptation of a previous version (Charman & Baron-Cohen, 1997; Fein, 1975). This task requires four objects: two realistic (e.g., toy horse and plastic grass) and two less realistic (e.g., horse and hay made from blocks). There are three conditions: baseline condition (two realistic), single substitution (1 realistic, 1 unrealistic), and double substitution (2 unrealistic). There are three trials for each condition: display (child asked to play with objects), modeling (experimenter pretends to feed horse), and suggestion (child asked to give horse something to eat). Children's responses in each of the nine trials are scored (1 point) for any use of pretend play actions (e.g., feeding horse), where the total score has a possible range from 0 to 9 points.

False-belief. The picture-book false-belief task (Hughes, 1998; Hughes & Esnor, 2005) is modeled after Gopnik and Astington's (1988) approach. This task utilizes a peep-through picture book (Moerbeek, 1994) in which a picture of an eye is visible through a hole, but on the last page the eye is revealed to be a spot on a snake. Children are asked two force-choice questions to assess their understanding of false beliefs: "Before we turned the page, what did you think this would be, an eye or a spot?" and "Look, this is Charlie [a puppet is shown]. Charlie has never seen this book before. If we show him this picture, what will he think it is, an eye or a spot?" After each, a reality control question was asked: "What is it really, an eye or a spot?" Children receive a score of 1 point for each false-belief question if they correctly answer the control question, for

a total score ranging from 0 to 2 points.

Task performance was filmed and subsequently reviewed for scoring. Tasks were double-coded for a random sample of children (n = 42; 23.6%), for which satisfactory inter-rater reliability was established (*ICC*s = .55 - .90). Scores on the Visual Perspective and Pretend Play tasks were significantly correlated (r = .233, p = .003), however these were weakly related to performance on the False-Belief task (r = .121, p = .133 and r = .154, p = .064, respectively). Partial correlations controlling for concurrent age, sex, number child-aged siblings and verbal ability as well as maternal education produced the same pattern. Following the method used by Hughes and Esnor (2007), a single aggregate score for theory of mind was computed by averaging standardized z scores from each task. Cronbach's alpha indicated moderate internal consistency between the standardized scores (α = .485). The aggregate was further supported by a principal component factor analysis with varimax rotation, which yielded a single factor solution explaining 49.32% of the variance with loadings ranging from .673 to .746.

Verbal Ability. Children's verbal ability was measured using the vocabulary checklist of the MacArthur Communicative Development Inventory (CDI; Fenson et al., 2007); the Level II form is normed and used for all French-speaking children (Frank, Poulin-Dubois, & Trudeau, 1997) and English-speaking children younger than 31 months of age (Fenson et al., 2000), the Level III form is normed and used for English-speaking children 31 months of age and older (Fenson et al., 2007). The mother was asked to indicate which of 100 words her child says, where higher scores indicate more advanced productive vocabulary. The CDI demonstrates good content and concurrent validity (Fenson et al., 2000; Fenson et al., 2007).

Data Analyses

Descriptive statistics, bivariate Pearson's *r* correlations, standardized scores, and principal component factor analysis were computed using SPSS Statistics 25 (IBM, USA). Regression-based moderation analyses with bootstrapping (20000 resamples) and 95% bias-corrected confidence intervals (where crossing zero indicates non-significance) were conducted using Mplus 7.11 software (Muthén & Muthén, Los Angeles, CA, USA). Overall, 3.5% of the data was missing and covariance coverage ranged from 0.95 to 1.00. The number of children who completed each theory of mind task ranged from 157 to 183, due to non-compliance or administration error. Missing data were handled using pairwise deletion in SPSS and Full Information Maximum Likelihood (FIML) in Mplus. FIML estimates values based on all available data and thus produces unbiased model parameters (Enders, 2010). Consistent with previous research on theory of mind development (e.g., Carlson et al., 2004; McAlister & Peterson, 2013), we controlled for children's age, sex, number of siblings between 1 to 12 years old, and verbal ability as well as maternal education (i.e., years of schooling). Given global DNA methylation has been observed to vary by race/ethnicity (e.g., Zhang et al., 2014), we used a dichotomous control variable for Western/non-Western origin (Kooijman et al., 2016) based on mothers' self-reported country of birth (Stronks, Kulu-Glasgow, & Agyemang, 2009).

Results

Descriptive Statistics

Descriptive statistics for the main study variables are reported in Table 1. Mean ratings fell within one standard deviation of previous research on maternal behavior (Biringen, Matheny, Bretherton, Renouf, & Sherman, 2010). Children's average OXTR

methylation was within one standard deviation of levels reported for individual CpG sites on exon 3 measured via cord blood (Cecil et al., 2014; Rijlaardsdam et al., 2017). Mean scores for each theory of mind task fell within one standard deviation of studies using similar aged samples of children (Hughes & Ensor, 2005; Müller et al., 2012).

Bivariate Correlations

Bivariate correlations between the main study variables are presented in Table 2. Results indicated that more maternal structuring was associated with better theory of mind performance, while higher OXTR methylation was associated with worse theory of mind performance. Therefore, both were included in the subsequent moderation analyses.

Moderation Analyses

Maternal structuring did not emerge as a significant individual predictor of theory of mind (b = 0.089, 95% CI: -.327, .020), while OXTR methylation did (b = 0.019, 95% CI: -.116, -.065). However, bootstrap estimates revealed a significant interaction (see Figure 1) between maternal structuring behavior and children's OXTR methylation on theory of mind performance (b = 0.019, 95% CI: .013, .024), when controlling for children's age (b = 0.301, 95% CI: .011, .558), sex (b = 0.124, 95% CI: -.067, .320), ethnicity (b = 0.243, 95% CI: -.045, .505), number of child-aged siblings (b = 0.134, 95% CI: .018, .272), verbal ability (b = 0.006, 95% CI: .001, .010) and maternal education (b = -0.012, 95% CI: -.047, .028). The overall model explained 48.4% of the variance in children's theory of mind (R^2 = 0.484). Simple slopes analysis revealed that OXTR methylation was only related to theory of mind among children whose mothers displayed lower levels of maternal structuring behavior (i.e., 1.5 standard deviations below the mean; b = -.039, p = .012).

Discussion

The current study investigated the interplay of social and biological influences on individual differences in theory of mind development. Maternal parenting behavior and children's OXTR methylation were differentially associated with early emerging theory of mind abilities. An interaction also emerged such that methylation within exon 3 of the oxytocin receptor gene was negatively related to theory of mind performance among children whose mothers displayed less structuring, when controlling for several well-established predictors.

As expected, higher OXTR methylation was associated with worse theory of mind performance, which may reflect the impact of gene suppression on oxytocinergic system functioning. Given that the actions of hormones are exerted through binding to their receptors (Molnar & Gair, 2012), increased methylation within the OXTR exon 3 protein-coding region may suppress the transcription and production of oxytocin receptors, which could potentially decrease cell receptivity to circulating oxytocin, and in turn may lead to reduced binding in oxytocin. Such down-regulation of the oxytocinergic system could have a functional impact on social cognitive processing if it were to occur in the tissue of oxytocin-sensitive brain areas associated with theory of mind such as the amygdala and prefrontal cortex (e.g., Baron-Cohen et al., 1999; Gallagher et al., 2000; Gordon et al., 2013). The results of the current study are also consistent with previous research demonstrating that hypermethylation of the oxytocin receptor gene is associated with theory of mind-related deficits among children and adolescents (Cecil et al., 2014; Dadds et al., 2013; Gregory et al., 2009; Rijlaarsdam et al., 2016). In studies where hypomethylation was associated with increased impairments such as conduct problems

(Milaniak et al., 2017) and ASD diagnosis (Yuksel et al., 2016), it was speculated that this opposite pattern of findings may be attributable to the complexity of methylation mechanisms including differential relationships with transcription between individual CpG sites or possible effects on chromatin structure leading to genomic instability. Our findings suggest that this discrepancy may also reflect the moderating role of different social influences, such as parenting behavior.

The results of the current study indicate that maternal parenting behavior moderates the influence of gene suppression on children's early theory of mind abilities, such that exposure to more structuring buffers the impact of high levels of OXTR methylation, when the oxytocinergic system is presumably down-regulated, while receiving less structuring is associated with poorer performance. This pattern is in line with the two previous studies (McDonald et al., 2016; Wade et al., 2015) that demonstrated gene–environment interactions between OXTR polymorphisms and parental behavior on children's theory of mind and empathy. Taken together, these findings suggest that OXTR genetic biomarkers, such as hypermethylation and "risk" alleles, confer susceptibility to the social influences of optimal and less optimal parenting on theory of mind development.

Interestingly maternal structuring, but not sensitivity, was associated with better performance on theory of mind tasks. The EAS structuring scale measures the supportive organization of a child's play and learning by matching responses to the child's needs for assistance or autonomy (Biringen, Robinson, & Emde, 1998). It could be the case that mothers who engage in more optimal structuring are better able to recognize that children are struggling socially (i.e., those with higher OXTR methylation), and thus adjust their

interaction style to provide more guidance and scaffolding, which may involve more explicit explanations about mental states and perspective-taking that would in turn promote theory of mind development. The EAS sensitivity scale places more of an emphasis on the affective quality of interactions (Biringen et al., 1998). Although a mother may demonstrate warmth and positive emotion, this alone may not be enough to facilitate learning about mental states and perspective-taking, especially among children with higher methylation whose down-regulated oxytocinergic system may be impeding theory of mind development. It is also possible that these two dimensions of maternal behavior are differentially related to cognitive and affective components of social cognition. For example, Wade and colleagues (2015) found that a measure of maternal cognitive sensitivity, which taps aspects of structuring such as interpreting a child's level of understanding and providing support that matches, was related children's theory of mind performance. Whereas, McDonald and colleagues (2016) found that affective mutuality (i.e., emotional availability and shared positive affect), but not parent supportiveness (e.g., responsiveness to needs, balance of involvement and respect for independence), was related to children's empathy, as measured by observed caring and concerned responses to parental distress. Indeed, sensitivity is known to influence children's emotional development (e.g., attachment security), whereas parenting that follows the child's cues and supports their engagement with the environment promotes cognitive development (for reviews see Murray, 2014; Murray, Cooper, & Fearon, 2014).

Maternal behavior was not related to children's OXTR methylation. DNA methylation patterns can be largely influenced by genetic variation in a heritable and stable manner throughout a lifetime (Gaunt et al., 2016; McRae et al., 2014). However, as

an epigenetic process DNA methylation is also considered to be responsive to environmental influences (for reviews see Lewis & Olive, 2014; McGowan & Roth, 2015), particularly to significant stressors (e.g., abuse/neglect) during sensitive periods of development (e.g., perinatal). For example, perceived low maternal care in childhood was associated with increased OXTR methylation in adulthood (Unternaehrer et al., 2015), but not in the region of exon 3 captured in the current study. Of note, a previous study by our team using the same sample (King et al., 2017) revealed that exposure to maternal depression during pregnancy and the early postpartum period was not associated with OXTR methylation profiles among children. This finding is consistent with the lack of epigenetic effect of concurrent maternal behavior observed in the present study.

To our knowledge, this is the first study to provide empirical evidence for the association of DNA methylation of the oxytocin receptor gene, and its interaction with maternal behavior, with individual differences in theory of mind development among young children. The results should, however, be interpreted with a few methodological limitations in mind. First, given the challenges of administering cognitive assessments to 2-year-old children (e.g., limited attention and verbal skills), only a few brief but engaging theory of mind tasks were selected for use in the current study. Consistent with previous research demonstrating that these tasks are developmentally appropriate (e.g., Hughes & Ensor, 2005), only a small percent (6.3%) of children failed to complete two or more. However, since the aggregate theory of mind score had only moderate internal consistency, future research would benefit from employing a wider variety of tasks and assessing other aspects of theory of mind (e.g., affective perspective-taking). While we included several well-established covariates, we were not able to control for cell

composition (e.g., epithelial, leukocyte) in the saliva sample. Therefore, differential methylation patterns between cell or tissue type (for review see Bakulski, Halladay, Hu, Mill, & Fallin, 2016) may have obscured the measurement, though this is less likely to occur in high-density CpG islands (Slieker et al., 2013). Similarly, we cannot assume that OXTR methylation profiles in salivary samples reflect those in brain regions implicated in theory of mind, although methylation in peripheral and central tissues have been found to be associated in some genome-wide studies (e.g., Davies et al., 2012; Farré et al., 2015; Smith et al., 2015). Moderate heritability of individual differences in theory of mind performance has been observed among younger, typically developing children, whereas environmental influences explained more variance following the transition to school (for review see Hughes & Devine, 2015b). In addition, DNA methylation patterns may differ by genotype (for review see Meaburn, Schalkwyk, & Mill, 2010). Unfortunately, our targeted amplicon approach did not allow us to investigate sequence variation at associated SNP loci in relation to the methylation findings. Future research should examine the allele-specific effects of OXTR methylation on theory of mind development. Nevertheless, the findings are suggestive of a potential interaction between genetic and environmental influences, and thus further investigation in a larger, prospective sample is warranted.

Conclusions

The current study examined the interplay between environmental and biological factors, providing new evidence that both maternal behavior and children's OXTR methylation influence early emerging theory of mind abilities. Further, their statistical interaction suggests that maternal structuring behavior becomes particularly important for

theory of mind development when children's oxytocin receptor gene is more highly methylated. Maternal parenting behavior may buffer the potentially negative effects of OXTR methylation on oxytocinergic system functioning. Given the role of theory of mind deficits in psychopathology, elucidating such interactions between genetic and environmental influences improves our understanding of risk and resiliency, and in turn points to potential targets (i.e., children with high OXTR methylation) for early intervention (e.g., parent training).

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Table 1

Descriptive Statistics for Main Study Variables

	n	*M*	*SD*	*Range*
OXTR methylation	166	15.04	4.48	3.81 – 28.13
Maternal Behavior	185			
Sensitivity		6.68	.84	3 – 8
Structuring		3.90	.80	2 – 5
Non-intrusive		4.05	.89	2 – 5
Non-hostility		4.97	.19	2 – 5
Theory of Mind				
Visual Perspective	183	15.01	3.91	4 – 20
Pretend Play	166	5.04	2.26	0 – 9
False-Belief	157	.46	.66	0 – 2

Note. Unstandardized theory of mind scores are presented; OXTR = oxytocin receptor gene

Table 2

Bivariate Correlations between Main Study Variables

Variable	1	2	3	4	5
1. OXTR methylation	--				
Maternal Behavior					
2. Sensitivity	.05	--			
3. Structuring	-.10	.50***	--		
4. Non-Intrusive	-.02	.17*	.24**	--	
5. Theory of Mind	-.22*	.14	.21*	.01	--

Note. OXTR = oxytocin receptor gene

* $p < .05$ ** $p < .01$ *** $p < .001$

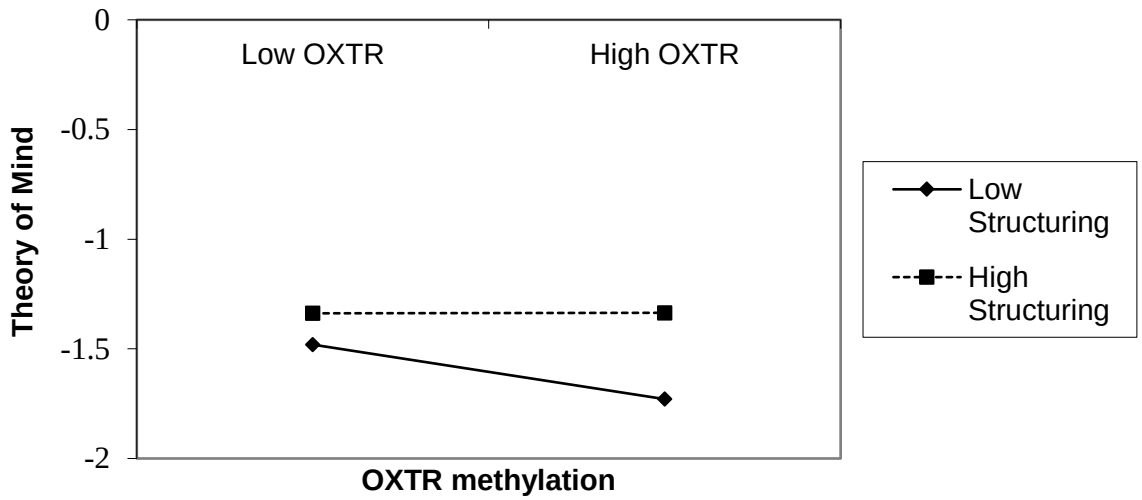

Figure 1. Interaction between OXTR methylation and maternal structuring behavior on children's theory of mind performance. Theory of mind performance represents the standardized aggregate variable. OXTR methylation represents the mean percent of methylation across the 22 CpG sites captured on exon 3.

General Discussion

Given that "social interaction permeates the whole of human society, and the fundamental ability to form attachment is indispensable for social relationships" (Heinrichs, von Dawans, & Domes, 2009), a growing field of research continues to explore the neurobiological underpinnings of human sociality and affiliation. The overall objective of the present thesis was to elucidate the role of the oxytocinergic system in facilitating or coordinating social cognitive and behavioral processes. Articles 1 and 2 examined maternal caregiving following the important role transition from pregnancy to postpartum, while Article 3 examined emerging theory of mind abilities during the early years when children start learning to navigate the social world. Overall the findings of the present thesis are suggestive of a role for the oxytocinergic system in reproductive and developmental plasticity of the social brain.

Article 1 demonstrated that increased levels of plasma oxytocin during the third trimester of pregnancy predicted better performance on an experimental theory of mind task in the early postpartum. Theory of mind, in turn, was associated with less remote and less depressive maternal interactive behaviors (e.g., more engaged and relaxed; less focused on own experience). This finding is consistent with the notion that endogenous oxytocin may represent a biomarker for sensitivity to social cues (Bartz et al., 2011a). Moreover, plasma oxytocin was indirectly related to less depressive maternal behavior at 7-9 weeks postpartum via theory of mind ability. Article 2 confirmed and extended these findings, by demonstrating that plasma oxytocin during late pregnancy was indirectly associated with more structuring and less intrusive maternal behavior at 2–3 years postpartum via mothers' theory of mind ability. Together the results of Articles 1 and 2

suggest that theory of mind may represent a social cognitive mechanism through which oxytocin promotes maternal caregiving by enhancing awareness of and ability to interpret social cues. The natural increase of peripheral oxytocin during late pregnancy may reflect a priming function of the oxytocinergic system on the social cognitive processes that facilitate the maternal caregiving that is required during infancy and early childhood. These findings are also consistent with the notion that the neuroendocrine adaptations of pregnancy may impart long-lasting effects on postpartum maternal caregiving behavior (Kinsley, Bales, Bardi, & Stolzenberg, 2015). In particular, the changes in the oxytocinergic system during pregnancy may lead to lasting changes in neuronal structure and brain functioning (e.g., Kinsley et al., 2006), possibly including areas associated with theory of mind ability, such as the amygdala and prefrontal cortex (e.g., Baron-Cohen et al., 1999). Thus, the oxytocinergic system may play an important role in the reproduction-induced neuroplasticity that prepares for motherhood (Kinsley & Lambert, 2008) by coordinating the processes that facilitate maternal caregiving and affiliation.

Article 3 demonstrated that another component of the oxytocinergic system—methylation of the oxytocin receptor gene—influenced early emerging theory of mind abilities, which are an important aspect of children's social development. The findings revealed that higher levels of OXTR methylation, which down-regulates oxytocinergic system functioning by blocking receptor transcription and thus preventing oxytocin signalling, predicted worse performance on a battery of theory of mind tasks among 2- to 3-year-old children. This finding is suggestive of a functional impact of OXTR gene suppression on social cognitive processing. Moreover, exposure to more maternal structuring behavior buffered the impact of increased OXTR methylation on theory of

mind performance. This finding is consistent with the contextual-dependence of oxytocin effects (Bartz et al., 2011a) and, further, is suggestive of differential susceptibility. When considered together with previous findings of gene–environment interactions between OXTR single nucleotide polymorphism (SNP) genotypes and parental behavior on children's theory of mind and empathy (McDonald et al., 2016; Wade et al., 2015), this pattern indicates that OXTR genetic biomarkers, such as hypermethylation and "risk" alleles, may confer plasticity to the influences of optimal and less optimal parenting on theory of mind development.

The articles in the present thesis are the first, to my knowledge, to provide empirical evidence for a) the association between circulating oxytocin and theory of mind, among mothers, and b) the influence of DNA methylation of the oxytocin receptor gene, and its interaction with maternal behavior, on individual differences in theory of mind development among young children. These findings broadly support the social saliency hypothesis that oxytocin promotes social functioning by increasing awareness of and sensitivity to social cues. In contrast, the results of Article 1 were not consistent with the anxiolytic hypothesis since pregnancy levels of plasma oxytocin were unrelated to self-reported symptoms of anxiety and worry, which in turn were not related to theory of mind or maternal behavior. Taken together, the results of the present thesis contribute to the extant literature exploring the role of the oxytocinergic system in promoting human sociality and affiliation, as one of the most comprehensive longitudinal investigations from pregnancy through early childhood in a large, culturally diverse, non-clinical sample.

The present thesis aimed to adopt a biopsychosocial approach and thus utilized

multiple methods including molecular biological measures of circulating oxytocin and DNA methylation of the oxytocin receptor gene, experimental tasks tapping social cognition, as well as behavioral observations. As described in more detail in the articles above, these measures are not without limitations and thus the results should be interpreted with caution. Several larger methodological issues are worth reiterating here when interpreting the totality of the findings. First, given the ethical and technical difficulties of measuring central oxytocin hormone and receptor levels in humans, all data in the present thesis were collected from peripheral tissues (e.g., blood and saliva). However, it is not possible to make clear inferences about whether plasma levels reflect oxytocin activity in the brain. Although peripheral and central oxytocin release are thought to be coordinated (e.g., Burri, Heinrichs, Schedlowski, & Kruger, 2008), the research findings are inconsistent (e.g., Lefevre et al., 2017). Similarly, it cannot be assumed that OXTR methylation profiles in saliva cells reflect those of neurons in brain regions associated with social cognition, though methylation in peripheral and central tissues were correlated in some genome-wide studies (e.g., Davies et al., 2012; Farré et al., 2015; Smith et al., 2015).

Second is the fact that the oxytocinergic system does not function in isolation, but interacts with other systems including the gonadal hormone system and the dopaminergic system. For example, the influence of oxytocin may be modulated by female sex hormones as oxytocin production and receptor affinity is up-regulated by estrogens and progesterone (Gimpl, Wiegand, Burger, & Fahrenholz, 2002). Animal research suggests that these sex hormones stimulate postpartum maternal behavior by promoting oxytocin synthesis, transport, release, and binding in brain areas associated with maternal behavior

(for review see Pedersen, 1997). Similarly, the relationship between oxytocin and social cognition may reflect an interaction with the sex hormones. Changes in estrogens and progesterone have been associated with altered emotion processing of visual stimuli across the estrous cycle and during pregnancy (for review see Little, 2013). Consistent with the integrated models reviewed in the introduction, it has also been suggested that the oxytocinergic system may interact with dopamine reward circuitry to prime maternal caregiving (Galbally et al., 2011; Numan, 2006) and motivate social behavior (Gordon et al., 2011; Love, 2014). For example, an increased peripheral oxytocin response to infant contact among human mothers was associated with neural activation in dopamine reward processing brain regions (Strathearn et al., 2009). Intranasal administration of synthetic oxytocin also is associated with increased neural activity in reward regions and enhanced processing of social stimuli when women view friendly faces and when men view faces of their romantic partners (Groppe et al., 2013; Scheele et al., 2013). Moreover, estrogen and dopamine may differentially regulate oxytocin receptor expression and binding in different areas of the brain with different behavioral effects. For example, among female rats estrogen signal transduction pathways induce oxytocin receptor expression in the hypothalamus, where oxytocin infusion is related to increased sex behavior, while dopamine signal transduction pathways induce oxytocin receptor expression in the amygdala, where oxytocin binding/infusion is related to reduced anxiety responses (Bale, Davis, Auger, Dorsa, & McCarthy, 2001). It would be interesting for future research to explore patterns of interaction between the oxytocinergic, dopaminergic, and gonadal systems, including temporal release of hormones and neurotransmitters as well as functional connectivity in neural activation, in response to social stimuli or real-time

social interaction.

In addition, DNA methylation is considered to be an epigenetic process whereby gene expression, and in turn phenotypic variation, can be altered by environmental influences (for reviews see Lewis & Olive, 2014; McGowan & Roth, 2015), particularly significant stressors (e.g., abuse/neglect) during sensitive periods of development (e.g., perinatal). For example, individuals who perceived receiving low maternal care in their childhood were observed to have increased OXTR methylation in adulthood (Unternaehrer et al., 2015). It would have been interesting to determine what environmental factors influenced children's OXTR methylation levels in Article 3. However, a previous study by our team using the same sample (King et al., 2017) revealed that exposure to maternal depression during pregnancy and the early postpartum period was not associated with OXTR methylation profiles among these children. This lack of effect of adversity may reflect the fact that DNA methylation patterns are to a large extent genetically determined, heritable, and stable across the lifespan (Gaunt et al., 2016; McRae et al., 2014). However, DNA methylation patterns also may differ by genotype (for review see Meaburn, Schalkwyk, & Mill, 2010). For example, one study demonstrated that approximately 75% of variably methylated regions of the methylome (i.e., set of methylation profiles across the genome) were explained by the interaction between genotype and prenatal environment factors such as maternal depression and smoking (Teh et al., 2014). Therefore, future research may benefit from examining the allele-specific effects of OXTR methylation on theory of mind development.

Although Articles 1 and 2 controlled for some contextual and individual factors (e.g., supportive mother, history of abuse), maternal behavior is not independent from

other influences including mothers' early childhood experiences (e.g., Barrett & Flemming, 2011; Belsky, Jaffee, Sligo, Woodward, & Silva, 2005), attachment style (e.g., Strathearn et al., 2009), and child characteristics (e.g., Belksy, 1984; Moore, 2007). Some studies have also examined the oxytocinergic system in relation to the dyadic nature of the mother–child relationship by assessing quality, sychronony, and reciprocity during interaction (e.g., Feldman et al., 2013). Moreover, when considering the influences on development it is important to note that many children also receive caregiving from another parent. To this end, other studies have examined fathers' behavior (e.g., Naber, van Ijzendoorn, Deschamps, van Engeland, & Bakermans-Kranenburg, 2010), neural coordination between mothers and fathers (e.g., Atzil, Hendler, Zagoory-Sharon, Winetraub, & Feldman, 2012), as well as triadic interaction with their child (e.g., Gordon et al., 2010b). Article 3 focused on maternal caregiving as the environmental influence on children's emerging theory of mind abilities, while accounting for possible effects of siblings. However, other environmental factors are thought to influence children's theory of mind development as their social world widens with the transition to school, a growing peer group, and new experiences outside of the family (Hughes & Devine, 2015). Future research would benefit from incorporating peer influences by including assessments of social network size or teacher ratings of peer relations, on a wider variety of tasks tapping other aspects of theory of mind (e.g., affective perspective-taking) as well as measures of prosocial behavior across various settings. Indeed, it would be interesting to continue following the mothers and children from the present thesis as they transition to school in order to explore how changes in family and peer relationships influence social development and the application of theory

of mind skills in a range of contexts.

Although the research in the present thesis was conducted with a "normal" or typically developing population (e.g., mothers self-reported low rates of psychiatric symptoms), the findings have important clinical implications. Consistent with the present findings suggesting that the oxytocinergic system is involved in promoting sociality and affiliation, specifically theory of mind abilities and maternal caregiving, research in translational medicine has been increasingly investigating the therapeutic potential of intranasal administration of synthetic oxytocin in the treatment of disorders characterized by social deficits such as autism, schizophrenia, social anxiety and borderline personality disorder. For example, in two recent clinical trials a single-dose of intranasal oxytocin was associated with increased neural activation in the medial prefrontal cortex and anterior insula, areas involved the processing of others' feelings, as well as improved performance on theory of mind and social communication tasks, among males with autism spectrum disorder (Aoki et al., 2014; Watanabe et al., 2014). In addition, intranasal administration of synthetic oxytocin among women with postpartum depression, who often exhibit impaired parenting skills (for review see Murray, Halligan, & Cooper, 2010), increased protective behaviors and positive perceptions of the quality of their relationship with their infant (Mah et al., 2013; 2014). However, given the contextual and individual dependence of oxytocin's effects, Bartz and colleagues (2011a) recommended careful consideration regarding whether increasing salience of social cues via oxytocin administration would be beneficial or potentially intensify already negative biases and maladaptive responses to social stimuli. Instead, the authors suggest that oxytocin administration may be best used in conjunction with psychosocial interventions

that target these social deficits. Moreover, it is not clear to what extent intranasally administered oxytocin crosses the brain barrier (e.g., Leng & Ludwig, 2016) or interferes with pregnancy and lactation among women (MacDonald & MacDonald, 2010).

Alternatively, given these caveats and concerns regarding the use of oxytocin for pharmacotherapy, the findings of the present thesis also suggest that oxytocin could be used as a potential biomarker to identify individuals (i.e., women with low plasma oxytocin during the perinatal period and children with high OXTR methylation) who would benefit from psychosocial prevention and intervention programs that target theory of mind such as mental state and perspective-taking training (e.g., Lecce, Bianco, Devine, Hughes, & Banerjee, 2014; Mori & Cigala, 2016) and maternal caregiving such as attachment and parenting skills training (e.g., Circle of Security; Powell, Cooper, Hoffman, & Marvin, 2014). This approach would fit well within the broader movement toward personalized medicine wherein unique biomarkers of differential susceptibility are identified to guide more targeted treatment, with the overall goal of optimizing development and family wellbeing. Interestingly, psychosocial interventions have been shown to have epigenetic effects. For example, Smearman and colleagues (2016) reported that youth with the risk allele (GG) for the OXTR rs53576 SNP evidenced reduced telomere shortening (i.e., the protective caps on chormosomes) in response to a family-based prevention program, despite previous exposure to non-supportive parenting (e.g., high conflict, low warmth and emotional support). In another study, a nurse-visitation program targeting maternal health and mother–child interaction among women at risk for abusive parenting was associated with DNA methylome variation (O'Donnell et al., 2018). Together, this work points to new ways to identify who is at risk for

problems in social functioning and who is likely to respond to psychosocial intervention. Such tailoring would improve the effectiveness of mental health care and better meet the needs of mothers and their children.

Conclusions

Overall the findings of the present thesis suggest that the oxytocinergic system plays an important and dynamic role in the reproductive-induced and developmental plasticity of the social brain that enables human sociality and affiliation in varying contexts. It appears that the oxytocinergic system is involved in the adaptations during pregnancy that prepare for motherhood to enable bonding as well as and during the early childhood years to promote social development.

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