Postnatal depression, oxytocin and maternal sensitivity

Mah, B.L.

Postnatal depression, oxytocin and maternal sensitivity

Beth L. Mah

Postnatal depression, oxytocin and maternal sensitivity

Proefschrift

ter verkrijging van
de graad van Doctor aan de Universiteit Leiden,
op gezag van Rector Magnificus mr. C.J.J.M. Stolker,
volgens besluit van het College voor Promoties
te verdedigen op woensdag 7 januari 2015
klokke 13.45 uur

door

Beth Lynette Mah

geboren te Lower Hutt, New Zealand
in 1966

Promotiecommissie

Promotores

Prof. dr. M. J. Bakermans-Kranenburg

Prof. dr. M. H. van IJzendoorn

Prof. dr. R. Smith, University of Newcastle

Overige leden

Prof. dr. L. R. A. Alink

Prof. dr. B. M. Elzinga

Prof. dr. L. Murray, University of Reading

Table of Contents

Thesis Overview

This thesis addresses the influence of oxytocin on parenting of mothers with a diagnosis of postnatal depression. The first chapter is a general introduction to the overarching topic of postnatal depression, oxytocin and parenting. A systematic review was completed focusing upon three interconnecting topic areas: i) the effect of postnatal depression upon parenting quality, ii) oxytocin and parenting and iii) postnatal depression and oxytocin. The review seeks to answer four pertinent questions. Does depression affect the quality of parenting? Do interventions in a depressed population improve parenting? What is the effect of oxytocin on parenting in a community sample? What are the effects of oxytocin on postnatal depression?

In an empirical study a within-subject, randomized, double-blinded, placebo-controlled design was used, and several parent-infant interaction measures were investigated. The following three chapters report on findings from this randomized controlled trial. Chapter 2 considers the effect of administration of oxytocin to a

group of mothers with postnatal depression on their mood, Expressed Emotions and verbal fluency. Chapter 3 explores how mothers with postnatal depression behave with respect to their level of protectiveness towards their infant after intranasal oxytocin administration. Chapter 4 reports on study findings which sought to confirm our hypothesis that oxytocin administration to mothers with postnatal depression would improve aspects of sensitive parenting especially if the mother had experienced a supportive childhood.

The final chapter provides a summary and general discussion of the findings.

1

General Introduction

Parenting, Postnatal Depression and Oxytocin. A systematic review.

Beth L. Mah

Submitted for Publication

Abstract

Context*:* In the past decade there has been a surge of behavioral science research interest in the neuropeptide oxytocin. Interest has included understanding the role of oxytocin in parenting as well as its use in clinical populations.

Objective*:* A systematic review to examine and summarise the current literature exploring the topics of i) postnatal depression and parenting, ii) parenting and oxytocin and iii) oxytocin and postnatal depression, to address the issues of whether postnatal depression has negative effects on parenting and can these be mitigated by intervention, is parenting enhanced by oxytocin, and what effect does oxytocin have, if any, in postnatal depression?

Data Sources*:* A systematic review of English articles using EMBASE, MEDLINE, PUBMED, PSYCHINFO and WEB OF SCIENCE. Search terms included oxytocin, parenting, mother infant interaction, parent infant interaction, parent child interaction, postnatal depression and postpartum depression.

Study Selection*:* Inclusion and exclusion criteria were established to inform the process of selection for each of three topic areas.

Data Extraction*:* Independent extraction of data using a predefined system occurred.

Results*:* Mothers with postnatal depression (PND) reported higher parenting stress, felt less competent and less able to cope. They also experienced more negative attitudes towards their infants compared to controls. In terms of parenting behavior, mothers with PND interrupted exclusive breastfeeding earlier, and used less health promoting practices compared with non-depressed controls. The majority of experimental studies exploring the effectiveness of psychological interventions for mothers with PND found positive effects on the quality of mother-infant interaction. Our review found that oxytocin may play an additional role in improving parental behaviors. Findings exploring the association between oxytocin and postnatal depressive symptoms however were inconsistent. Lower plasma oxytocin levels were associated with higher depressive symptoms but administration of exogenous oxytocin resulted in higher depression scores.

Conclusions*:* Our systematic review on oxytocin, parenting, and PND suggests that there is promising evidence for the neuropeptide

oxytocin to be of interest in the broader psychiatric field. It may be of value to target improvement in parent-infant interaction in postnatally depressed mothers, but more research needs to be conducted to establish its safety with respect to effects of oxytocin administration upon maternal mood.

Introduction

Postnatal depression (PND) is a common disorder with an incidence of approximately thirteen percent [1]. Outcomes for children cared for by a mother with a diagnosis of PND are concerning. They have higher rates of psychiatric diagnoses by the age of six and poorer social-emotional outcomes [2]. Children with depressed mothers are more often classified as insecurely attached and are hampered in their cognitive development [3]. The potential mechanisms of the link between maternal PND and these child outcomes have been investigated in various behavioral and neurobiological studies. Depressed mothers are less likely to accurately identify infants' facial expressions [4]. Mothers with PND have a decreased neural response to infant smiles compared with non-depressed controls [5]. Mothers with PND also have more difficulty interpreting the urgency of their infants' cry [6]. At the most serious end of a spectrum of caregiving, mothers with PND are more likely to use a neglecting or an aggressive parenting style [7], and their infants' mortality rates are higher than those of non-depressed controls [8]. In addition to improving treatment for women with PND it is also

important that we continue to discover methods of reducing the poor outcome for their children.

The processes involved in the ability to parent are complex. One recent area of interest in bio-behavioral science is the oxytocinergic system. Oxytocin (OT) is a hormone and neurotransmitter produced centrally in the paraventricular and supra optic nuclei. It functions in physiological processes of parturition [9] and lactation [10]. OT aids social affiliative processes [11] and is involved in parenting behaviors [12] including bonding [13]. The effects of OT have been studied in community populations. OT levels in community mothers is increased after affectionate contact with their infant [14]. Administration of intranasal OT to community fathers increases their responsive structuring and decreases their hostility when interacting with their pre-school aged child [15].

Our understanding of the association between OT and depression generally or PND specifically, is limited. Human post-mortem studies have documented anatomical differences in the brains of previously depressed deceased individuals compared to controls. In previously depressed individuals an increase in the number, size

[16] and mRNA concentration [17] of OT neurons has been found. It is not established if these differences are a result of depressed mood, or conversely, cause depressive symptoms. In living participants lower plasma OT levels were found to be related to depressive symptoms [18]. When considering PND, women at risk for developing this illness have lower mid-gestation plasma OT levels [19]. Intranasal OT administration has been considered as an adjunctive therapy for numerous psychiatric disorders including schizophrenia, obsessive compulsive disorder, and autism [20], but not enough evidence exists yet for this intervention to be indicated. In terms of the effect of intranasal OT administration on mood, one finding is an immediate increase in feelings of depression in mothers with PND [21]. However, in community samples the administration has produced no effect [22, 23] and in a clinical sample of non-parents with an anxiety disorder again there was no effect of OT administration [24].

In the past decade a number of systematic reviews have been published about PND, covering various areas of interest. The association between health conditions such as obesity, preeclampsia

and gestational diabetes and PND has been explored [25-30]. Adolescent mothers [31, 32] fathers [32], preterm birth [33] and multiple births [29] have been considered in relation to PND. Transcultural studies have also been published [29, 33-35]. Reviews have focused upon aspects of the illness and provision of health care such as prevention [36], recognition [37], the course of [38] and the treatment for [28, 30, 39] PND. One systematic review considered the health economic implications of PND [40]. However few have focused on outcomes for the parent and child as a result of PND. Hendricks et al. summarised findings of PND leading to childhood aggression [41] and Misri et al. examined the effect of PND on attachment between mother and infant [42].

In the past five years authors have summarised recent findings in the field of OT and its effects upon general social behavior [43, 44] in systematic reviews. More specifically, social cognition [45], behavior and affect [46] and the effects of OT on cooperation and competition [47] have been published. One recent systematic review looked at the role of OT in mother-infant relations [48]. Researchers have also explored the area of psychiatric illness and OT. One review

included various psychiatric conditions [49]. Others have focused on an individual disease such as anorexia nervosa [50], autism [51] and schizophrenia [52]. To our knowledge a systematic review has not yet been published exploring the association between depression generally or PND specifically, parenting and OT.

Thus we embarked upon a systematic review to summarise findings with the following three aims:

i) to explore the association between PND and parenting

ii) to explore the association between OT and human parenting, both correlational (OT level in saliva or plasma), and experimental (intranasal administration of OT as an intervention).

iii) to explore the association between OT and PND

Methods

Methods of the literature search, inclusion and exclusion criteria were specified in advance for the three areas of interest as follows:

i) Postnatal depression and parenting

Empirical studies with a primary stated aim to explore the association between depression and parenting were included. Participants were diagnosed with depression (including major depression in the postnatal period, postnatal depression, postpartum depression), but could have co-morbid diagnoses such as anxiety or substance abuse. In addition, studies were also included if a subgroup of the sample was depressed, but only if the outcome measures were reported on separately for the depressed subgroup. Studies whose participants were mothers, fathers or non-parents were included. Papers testing the following interventions were included: Parent-infant/child relationship intervention including parent training; Parenting knowledge/confidence intervention (parent education); intranasal OT. Outcome measures specified to be inclusion criteria were: a measure of relationship quality (maternal sensitivity or emotional availability, infant-mother attachment, breastfeeding rates); a measure of parental attachment, parental cognitions, parental representations, parent stress or satisfaction and studies measuring brain function expected to mediate parenting behaviors.

Exclusion criteria included non-English papers; empirical papers reporting only on outcomes for offspring; empirical studies with a primary stated aim to explore the association between an infant factor and the incidence of depression (e.g.: temperament, sleep/settle, prematurity causing PND); empirical studies with a primary stated aim to explore the association between conception method or delivery style and the rate of depression; studies with the stated primary aim to explore causes of, or risk factors for PND; or any study developing tools for diagnostic assessment of PND. Review articles and case studies were also excluded. Studies with participants experiencing a primary diagnosis that was not depression were excluded, unless the effects of depression were reported upon separately. If papers reported on the following outcome measures only, they were excluded from our review: depressive symptom change or comparison of depression rates between populations; health care use or engagement in samples with PND; health worker competence in the area of PND; and marital relationship outcomes. Animal studies and those exploring outcomes related to Oxytocin Receptor Gene (OXTR) polymorphisms were also excluded.

We searched the following databases: PUBMED, MEDLINE, PSYCHLIT, EMBASE, and WEB OF SCIENCE from as far back as each database stored records until October 2013. The following is a summary of the search terms used:

01. Postnatal depression

02. Postpartum depression

03. #1 or #2

04. Parenting

05. Mother infant interaction

06. Parent infant interaction

07. Parent child interaction

08. #4 or #5 or #6 or #7

09. #3 and #8

ii) Oxytocin and parenting

Empirical studies with a primary stated aim to explore the association between OT and human parenting, both OT plasma level or administration of OT as an intervention were included in the review.

Studies were excluded if they were non-English, were review articles or case studies, animal studies and those exploring the OXTR genotype. The following is a summary of the search terms used for this section of the review:

01. Oxytocin

02. Parenting

03. Mother infant interaction

04. Parent infant interaction

05. Parent child interaction

06. #2 or #3 or #4 or #5

07. #1 and #6

iii) Oxytocin and PND

Studies were included if the primary stated aim was to explore association between OT (level or as intervention) and PND.

Exclusion criteria were: non-English articles, articles in which an assumption was made about OT if the mother was lactating without explicitly measuring the OT level by any method, review

papers, case studies, animal studies and those exploring the OXTR genotype. The following is a summary of the search terms used:

01. Oxytocin

02. Postnatal depression

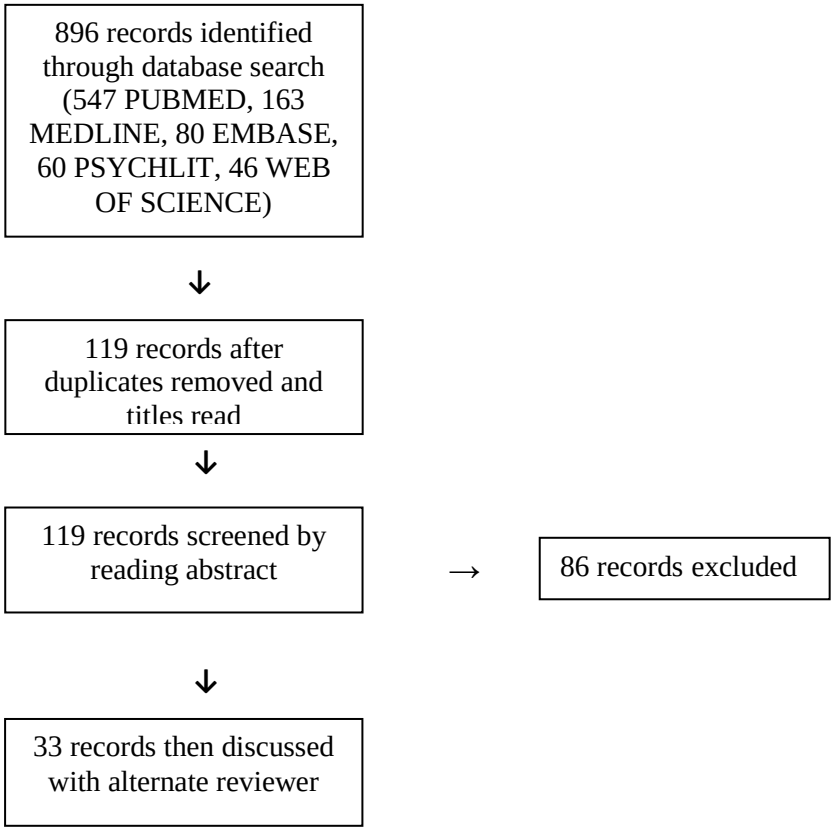
03. Postpartum depression

04. #2 or #3

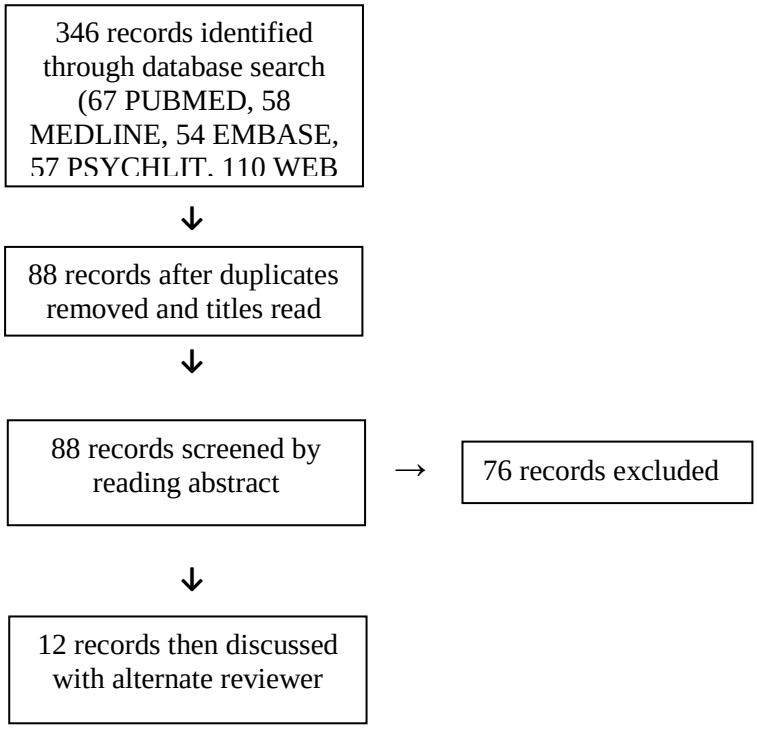
05. #1 and #4

Study selection was performed independently in a standardized manner by two reviewers. Disagreements between reviewers were resolved by consensus.

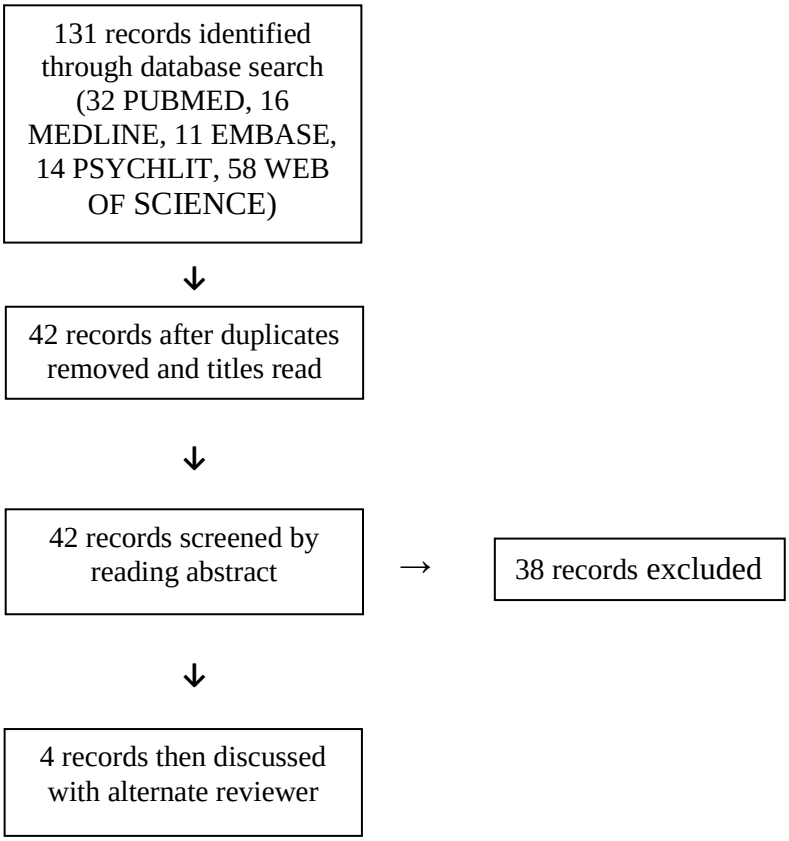
Flowchart 1:
PND and parenting:



OT and parenting:



OT and PND:


131 records identified through database search (32 PUBMED, 16 MEDLINE, 11 EMBASE, 14 PSYCHLIT, 58 WEB OF SCIENCE)
42 records after duplicates removed and titles read
42 records screened by reading abstract
38 records excluded
4 records then discussed with alternate reviewer

The data collection process involved one reviewer extracting details from each paper using previously established categories. See Appendix 1 for details.

Results

i) Postnatal depression and parenting

Table 1: PND and parenting

Authors	Subjects	Study Design	Main finding
Alder et al. [53]	27 mothers with PND	Longitudinal	Counselling reduced parenting stress and increased self-efficacy
Arteche et al. [4]	21 mothers with PND, 34 controls	Correlational	PND less accuracy identifying infant happy expression
Campbell et al. [54]	67 mothers with PND, 59 controls	Longitudinal	PND perceived infants as more difficult and had less positive engagement
Chabrol et al. [55]	20 families (10 with PND in mother, 10 controls)	Correlational	No difference in quality of parent-infant interaction
Crockenberg et al. [56]	92 mothers with PND	Correlational	Severity of depression correlated with poorer maternal sensitivity

Forman et al. [57]	120 mothers with PND (60 received intervention, 60 waitlist and 56 controls)	Randomised controlled trial	Response to Interpersonal Therapy did not improve child outcomes
Goodman [58]	128 families (60 mothers with PND, 68 controls)	Correlational	Fathers in families with a depressed mother were more depressed, stressed and had poorer infant interactions
Goodman et al. [59]	43 mothers (19 with PND, 25 controls)	Non-randomized trial	Medication and counselling resulted in improved quality of interaction
Hasselmann et al.[60]	423 mothers (95 with PND, 328 controls)	Correlational	PND associated with increased risk cessation exclusive breastfeeding
Herrara et al. [61]	72 mothers (36 with PND, 36 controls)	Correlational	Depressed mothers had decreased quality of interaction
Horowitz et al. (2001) [62]	134 mothers with PND (66 received intervention, 68 controls)	Randomized controlled trial	Both those receiving relationship focused intervention and controls

			improved their quality of interaction
Horowitz et al. (2013) [63]	117 mothers with PND (60 received intervention, 57 controls)	Randomized controlled trial	Depressed mothers receiving interaction based coaching improved quality of interaction
Loh et al. [64]	41 mothers with PND	Correlational	Majority of mothers with PND self-report interaction difficulty
Murray et al. [65] (2003)	193 mothers with depression	Randomized controlled trial	Treatment improved self-report relationship difficulty. Complex interplay of treatment and social adversity on observed measure.
Murray et al. [66] (1996)	49 mothers (29 with PND and 20 controls)	Correlational	Depressed mothers observed to be less sensitive.
Milgrom et al. [67]	38 couples (mothers with PND), 46 controls	Correlational	Mothers with PND and their spouses rated themselves as less competent.
Noorlander et	25 mothers	Correlational	Mothers with

al. [68]	admitted to psychiatric hospital (13 PND, 12 PPP)		PND rated their bond as poor and this correlated with observations
Onozawa et al. [69]	34 mothers with PND (19 intervention group, 15 controls)	Randomized controlled trial	Interaction improved for mothers receiving support by baby massage group
Paris et al. (2011) [70]	25 mothers with PND	Correlational	Both parents' self-perception and quality of interaction improved after counselling intervention
Paris et al. (2009) [71]	32 mothers with PND (15 with low levels of suicidal ideation, 17 with high levels)	Correlational	Mothers with PND and high level suicidal thinking had poorer quality of interaction
Paulson et al. [72]	5089 parents (733 with PND, 4536 controls)	Longitudinal	Parents in depressed group more likely to engage in poorer parenting choices
Pritchard et al. [73]	123 mothers of preterm infants (21 with PND at 6 weeks, 102	Correlational	PND mothers had higher parenting stress one year

	controls)		postnatal
Puckering et al. [74]	17 mothers with PND (11 receiving intervention, 6 controls)	Randomized controlled trial	Mothers attending group therapy had improved quality of interaction
Reissland et al. [75]	64 mothers (32 with PND, 32 controls)	Correlational	Depressed mothers read to infant using less attuned features
Sagami et al. [7]	215 mothers (38 with PND, 177 controls)	Correlational	Depressed mothers engaged in aggressive parenting more
Seimyr et al. [76]	434 mothers (63 with PND, 235 controls)	Correlational	Depressed mothers experienced motherhood as more negative
Smith et al. [77]	106 mothers with PND (74 receiving intervention, 32 controls)	Experimental	Mothers receiving parent infant relationship support had greater improvement of quality of interaction
Stanley et al. [78]	122 mothers (72 with PND, 50 controls)	Correlational	Depressed mothers had poorer quality of interaction
Stein et al. [79]	98 mothers (49 with PND, 49 controls)	Correlational	Poorer quality of observed interaction for

			depressed mothers
Væver et al. [80]	74 mothers (28 with PND, 46 controls)	Correlational	Depressed mothers changed their proximity to infant less
Wan et al. [81]	254 mothers with PND (129 on AD, 125 receiving psychological support)	Randomized controlled trial	Reduction in depressive symptoms resulted in improved adjustment to motherhood. Neither treatment modality conferred greater benefit
Weinberg et al. [82]	81 mothers (33 with PND, 48 controls)	Correlational	No observed interaction difference between groups
Zajicek-Farber [83]	134 mothers (74 with PND, 60 controls)	Correlational	Depressed mothers chose less safe parenting practices more frequently and had less knowledge of sensitive parenting

AD=Anti-Depressant medication, PPP=Postpartum psychosis

Thirty-three papers were found. The following summary of findings is organized by considering results for papers using a correlational design which generally focus on the relations between PND and parenting. This section will initially cover those papers which measured mother-infant interaction by independent observation. Then correlational studies using self-report outcome measures will be presented. These are again divided for ease of understanding into papers measuring parental stress or attitudes, a paper measuring parent-infant relationship difficulties and then those measuring instrumental or practical parenting outcomes. Finally results are presented for studies using an experimental design. Initially studies which used an experimental but not randomized design, followed by those which used a randomized controlled design (RCT) will be presented. These experimental studies investigate effectiveness of interventions on parenting interactions for those with a diagnosis of PND.

Twenty-three papers identified in our search used a correlational design [4, 7, 54-56, 58, 60, 61, 64, 66-68, 71-73, 75, 76, 78-83]. Of these, twelve papers reported findings using independent

mother-infant observations as an outcome measure [54-56, 58, 61, 66, 68, 71, 78-80, 82]. Ten papers found effects, of varying magnitude. Mothers with depression showed less positive engagement and more negative behaviors with their infant compared to non-depressed controls [54]. Severity of depression in mothers was found to be correlated with maternal sensitivity score [56]. In families with a depressed mother, compared to families where the mother was not depressed, mothers and fathers were found to have less optimal interaction with their infants [58]. Depressed mothers were found to touch their infant less often, use less attuned and less informative speech [61]. Depressed mothers were less sensitive towards, less affirming of and more negating of their infants compared to controls. However, there was no difference in levels of intrusion or withdrawal between groups [66]. Hospitalized depressed mothers were found to have poor interactions with their infants, and severity of depression was correlated with dyadic observations [68]. Depressed mothers with high levels of suicidal ideation, compared to those with low levels, were less sensitive and responsive to infant cues [71]. Compared to non-depressed mothers, those with depression were less contingent

with and more negating of their infant [78]. Depressed mothers had poorer quality of observed interaction with mild improvements as they recovered compared to control mothers [79]. When considering how many times a mother changed her proximity to her infant, mothers with depression compared with those who were not depressed had 17% fewer changes in proximity [80]. There were no significant findings for the final two papers using mother-infant observations. Ten families with a depressed mother and ten with a non-depressed mother were compared. The small numbers may indicate insufficient power to find significant differences in parenting between the two groups [55]. No difference was found in the patterns of observed interaction for depressed mothers compared with controls, using the Still-face paradigm [82].

Two papers with a correlational design used unique outcome measures of communication aspects to measure group differences [4, 75]. The first found that mothers with PND were less accurate in identifying happy infant facial expressions than controls [4]. The second reported that more mothers with PND compared to controls

used a voice pitch likely to communicate stress when reading to their infants [75].

The final set of correlational studies measured outcome by way of self-report, which occurred in nine studies [7, 60, 64, 67, 72, 73, 76, 81, 83]. Of these, four measured parental stress or sense of competence [67, 73, 76, 81]. Depressed mothers with very premature babies had higher stress at one year post-partum when compared to non-depressed mothers of pre-term infants [73]. Mothers with PND rated themselves as less competent than non-depressed controls [67]. More depressed mothers compared with non- depressed controls felt that they weren't coping with parenthood [76]. In parents with lower depression scores, compared to those with higher scores, there was an increase in positive attitude to infant scores and maternal feelings scores [81].

One study, using a correlational design with a self-report measure of relationship difficulties, found that 66% of depressed mothers had at least mild to severe self-reported relationship difficulties, and this was correlated with interview results.

Unfortunately, this study did not use control mothers without a diagnosis of depression for comparison [64].

The final type of outcome used in the correlational designs concerned aspects of practical or instrumental parenting. Four papers were in this group [7, 60, 72, 83]. Mothers with PND had higher rates of interruption of exclusive breastfeeding within the first two postnatal months (75% of mothers with PND vs. 56% controls) [60]. Mothers with PND were more likely to engage in less optimal parenting practices such as putting their infant to sleep in a non-recommended position or not breast-feeding, compared to non-depressed mothers [72]. Depressed mothers were found to use aggressive parenting styles more frequently than non-depressed controls [7]. The final paper measuring instrumental parenting outcomes found that mothers with PND were more likely to place their infant to sleep in an unsafe position (31% vs. 15%), more frequently had no protective cover for electricity inlets (30% vs. 15%) and had inadequate knowledge of sensitive parenting (69% vs. 38%) [83].

Four papers used an experimental design and all reported positive effects [53, 59, 70, 77]. The first two used a non-randomized control group for comparison; the last two measured an outcome before and after an intervention (pretest- posttest single group design). Mothers with PND were treated with medication and they were compared with non-depressed controls. At baseline the depressed mothers had poorer quality of interaction with their infants. However at six months after commencing medication depressed mothers' interaction showed no difference to the control group [59]. In the second study, the quality of maternal interaction was compared for two groups of mothers with PND, one receiving 'Parent and Infant Relationship Support' intervention of ten sessions lasting two hours each in a group setting [77]. The mothers receiving the intervention showed improvements in the interaction with their infant. Finally, two experimental studies didn't use controls. Depressed mothers' sensitivity and responsivity improved after receiving a home-based dyadic therapy, weekly for 12-16 weeks compared to baseline observations [70]. Maternal stress was reduced and self-reported sense of parenting efficacy was improved after mothers with PND

received counselling with trained volunteers compared with their baseline scores [53].

Six studies used a RCT design [57, 62, 63, 65, 69, 74]. Two of the articles found no effect of a specific intervention on the quality of mother-infant interaction for mothers with PND [57, 63]. Mothers with PND receiving a twelve week manualized Interpersonal Therapy showed no improvement in responsiveness to infant compared to non-depressed mothers [57]. The other study which found no effect provided a group of depressed mothers with a relationship-focused behavioral nursing intervention called Communicating and Relating Effectively [63]. Compared to a control group of depressed mothers not receiving the intervention both groups displayed improved responsiveness towards their infant at the posttest, with no differential outcomes for the intervention group. The four remaining RCTs report positive or mixed findings [62, 65, 69, 74]. Depressed mothers receiving 'Interaction Coaching for At-Risk Parents' on three occasions for fifteen minutes had improved maternal responsiveness compared to depressed mothers not receiving the intervention [62]. The effects of three different psychological treatments were compared

to a control group of depressed mothers receiving usual primary care. Interventions included non-directive counselling, cognitive behavior therapy and psychodynamic therapy. For all treatment types there was an improvement in quality of relationship self-reported by depressed mothers. For depressed mothers experiencing high rates of social adversity, non-directive counselling resulted in higher observed sensitivity towards their infants. For depressed mothers experiencing low levels of social adversity both cognitive behavior and psychodynamic therapies had negative effects by resulting in lower sensitivity scores compared with control depressed mothers [65]. Mothers with PND demonstrated improved interaction with their infant after attending an infant massage group intervention for five weekly one-hour sessions compared to control mothers with PND not receiving the intervention [69]. Another sample of depressed mothers were provided with an intervention titled 'Mellow Babies', which focused upon addressing mother-infant interactions, fourteen weekly group sessions of five hours [74]. Intervention mothers improved in positive and decreased their negative interaction with their infant compared to depressed control not receiving the intervention.

In summary, the answer to our initial question: *Does PND result in negative effects upon parenting?,* the overwhelming answer is yes. Studies using independent observation of parent-infant interactions measured slightly different concepts of interactions but found that mothers with PND, when interacting with their infant, are less engaged, less responsive, less attuned, less sensitive, use more negative behavior and touch less frequently than non-depressed controls. Studies using self-report outcomes concur with this trend. Depressed mothers feel more stressed, less competent, feel they are not coping and choose poorer practical parenting choices compared with mothers that aren't depressed. We also wondered if interventions were successful in improving mother-infant interactions and the majority of findings were positive for both observed and self-report mother-infant relationship measures.

ii) Oxytocin and parenting

Table 2: OT and parenting

Authors	Subjects	Study Design	Main finding
Feldman et al. 2007 [13]	62 pregnant community women	Correlational	Increased plasma OT level associated with higher maternal behavior and attachment

			representation scores
Feldman et al. 2011 [84]	112 community parents	Correlational	Plasma and saliva OT level associated with parent child synchrony, engagement and communication sequence
Feldman et al. 2010[1] [14]	112 community parents	Correlational	Plasma and saliva OT level was positively correlated with high levels of affection in mothers and stimulatory contact in fathers
Feldman et al. 2010[2] [85]	55 community parents	Correlational	Both parents' and infants' saliva OT levels rose after interaction, this was more marked if there were higher shared affect synchrony
Feldman et al. 2012 [86]	272 community parents	Correlational	Increased plasma OT level associated with longer gaze duration
Gordon et al. 2010[1] [87]	37 community families[*] with only one infant	Correlational	Increased plasma OT level associated with higher triadic synchrony

Gordon et al. 2010[2] [88]	80 community families* with only one infant	Correlational	Plasma OT level was positively correlated with high levels of affection in mothers and stimulatory contact in fathers
Gordon et al. 2010[3] [89]	43 community fathers	Correlational	Increased plasma OT level associated with higher affect synchrony
Naber et al. 2010 [15]	17 community fathers	Double blind, placebo controlled within subject trial	In the OT condition fathers were more stimulating and less hostile
Naber et al. 2013 [90]	32 community fathers	Double blind, placebo controlled within subject trial	In the OT condition fathers were more sensitive, more stimulating and less hostile
Strathearn et al. 2009 [91]	30 community mothers	Correlational	Higher plasma OT response to interaction if mother secure attachment classification
Strathearn et al. 2012 [92]	55 community mothers	Correlational	Higher plasma OT response to interaction if mother has sensitive non schedule driven temperament
Weisman et	35 community	Double blind,	In OT condition

al. [93]	fathers	placebo controlled within subject trial	increased behaviors promoting bonding. Both father and infant saliva OT rose after interaction in the OT condition

*-both parents participated

Thirteen papers reached our inclusion criteria for this topic. By far the majority of papers were of a correlational design, with the remaining three papers being double-blinded, placebo-controlled within-subject designs. Participants used in the correlational studies included unrelated mothers and fathers as well as co-habiting parents of infants. Remarkably, participants in the studies that administered OT were all fathers. Results for all papers shared a similar finding, that OT has a role in improving parental behaviors.

All correlational studies found a clear positive association between OT level and parental behaviors likely to improve bonding [13, 14, 84-86]. Seven of the studies used plasma OT level to correlate with an aspect of parenting. Plasma OT level during pregnancy and one month postnatal was positively correlated with

maternal behavior and attachment representations [13]. Plasma OT level at baseline was also found to be positively correlated with gaze duration of parent towards their infant [86]. Plasma OT level was considered in triadic interactions between first-time parents and their infant. Again, a positive correlation was found between OT level and triadic synchrony [87]. Families were investigated again in a longitudinal study. Plasma OT level at one week and six months postpartum positively correlated with affectionate behavior in mothers and stimulatory behavior in fathers [88]. A positive correlation was found between plasma OT level in community first-time fathers and affect synchrony shared with their infants [89]. Two studies considered plasma OT level in response to a parenting event. There was an increase in OT release on reunion after initial separation for mothers with a secure attachment classification [91]. Interaction with their infant led to an increased OT response for mothers with specific temperamental features such as those sensitive to moods, emotions and physical sensations and those less task driven [92]. In terms of laboratory processing of OT levels only two of the studies used the radio immune assay (RIA) method and both failed to report

if an extraction step was used [91, 92]. The other five papers used an enzyme immunoassay (EIA) method but again none of them reported if an extraction step had been utilized. This is an important issue as OT levels have been shown to vary immensely depending on use of this labor-intensive but important extraction step for specificity of the assay [94].

The final three studies using a correlational design used baseline plasma OT levels and salivary OT levels after interaction with infant. A positive correlation was found between salivary OT level and parent child synchrony, engagement, and communication [84]. Maternal salivary OT level increased after infant contact if the mother showed high levels of affection. Fathers' OT level rose if he exhibited high levels of stimulatory contact with his infant [14]. In the final study both parents' and infants' salivary OT levels were measured. There was a rise in OT level for parents and infants alike after contact and this was especially marked if the contact included high levels of affect synchrony [85]. Laboratory processing of the saliva samples for all three studies used EIA methodology but none reported using an extraction step in the processing.

All three RCTs found that in the OT condition (ie: after intranasal OT administration compared with blinded placebo administration) parental attunement was enhanced [15, 90, 93]. Community fathers, in the OT condition, given 24 international units (IU) forty-five minutes before measuring outcome, were more stimulating and less hostile towards their children compared to the placebo condition [15]. The sample was then combined with a sample of fathers with children with a diagnosis of autism. Fathers were given 24 IU of intranasal OT, forty-five minutes prior to dyadic observations. The diagnosis of the child had no effect on the positive results. In the OT condition fathers were more stimulating and less hostile compared to the placebo condition [90]. Another cohort of community fathers were administered 24IU OT and waited forty minutes prior to dyadic observation. In the OT condition, compared to placebo there was an increase in parenting behaviors that support infant bonding. This study also measured both paternal and infant salivary OT after interaction. Interestingly, when fathers were in the OT condition their infants' also experienced a larger OT increase as measured in their salivary level [93].

The question we wanted to explore in this section was whether parenting in community samples is enhanced by OT. Studies used both measurement of OT level (in plasma or saliva) and administration of intranasal OT to answer this question. Results were clearly positive. OT is associated with improved parenting behavior. Again, studies used different measures of parent-infant interaction quality. OT is associated with parents observed to have improved synchrony, engagement, levels of affection and stimulation and less hostility when interacting with their infant.

iii) Oxytocin and PND

Table 3: OT and PND

Authors	Subjects	Study Design	Main finding
Hinshaw et al. [95]	412 low risk nulliparous women in term spontaneous labour with primary dysfunctional labour	Double blinded RCT testing timing of administration of IV OT with outcome measure	EPNDS >12 20% in group allocated to immediate OT administration vs. 15% in group OT withheld from
Mah et al. [96]	25 mothers with a diagnosis of PND made by clinical interview	Double blinded, placebo controlled within-subject RCT testing effects IN OT	Lower mood in OT condition as measured by SAM; infant described as more difficult,

		on outcome measure	but quality of relationship more positive in OT condition as measured by FMSS
Skrundz et al. [97]	74 pregnant community women	Correlational study examining association between plasma OT level in pregnancy and mood symptoms in the postpartum period	Lower OT level mid pregnancy predicted higher EPNDS at 2 weeks postpartum
Stuebe et al. [98]	47 pregnant community women with intention to breastfeed	Longitudinal cohort study examining association between mood and OT response to lactation	Third trimester-OT inversely correlated with EPNDS, 8 weeks postpartum- OT during breastfeeding inversely proportional to EPNDS, STAI scores

EPNDS = Edinburgh Post-natal Depression Scale, FMSS = Five Minute Speech Sample, IN = Intra-nasal, IV = Intravenous, OT = oxytocin, PND = postnatal depression, RCT = randomized clinical trial, SAM = Self-Assessment Manikin, STAI = Spielberger State and Trait Anxiety Inventory.

We found only four papers on oxytocin and PND meeting our inclusion criteria. Two of these looked at the association between

maternal plasma OT level and an outcome measure related to depressive symptomatology [97, 98]. These studies both found that lower plasma OT is associated with higher depressive symptoms, both using the EPNDS [99]. The studies considered different contexts. One study collected maternal plasma OT samples midway through gestation and then measured depression score, using the EPNDS. Lower OT levels early in the third trimester predicted PND symptoms at two weeks postnatal [97]. The second study used a structured clinical interview to establish the diagnosis of depression, then the EPNDS to measure fluctuations in mood symptoms. Plasma OT levels were taken sequentially at baseline, 1, 3, 7, and 10 minutes during lactation at two and eight weeks postpartum. Another level was taken after breastfeeding. EPNDS and plasma OT level were inversely correlated at eight weeks postpartum [98]. Both studies used differing methods of sample analysis, RIA (not reporting on whether an extraction step was used) [97] and EIA with an extraction step [98].

The other two papers measured depressive symptomatology after administration of exogenous OT. One study administered

intravenous (IV) OT in a community sample of laboring primiparous women with dysfunctional labor. The main outcome measures of this obstetric study were to determine differing Cesarean Section, operative vaginal rates and labor duration if the labor was augmented with IV OT immediately compared to being withheld for eight hours. However, depressive symptoms at 48 hours postpartum were also measured, by use of the EPNDS with a cut-off score of 12. Doses of OT were administered according to a standard increasing regime based on duration and timing of contractions. The group receiving OT immediately had higher depression scores (20%) compared to those receiving OT eight hours into their dysfunctional labor (15%). Cesarean Section rate was no different between groups but the operative vaginal rate was reduced and labor duration was shorter for the group receiving immediate OT administration. These could have been potential confounders, a longer labor duration leading to higher depression scores, but it is clear that the high depression rate was in the group with shorter labors with less surgical intervention [95]. The other study administered intranasal OT (24 IU) in a clinical cohort of mothers with a diagnosis of postnatal depression using a double

blinded, placebo controlled within subject design [21]. Forty-five minutes after nasal spray administration mood was assessed using the Self-Assessment Manikin. Participants reported lower mood in the OT condition.

Our final question was to explore whether OT has an effect in PND. The findings are divergent. Exogenous administration of OT resulted in more depressive symptoms, whereas lower plasma levels of OT are predictive of higher depression scores in correlational studies.

Discussion

This systematic review aimed to explore three interconnected topics, not yet considered together in one individual review. Our aim was to summarize findings in the literature to explore the association between PND and parenting, between OT and human parenting and the association between OT and PND. Results were overwhelmingly convergent for the finding that depression in mothers worsens many aspects of their ability to be an adequate parent. Interventions to improve parenting for mothers with PND had mixed results but most led to improvement. Considering the association between OT and

human community parenting it was found that OT improves various parenting outcome measures. Exploring the role of OT in a clinical population with PND resulted in somewhat inconclusive or even contrasting findings. Lower plasma OT was associated with increased depression; however administration of intranasal OT also leads to increased symptoms.

There are numerous limitations to consider with regard to the comparability of the studies. Of the studies extracted to consider the role of PND there were various methods of establishing either the diagnosis of PND or the illness severity. Structured clinical interview was used by some (for example: [4, 57, 59]); many used varying screening questionnaires such as the EPNDS [55, 67, 83] which was the most commonly used, or the Beck Depression Inventory [63, 80]. There were several other screening tools used. There were different cut-off points to establish a likely diagnosis of PND ranging from ≥ 9 [7, 76] to ≥ 14 [53] for the EPNDS. This has obvious effects for the comparability of results among studies. A systematic review to validate the EPNDS found marked heterogeneity among 37 pertinent studies. Sensitivity and specificity results showed very large ranges

(34-100% for sensitivity and 44-100% for specificity) [100]. A future direction to increase the comparability of results would be to use various forms of screening concurrently and to report the correlations or use the same outcome measure with identical cut off score. Of the eleven papers we included in our review (out of 34 reporting on PND) that used more than one measure to establish diagnosis or symptom severity [54, 55, 57, 59, 62, 64, 70, 71, 80, 81, 83], only one reported a correlation between the measures [64]: scores on the EPNDS and the Checklist of Symptoms of Depressive Illness correlated $r_s = .70$.

There were also varying outcome measures for parenting. Arguably more robust findings are established by the use of independent observation, and it was fortunate that we identified many studies including such outcomes. However, various observation settings and coding systems for the observation of parent-infant relationships were used, limiting our ability to directly compare results. It is helpful when studies measure both observed and self-report measures and establish the correlation between the two. This would add to the body of knowledge of the validity of self-report

measures in this field, allowing studies to be completed in environments that are less resource rich.

Different ways of considering the role of OT were used in the very small number of studies on the association between OT and PND we were able to identify. Two studies used plasma OT level and two used administration of OT (one with intra-nasal spray and one with intravenous infusion.) This was a major limitation given this was our least represented area, and perhaps the most important when considering if OT could have a treatment role in PND.

Various methods of measuring OT levels were used in the studies we identified. A recent review exploring the validity of peripheral OT level measurement makes a number of important points [94]. This review concludes that the most stringently validated method of measurement is the use of RIA with an extraction step for samples of plasma. Measurement of saliva is more problematic. More recently used, a cheaper and less time laborious method of EIA is producing results two to three times higher, and hasn't been adequately validated for either plasma or saliva processing. It is

important that the field establishes a standard validated method of peripheral OT measurement to compare and make sense of findings.

We acknowledge that considering OT alone is too simplistic and the interaction between OT and other hormones or environmental factors should be considered. One such area is the moderating effects of childhood experience on the efficacy of OT administration. In community samples, absent or reduced pro-social effects of administration of OT were found for participants who had experienced adversity during their childhoods [101-103]. In a clinical sample with a diagnosis of Borderline Personality Disorder, known to have experienced high rates of childhood adversity, the administration of intranasal OT resulted in lower levels of trust and cooperation [104].

Another body of knowledge to consider is the influence of polymorphisms of the oxytocin receptor gene (OXTR) upon mood. A recent meta-analysis explored the contribution of the two most frequently studied single nucleotide polymorphisms (rs53576 and rs2254298) on biology, personality, social behavior, psychopathology and autism. Combined effect sizes did not differ from zero and it was

concluded that the effect of these two polymorphisms fail to account for the aforementioned aspects of human behavior [105].

In terms of investigating the interaction of OT with other hormones, there are several examples. First, the interaction between cortisol and OT has been considered. In a double-blind placebo-controlled study of couple conflict, intranasal administration of OT was associated with lower salivary cortisol level and more positive communication in a conflict situation [106]. This finding is in keeping with previous reports of OT acting to attenuate anxiety [107]. Opposite findings have been reported from a double-blind, placebo-controlled within-subject study of community fathers who were asked to interact with their infant and follow this with a period of forced non-interaction, considered stressful to both parent and infant. In the OT condition salivary cortisol levels were raised after the stressor [108]. It is clear from these opposing findings that the interplay between OT and cortisol is complex and further work needs to be completed to clarify in which contexts OT has an anxiolytic role. It may be the salience of the parenting context which explains the raised

stress response due to the importance for infant survival to receive responsive parenting.

Another hormone of interest which has been considered in conjunction with OT and parenting effects is testosterone. In a within-subject double blinded, randomized placebo controlled trial, more optimal parent-infant interaction was found for fathers with lower baseline plasma testosterone levels. However after administration of intranasal OT, testosterone levels were higher compared with the placebo condition but parenting behaviors were more positive in the OT condition [109].

Given that the serotonin system is implicated in depression, the link between the OT and serotonin systems is also important to consider. Indeed a positive correlation has been found between two peripheral markers of these systems, plasma OT levels and the serotonin transporter [110]. Administration of a serotonergic agonist has also been found to increase plasma OT levels [111]. The complex interplay between a number of neurochemicals has been explored with respect to resilience in children exposed to maltreatment. Resilience has been found to be due to an interaction between variants

of genes related to the OT, serotonin, cortisol and dopamine systems [112]. Participants with specific gene variants of both the OT and serotonergic system (LL-variant of the serotonin transporter polymorphism and the TT variant of the single nucleotide polymorphism rs2268498 on the OXTR) were found to have the lowest scores of negative emotionality [113]. This points to the need to continue sophisticated research, considering the combination of environmental or biological factors, to more fully understand the role of OT. This idea is supported by a very recent review article in the area of molecular genetics and personality [114].

Perhaps the most important future direction in the field of clinical application/practice includes establishing if OT is an effective treatment for PND. This is particularly important given our findings that low plasma OT is associated with increased depressive symptoms; however the administration of OT resulted in poorer mood in at least two studies. An important question to be answered is whether OT is an effective and safe aid in improving the relationship between a depressed mother and her at-risk infant.

Appendix 1.

Detailed description of data extraction

Variable	Description
Subjects	-Participant number -number with a diagnosis of PND -number of controls -gender -infant age
PND diagnosis	-Use of self-report screening questionnaire including cut-off score -clinical interview
Study design	Longitudinal, correlational, RCT etc.
Oxytocin	-Plasma or saliva level, details of laboratory method including use of extraction step. -administered: placebo controlled, dose in IU, time between administration and outcome measure
Intervention	Intervention focus, group or individual, duration and frequency
Main finding	Outcome measure: observed including method of coding observations or self-report

Notes- IU = International Unit, PND = Postnatal depression, RCT = Randomized Controlled Trial

2

Oxytocin in Postnatally Depressed Mothers: Its influence on Mood and Expressed Emotion

Beth L. Mah

Marinus H. Van Ijzendoorn

Roger Smith

Marian J. Bakermans-Kranenburg

Progress in Neuro-Psychopharmacology & Biological Psychiatry

Vol. 40 (2013) 267–272

Abstract

Background: Postnatal depression is common and negatively affects the mother–baby relationship; oxytocin has been found to have positive effects on parenting behavior. We hypothesize that intranasal administration of oxytocin to mothers with depression will influence their parenting related expressed emotion, creating a better basis for sensitive parenting.

Methods: Twenty-five depressed mothers with infants under one year participated in a randomized, double blinded, placebo controlled within subject clinical trial in 2011. Mothers attended an out-patient perinatal psychiatry setting in NSW, Australia. They received 24IU of oxytocin alternating with placebo approximately one week apart in random order, prior to completing outcome measures. The outcome measures were the Five Minute Speech Sample, the Self-Assessment Manikin and the Controlled Oral Word Association Test.

Results: In the oxytocin condition mothers with postnatal depression were sadder (p = .01), more often initially described their babies as

difficult (p = .038) but reported that the quality of their relationship with their infant was greater (p = .036).

Conclusion: Oxytocin did not make depressed mothers happier but their perception of the relationship with their baby improved. Treatment with intranasal oxytocin might show some unwanted side-effects in depressed individuals.

Keywords: Oxytocin, postnatal depression, Expressed Emotion, mood, Self-Assessment Manikin, Randomised Controlled Trial

Introduction

Postnatal depression (PND) is a common mental health problem. A meta-analysis of fifty-nine studies (including 12,810 women) found the prevalence of maternal depression in the early postnatal period to be thirteen percent [1]. Depression during the postnatal period has effects upon the mother, the infant, and the broader family. The disorder affects the mother's mood, thought processes [115] and ability to parent [116]. Children whose mothers experienced chronic depression had various negative outcomes by the beginning of primary school [116]. The current study explores the effects of oxytocin administration on parenting related mood, cognition, and expressed emotion in mothers with a diagnosis of PND.

The processes involved in the ability to parent are complex. One recent area of interest is the oxytocinergic system. Oxytocin (OT) is a hormone and neurotransmitter produced centrally in the paraventricular (PVN) and supra optic nuclei. It functions in the physiological processes of parturition [9], aids social affiliation

processes [11], and is involved in parenting behaviors [12]. Animal studies have shown that maternal behavior such as licking and grooming of pups can be induced or inhibited by central administration of OT or an OT antagonist respectively [117, 118]. In a non-clinical sample plasma OT levels taken during pregnancy and early postpartum were found to be stable and predict maternal bonding behaviors[119]. In addition, maternal OT levels increased after affectionate contact with the infant [120], and this effect was enhanced if the mother had a secure attachment classification [121].

Given the above, understanding associations between OT and depression generally, and PND specifically, is important for potential clinical benefits. Human post mortem studies have documented anatomical and physiological differences in the brains of those previously depressed compared to controls. In previously depressed individuals an increase in the number, size [16] and mRNA concentration [17] of OT neurons in the PVN was found. It is not known whether these differences are a result of depressed mood, or conversely, cause depressive symptoms. However, in living participants, lower plasma OT levels were found to be related to

depressive symptomatology [18]. With regard to PND, in women at risk for developing PND lower plasma OT levels in mid-gestation have been found to be predictive of PND symptoms [19].

Understanding the role of OT in parenting is in its infancy [12]. Initial findings include a significant association between OT levels and the quality of community mothers' interactions with their infants [12]. Studies with intranasal OT administration have added to the body of knowledge, though most of them focused upon non-parents, for whom OT administration has been reported to result in changes in brain function. Exposed to infant cry sounds, brain areas involved in empathy are more activated whilst those related to fear and aversion are attenuated after OT administration [122]. Conversely, during exposure to infant laughter OT reduces activity in brain areas related to emotional arousal whilst enhancing reward areas [123]. Other studies, not using infant cues, have found that OT administration enhances altruism [124], increases duration of gaze to eyes [125] and promotes the ability to interpret social cues [126]; all processes likely to be helpful when parenting an infant. A study

specific to parental behavior found that community fathers were more responsive to their toddlers after administration of OT [15].

In the current study we tested the effects of intranasal OT administration on maternal expressed emotion, mood, and cognitive processes in a double-blind randomized within-subject design with postnatally depressed mothers of 3-12 month old infants. Expressed Emotion (EE) is a construct originally used to establish rates of criticism and emotional over-involvement in relatives of adults with a diagnosis of schizophrenia [127]. Relapse rates are higher if the patient has a relative who either criticizes more frequently or is too emotionally involved (high EE) [127, 128]. In previous research EE was measured using a long semi-structured interview [129]. A shorter version, the Five Minute Speech Sample (FMSS), has been validated and is now widely used [130]. In addition to scoring criticism and emotional over-involvement it also takes into account the quality of the initial statement and the reported quality of the relationship. Studying different age groups, including adolescents [131], and diagnoses other than schizophrenia, such as mood disorders [129], has documented the relevance of EE for a variety of

psychiatric disorders. EE in parents of young children was associated with children's disorganised attachment [132],. In mothers with depressed mood, EE has been found to be higher than in controls [133], and is one factor linked to the intergenerational transmission of depression [134]. To our knowledge no published work has tested the effect of OT administration upon EE. We predict that oxytocin administration will lead to less critical, less over-involved EE, more positive initial statements and greater quality of relationship reported, creating a better basis for sensitive parenting in depressed mothers of infants.

In terms of the effect of intranasal OT administration on emotional experience and mood, it is difficult to compare published results given varying methodologies used. Some studies not specific to parenting found that intranasal OT either did not improve anxiety levels or even increased negativity in response to social situations [23, 135]. Conversely, OT reduced anxiety levels but only if participants coped poorly [136]. OT administration has been found to produce no effect on mood in both a community sample [22] and a clinical sample of participants with anxiety [24]. Given that OT appears to

have either no effect or amplifies mood experience [23], we predict that OT will not improve PND mothers' current mood.

The effect of OT on cognition has been studied both in the peripartum period and in non-parents. Studies reported either no effect, or a negative effect, of either plasma level or administration of OT upon various cognitive processes [137-139]. These studies used different tests of multiple aspects of cognition including visual memory, retention, recall and alertness. OT had a negative effect on recall [137, 138] but no effect could be established when numerous cognitive tests were performed [139]. To our knowledge, no study has explored the effect of OT upon verbal fluency.

The Controlled Oral Word Association Test (COWAT) is a measure of verbal fluency based on inhibitory control [140]. It requires the participant to attend to one task, filtering out extraneous stimuli and suppressing impulses to utter incorrect answers. Debatably, these executive skills are useful for parenting in a demanding setting [141]. No association between plasma oxytocin levels and various cognitive tasks was found in a non-parent sample with a diagnosis of depression [142]. However, participants with

severe depression produce lower scores than controls, and their scores improve if treatment is successful in ameliorating their depressive symptoms [143]. As we expect no effect of OT on current mood, we also expect no effect upon verbal fluency in this depressed cohort.

Finally, given that clinical populations with a diagnosis of PND have experienced increased rates of childhood abuse compared to community samples [144], we examined childhood abuse as a moderator of the effects of OT. Several experiments showed that the effects of OT are moderated by the type of parenting a participant experienced in childhood. Participants with a background of harsh and rejecting parenting seem less affected by intranasal OT administration than their peers with happier childhood experiences. For example, participants (community, non-parents) who had not experienced harsh discipline when they were children used less excessive handgrip force in response to an infant cry in the OT condition. There was no effect of OT on handgrip force if the participant had experienced harsh parenting [145]. In another experiment OT effects on processing facial expression, measured by electroencephalography, were also moderated by past parenting,

specifically maternal love withdrawal. Those participants who had not experienced high rates of love withdrawal were found to have heightened processing of happy and disgusted facial expressions after OT administration, whereas similar effects were absent in the group that had experienced more than average levels of love-withdrawal from the parents [146]. In yet another study individuals with a diagnosis of Borderline Personality Disorder with histories of abuse, became less trustful compared to controls who showed the expected increase in trust after administration of OT [104]. These findings point to the importance of including childhood experiences as a moderator of OT administration effects in clinical populations with an increased prevalence of adverse childhood experience.

In a within-subject study of mothers with a diagnosis of postnatal depression we expected that OT administration would be associated with less criticism about the infant, improved reported quality of relationship with the infant, a more positive initial statement, and less emotional over-involvement during the Five Minute Speech Sample but no improvement to current mood or cognitive performance.

Method

Procedure

Twenty five mothers (mean age 28.24 years, *SD* = 5.93, range 19-38) participated in the randomized double-blind, placebo-controlled, within-subject design. All participants received once intranasal oxytocin and once placebo on two visits with an intervening period of one week. Stenlake Compounding Chemist (Bondi, Australia) produced both the oxytocin and placebo, which contained all components except oxytocin. Sprays were bottled in identical containers for double blind purposes. Roughly half the participants (*n* = 13) received oxytocin during the first visit. Randomisation was conducted using block design and participants were stratified according to whether they were prescribed anti-depressant medication or not. The master file was held by Stenlake pharmacy until completion of the trial. The study protocol was approved by the Hunter New England Human Research Ethics Committee. All mothers gave written informed consent before their

participation. This informed consent included participation of their infant. The participants were recruited from various health agencies, and all had a diagnosis of postnatal depression made by the referring agency. Infants participating in the study were aged between 3 and 12 months (mean age 6.22 months, *SD* = 2.44).

The day before initial attendance, each participant was telephoned and completed the Edinburgh Post Natal Depression Scale (EPNDS) [99] to establish that symptoms were current, with a cutoff score of 12. On arrival a single dose of 24 IU oxytocin or placebo nasal spray was administered (One spray of 12IU per nostril). It has been shown that after intranasal oxytocin administration salivary levels of oxytocin remain elevated for more than two hours[147], which covered the duration of the visits. Forty-five minutes later participants were video-taped whilst interacting with their infants (results reported separately). During the waiting time between intranasal spray and the interaction session on the first visit, the mothers provided written demographic and pregnancy/delivery related information. They also completed a self-report questionnaire to establish occurrence of child abuse and neglect during their past

(Conflict Tactic Scales: Parent-Child Version [148]). During the final part of the interaction session the mothers completed the Self-Assessment Manikin [149], which measures current mood. At the conclusion of the interaction session the Five Minute Speech Sample was administered. This is an audio taped interview designed to elicit mothers' attitudes towards their baby and the relationship that they share. Finally participating mothers completed the Controlled Oral Word Association Test, a test of verbal fluency [150].

Participants underwent both the oxytocin and the placebo condition with an interval of one week in a balanced within-subject design. Both sessions took place within a clinical setting for families with young children (the Parent and Infant Mental Health Service, Wallsend, NSW, Australia).

Participants

Gestational age of the infants ranged from 26 - 41 weeks (mean 38.32, *SD* 3.35). Term babies, as defined by a gestational age between thirty-eight and forty weeks, comprised sixty-four percent (*n*

= 16) of the sample. Seventy-six percent (*n* = 19) of participants had delivered their babies vaginally, as opposed to by Caesarian Section. Birth weights of the infants ranged from 0.90 kg to 4.74 kg (mean 3.26, *SD* 0.90). Fifty-six percent (*n* = 14) of the infants were female. Forty percent (*n* = 10) of the infants were breast-fed.

Seventy-two percent (*n* = 18) of participants were either married or in a de-facto relationship; the remaining mothers were single. In terms of income, sixteen percent were well off, earning more than AUD$100,000 per annum as a household. Thirty-two percent (*n* = 8) of participants lived well under the poverty line, with access to less than AUD$20,000 per year. Twenty-eight percent (n = 7) of participants only completed the four years of high schooling legally required in Australia. Fifty-six percent (*n* = 14) of participants completed six years of high-school, but did not continue further study. Twenty-four percent of participants (*n* = 6) had completed a university degree. Two participants (8%) identified as Aboriginal or of Torres Strait Islander descent.

Sixty percent (*n* = 15) of participants reported that they were receiving treatment for their postnatal depression (*n* = 6 received both

medication and counseling; *n* = 6 received medication alone and *n* = 3 received counseling alone). Of those participants prescribed anti-depressant medication, the duration of administration ranged from one week to four years (mean 9.77 months, *SD* 15.48). Sixty percent (*n* = 15) were prescribed medication for another condition (apart from PND; *n* = 2 antipsychotic; *n* = 4 oral contraceptive pill; others include antibiotics, anti-epileptic, H_2 blocker, thyroid replacement.

Measures

Maternal Depression

The presence of recent depressive symptoms in the mothers was measured using the Edinburgh Post Natal Depression Scale (EPNDS) [99]. Mothers were asked to fill out a questionnaire indicating their level of affective symptoms during the previous week on a 4-point scale. Internal consistency (Cronbach's alpha) was .62. A score of 12 or higher was required for inclusion into our study. Coding occurred using the directions as established by Cox et al. Participants in our study presented on their first visit with scores ranging from 12 to 29 (mean 16.96, *SD* 3.41). Data inspection revealed a single

outlier, which was winsorized by replacing the outlying score with a score just above the next highest value (with $z < .29$) [151].

Childhood Abuse

Self-reported rates of child abuse in our sample was collected using the Conflict Tactic Scales: Parent Child Version [152] which have often been used to establish rates of child abuse [152]. Participants were required to indicate the frequency of occurrence of a parental strategy in the year that they turned thirteen. An example of a prompt is "My mother threw or knocked me down"; separate items are used for both parents. We used the scale for physical aggression. In our sample, internal consistency (Cronbach's alpha) for physical abuse was .84.

Current mood

Mothers completed the Self-Assessment Manikin [149] to rate their current mood. This 3 item, non-verbal, pictorial assessment tool was designed to measure the affective domains of pleasure, arousal and dominance in response to a variety of contexts. It can be used to

measure current mood, as opposed to depression scales which ask a participant to report on mood symptoms over the past week or more. The measure has been validated across adult age groups [153]. Both community participants [154-156] and clinical samples including those with depression [157-160], have been studied. Each domain is examined using five cartoon like drawings depicting a continuum of affective states on three scales: 'Happy to Sad', 'Calm to Agitated' and 'Controlled to In-control'. For these analyses we were interested in the two items most closely aligned to depression, the Happy to Sad scale and the Calm to Agitated scale. The manikin was scored from 1 - 9 with higher scores assigned to 'positive' aspects of the continuum (happy, calm).

Expressed Emotion

The concept of 'expressed emotion' (EE), refers to criticism and emotional over-involvement. The Five Minute Speech Sample [130] is a tool developed to assess high EE in a brief fashion. Participants were audio-taped whilst responding to the following verbal request: *"I'd like to hear your thoughts about [baby's name] in your own*

words and without my interrupting you with any questions or comments. When I ask you to begin, I'd like you to speak for 5 minutes, telling me what kind of a baby [infant's name] is and how the two of you get along together. After you have begun to speak, I prefer not to answer any questions. Are there any questions you would like to ask me before we begin?" The audiotape was subsequently coded by two independent coders and interrater reliability was established by double coding 20% of randomly chosen tapes (mean intraclass correlation = .86 (single measure, absolute agreement), range .84 - .89). The following categories were coded: quality of initial statement, number of criticisms uttered, quality of relationship and number of comments classified as emotional over-involvement [130].

Capacity to attend to a cognitive task

To test the mothers' ability to focus on one task, suppressing other input, the participants completed the Controlled Oral Word Association Test (COWAT) [150]. This is a test of executive cognitions, specifically verbal fluency. Participants were asked to

utter as many words as possible within one minute timed aliquots, from prompted categories. They were asked for words beginning with three separate letters, 'F', 'A', and 'S'; then asked to retrieve as many animals that they could think of. The test was audiotaped for subsequent collation of totals per category. Internal consistencies (standardized scores, Cronbach's alpha) for the first and second visits were .79 and .76, respectively.

Results

A multivariate repeated measures analysis of variance was performed on the four subscales of the Five Minute Speech Sample (FMSS) and the two Self-Assessment Manikin (SAM) mood items as dependent variables with condition (oxytocin or placebo) as a within-subject factor. Results showed an overall effect of oxytocin administration on expressed emotion and mood, $F(6, 18) = 2.76$, $p = .04$, $\eta^2 = .48$. Initially results for expressed emotion will be presented, followed by those for mood.

Univariate analyses showed significant effects for Quality of Relationship, $F(1, 23) = 4.99$, $p = .036$, $\eta^2 = .18$, and for Quality of Initial Statement, $F(1, 23) = 4.83$, $p = .038$, $\eta^2 = .17$. Effects for Emotional Over-Involvement, $F(1, 23) = 0.48$, $p = .50$, $\eta^2 = .02$, and for number of Criticisms uttered, $F(1, 23) = .06$, $p = .82$, $\eta^2 = .00$ were not significant. In the oxytocin condition depressed mothers were more likely to describe their baby as difficult in some way but reported a more positive relationship with their infant. Adding depression as a covariate did not yield a significant effect for depression ($p = .85$), showing that the effect of oxytocin was independent of level of depression at intake. Adding physical abuse as a covariate, and as a potential moderator, did not change results either ($p = .56$ for covariate; $p = .97$ as moderator). The effect of oxytocin upon aspects of expressed emotion was independent of and not moderated by depressed mothers having been physically abused during childhood.

Univariate analyses showed significant effects for the Happy to Sad item, $F(1, 23) = 7.39$, $p = .01$, $\eta^2 = .24$; but effects for the Agitated to Calm scale were not significant, $F(1, 23) = 2.86$, $p = .11$,

$\eta^2 = .11$. In the oxytocin condition mothers with a diagnosis of postnatal depression scored lower, that is sadder than in the placebo condition. Adding depression as a covariate and physical abuse as a covariate or as a moderator did not change the results. The effect of oxytocin on reported mood was independent of both depression at intake and whether the mothers had been physically abused during their childhood. The effect was also not moderated by the experience of severe physical abuse.

Univariate analyses showed no significant effect of oxytocin on performance on the verbal fluency task, $p = .38$. Adding abuse and depression at intake as covariates revealed no significant results ($p = .57$ and $p = .87$, respectively).

Figure 1

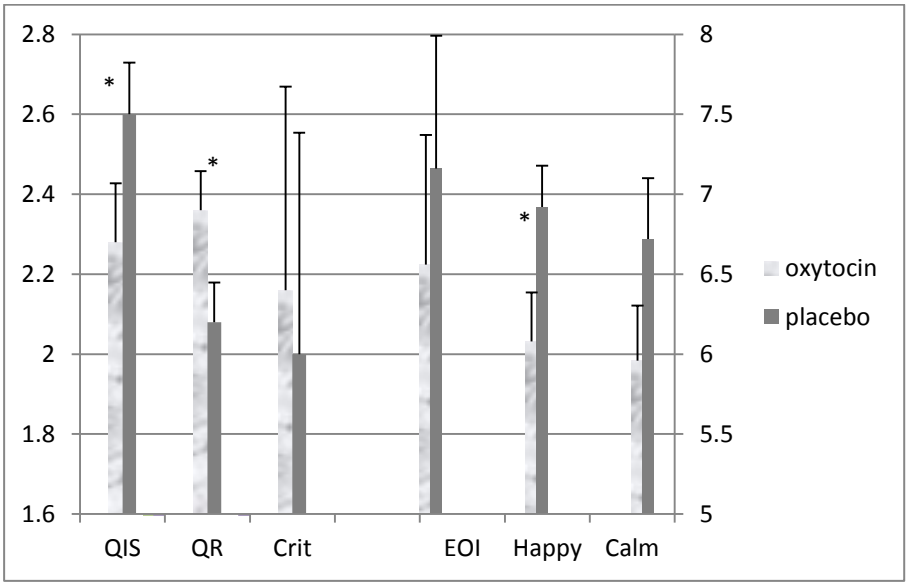


Fig. 1: The effect of oxytocin on expressed emotion and mood (mean, SE). Notes: QIS- quality of initial statement, QR- quality of relationship, Crit- number of criticisms uttered, EOI- emotional over-involvement. *p< .05. For ease of interpretation the first three columns use left and last three columns use right axes respectively.

Discussion

This is the first experiment to test the effects of OT administration on parenting related mood, cognition and expressed emotion in a clinical population with PND. We found that in the OT condition mothers with PND commence their description of their baby more negatively; the same mothers rate the quality of their relationship with their babies as more positive. In addition, after OT

administration, mothers with PND rate current mood as poorer. There was no effect of OT upon cognitive ability as tested by the COWAT.

OT was associated with lower current mood in this depressed sample. In previous studies oxytocin has been shown to increase the salience of a mood state [104, 123, 135], for better or for worse. In postnatally depressed mothers feelings of low mood might always be present in the background, and become more salient after the oxytocin inhalation. This magnifying effect of oxytocin on mood might be more pronounced when participants had been involved in a rather stressful and exhausting situation. In our case participants completed the self-report mood scale moments after being videoed interacting with their baby, a potentially stressful scrutiny. Our finding suggests that the use of OT in populations with depression might not always be positive and should be considered carefully if implemented in a therapeutic context.

We expected that in the OT condition participants would be more positive in their initial description of their baby, as well as more positive about their relationship to the baby in general. Only the latter prediction was borne out by our data. The instruction that participants

were given immediately prior to the commencement of the interview to measure expressed emotion may help us understand the findings. Mothers were asked to 'describe what kind of baby 'x' is and how the two of you get along'. In the OT condition two distinct differences occurred. On the one hand participants' first descriptor of their baby tended to be negative, such as 'he is a poor sleeper' but then more often this was followed up by examples of how closely connected they are in their relationship. An explanation of this seeming discordant response pattern may be that the OT condition enhances trust in the interviewer. OT has been found to enhance trust [124]. Thus the participant may feel more able to be honest about difficult aspects of her baby, but more primed to simultaneously reflect on the value the relationship holds for her. Given all participants were experiencing depressed mood, the presence of both an acknowledgement of how difficult their baby can be, but how connected the two of them feel is particularly poignant.

We predicted that childhood abuse would act as a covariate or moderator of our findings. The results did not support this prediction. A larger study with more statistical power or using alternate method

of collecting abuse data, such as child welfare records, may or may not lead to different results. The inclusion of a wider range of normal to clinical participants with varying childhood experiences might also lead to greater power to find the expected interaction between childhood experiences and oxytocin effects. In our sample only clinically diagnosed cases of postnatally depressed mothers were included which might have led to restriction of range in parenting experiences. Replication in a larger study would add to the reliability of our results.

The findings of this study prompt important questions. Are changes in expressed emotion sustainable, perhaps by the regular therapeutic use of intranasal OT? If EE changes persist, does this lead to enhanced infant outcomes? Future research should also establish if OT generally leads to lower mood in depressed populations which would imply a cautionary note on potentially unwanted side-effects of OT in therapeutic contexts with depressed patients. It should also be examined whether the inferred increased trust in the interviewer indeed can be substantiated and whether this effect generalizes to enhanced trust in therapists that could promote

the alliance between patient and therapist and aid future therapeutic interventions.

Conclusion

Mothers with a diagnosis of postnatal depression after administration of oxytocin, report poorer current mood, state that their baby is more difficult but rate the quality of the relationship with their baby as higher, compared to the placebo condition.

3

Oxytocin Promotes Protective Behavior in Depressed Mothers: A Pilot Study with the Enthusiastic Stranger Paradigm

Beth L. Mah
Marian J. Bakermans-Kranenburg
Marinus H. Van IJzendoorn
Roger Smith
Depression and Anxiety
Article first published online: 12 Feb 2014

Abstract

Background: Successful parenting requires maternal behaviors which promote infant survival such as protection from predators. In animal studies, oxytocin has been linked to maternal aggression to protect offspring. No human study has explored this topic. Mothers with a diagnosis of postnatal depression are at higher risk of neglecting their infants. We hypothesized that intranasal oxytocin administration would increase the protective behaviors of mothers with postnatal depression, towards their infants.

Methods: Sixteen mothers with a diagnosis of postnatal depression participated in a double blind, randomized controlled, within-subject pilot study. Participants received intranasal oxytocin during one visit and placebo spray on the alternate visit. Maternal protective behavior towards their infant was measured, in the presence of a socially intrusive stranger.

Results: The Enthusiastic Stranger Paradigm stimulated participants' protective responses in the presence of an intrusive stranger.

Furthermore, this protective response of mothers with a diagnosis of postnatal depression was increased in the oxytocin condition.

Conclusions: The study introduces a new paradigm, the Enthusiastic Stranger Paradigm, which may be used to examine a neglected type of parental behavior, i.e. protection of offspring. The protective response of mothers with postnatal depression increased, in line with the 'tend and defend' effects of oxytocin in animal models. In future work it should be tested whether this protection effect can also be found in non-clinical samples, or whether it is specific for clinically depressed mothers.

Introduction

There has been a relatively recent upsurge of interest in exploring the role of oxytocin (OT) in human social behaviors generally [161, 162], and parenting behaviors specifically [120]. Most studies exploring the role of OT in parenting behaviors have focused on affiliative aspects (for a review see Galbally et al. [12]). Successful parenting, however, requires both affiliative processes and behaviors which promote survival, such as protection of the infant from predation. In animal studies, OT has been linked to maternal reactive aggression in rodents to protect offspring [163]. As far as we are aware, no study has been completed investigating the role of OT in maternal reactive aggression or protection in humans. It would be interesting to discover if OT functioned in a similar way in humans as has been established for some animal species. Furthermore, it would be important to know if OT has the same protective role in a group of mothers at risk of neglecting their infants, those with a diagnosis of postnatal depression (PND) [164]. Thus, we designed an ethically acceptable paradigm (the Enthusiastic Stranger Paradigm) to measure

protective behaviors in our target population. In this pilot study, we investigated the effects of intranasal OT administration on protective behaviors in a population of mothers with a diagnosis of postnatal depression. Their 3- to 11-month old infants were exposed to a socially intrusive stranger, and the mothers' protective behavior was studied in both OT and placebo conditions in a randomized, double blind, within-subject design.

In animal studies, maternal reactive aggression towards a potential predator in the presence of their young has long been considered an essential maternal behavior [165]. Whilst studied extensively in animals, human behavioral correlates of maternal aggression have been less focused upon. However, the similarities between human mothers' protectiveness of their infants and animal maternal aggression has been commented upon [166]. Given the importance of protection of young to the survival of a species, it is relevant to test the role of OT, if any, in human parental protective behavior. Similarly, very little published work explores the factors involved in maternal protection. Animal studies have found that an identical stress, presenting fox urine, to a postpartum rat dam

produces opposite effects upon hormonal stress systems depending upon whether her pups are present or not [167]. In human studies, much has been published regarding the effects of maternal overprotectiveness upon toddler [168], child [169], and adult outcome [170]. The temperament of the child has been considered as a moderating effect upon levels of maternal protection [171]. However, the construct of maternal 'overprotectiveness' is one that is deemed negative and by definition more protection than that needed given the circumstance. No human studies have attempted to understand the biological aspects of maternal protectiveness. Nor have studies explored changes in level of protectiveness needed according to the age of an infant, to the best of our knowledge.

The association between OT and parenting behaviors was initially established in animal research. Virgin rats, previously with no maternal behavior, after administration of an intraventricular OT injection displayed full maternal behavior. Conversely, maternal behavior ceased following injection of an OT antagonist [118]. In rodents, it has been established that heightened maternal aggression is due to increased central OT production [172]. Research has

continued investigating the link between OT and human parenting behavior. A positive correlation between endogenous OT plasma levels and maternal behavior has been found [119]. Endogenous OT levels increase in mothers after affectionate contact with their infant [120]. Administration of intranasal OT to fathers increased their responsiveness whilst playing with their children [15]. Another study administering intranasal OT found that it increased brain connectivity in response to infant laughter [123].

There are limited studies exploring the associations between OT and depression. Human post mortem studies have found brain differences between those with a past diagnosis of depression compared to controls. Brains of those previously depressed showed an increase in the number, size [16] and mRNA concentration [17] of OT neurons in the paraventricular nucleus. Whether this finding is due to cause or effect of depressive symptomatology is not known. Lower endogenous OT levels have been found to be related to depressive symptoms [18]. In a sample of pregnant women at risk of developing PND, lower plasma OT levels in mid-gestation have been found to be predictive of PND symptoms [173]. Surprisingly, given

these findings, it has been found that the administration of intranasal OT to a cohort of women with a diagnosis of PND resulted in lowered mood [96].

As far as we know, this is the first pilot study designed to test the hypothesis that administration of intranasal OT will increase protective behaviors in human mothers with PND.

Method

Procedure

Sixteen mothers (mean age 26.50 years, *SD* = 4.71, range 19-33), comprising a subgroup of a larger study (results reported separately) participated in a double-blind, placebo-controlled, within-subject design. The participants were recruited from various health agencies, and all had a diagnosis of postnatal depression. Diagnosis was made by clinical interview, using DSM criteria, by the referring agency. Infants participating in the study were aged between 3 and 11 months (mean age 5.81 months, *SD* = 2.32). All participants received intranasal OT and placebo on separate visits, at the same time in the morning, to investigate the effects of OT on protective

behaviors in the presence of an intruding stranger. Stenlake Compounding Chemist (Bondi, Australia) produced both the OT and placebo, bottling the two in identical containers for double blind purposes. Randomisation was conducted using a block design and participants were stratified according to whether they were prescribed anti-depressant medication or not. Roughly half the participants received OT during the first visit. The master file was held by Stenlake pharmacy until completion of the trial. The study protocol was approved by the Hunter New England Human Research Ethics Committee. All mothers gave written informed consent before their participation. This informed consent included their infant.

The day before initial attendance, each participant was telephoned and completed the Edinburgh Post Natal Depression Scale [99] to establish that symptoms were current, with a cutoff score of 12. On arrival a single dose of 24 IU OT or placebo nasal spray was administered, and 55 minutes later the Enthusiastic Stranger Paradigm (ESP) took place. During the waiting time between intranasal spray and the ESP, on the first visit, the mothers provided written demographic and pregnancy/delivery related information. Duration

of intranasal OT effect has been found to last at least two hours [147] and in at least one study strongly elevated levels of salivary oxytocin were found even 7 hours after administration [174]. During both visits, mothers had constant access to their infants, caring for them as needed. Following the ESP a number of other outcome measures were completed. The Cry Paradigm [175], a computer based rating of audio-taped newborn cries; the Five Minute Speech Sample, an interview designed to elicit attitudes towards their baby and the relationship that they share; and the Controlled Oral Word Association Test, a test of verbal fluency [150] were completed. Results have been reported elsewhere [96].

Participants underwent the sessions in the oxytocin and the placebo conditions with an interval of one week in a balanced within-subject design. Both sessions took place within a clinical setting for families with young children (the Parent and Infant Mental Health Service, Wallsend, NSW, Australia).

Participants

Participants with a range of social demographic factors were included in this study (see Table 1). Income levels, educational levels, age of mother and cohabitation status were all broadly represented. Note that three participants were using oral contraceptives (OCP).

Table 1

Participant characteristics

	Mean	SD	Percent
Gestational age	38.25	3.92	
Birth Weight (kg)	3.1	0.97	
Delivery: NVD[a] (vs. Cesarian)			81.3
Gender: Female			55.6
Feeding: Breast fed (vs. bottle fed)			37.5
Family Status: cohabitation (vs. single)			68.8
Annual Household income:			12.5
>AUD$[b]100,000			
<AUD$20,000			31.3
Years of Higher Education	5.28	0.89	
Aboriginal[d]			6.25
Receiving Depression Rx			62.5

[a]NVD= Normal Vaginal Delivery
[b]AUD$=Australian Dollars, location of study was Parent and Infant Mental Health Service, Wallsend, NSW, Australia
[c]Rx=Treatment
[d]Indigenous Australians, who as a group have poorer health, educational and social outcomes compared with non-Indigenous Australians [176].

Measures

Edinburgh Post Natal Depression Scale [99].

This 10-item self-report screening tool to identify depression has a sensitivity of 86% and a specificity of 78% when used with a cutoff score of 12 [99]. A score of 12 or higher was required for inclusion into the study. Coding occurred using the directions as established by Cox et al [99]. Participants' scores ranged from 12 to 29 (mean 16.96, *SD* 3.41) on the first visit. Internal consistency was moderate (α=0.62). At the time of the second visit, the range of scores was 3-24 (mean 13.36, *SD* 5.00). Data inspection revealed a single outlier, which was winsorized by replacing the outlying score with a score just above the next highest value (with $z < 3.29$) [151].

Enthusiastic Stranger Paradigm

This novel video-taped, observer rated measure was developed for the current study to investigate the presence of trusting or conversely protective behaviors by the parent in the face of a socially intrusive female stranger. The mother was unaware that she would

be interrupted by a stranger. The stranger was identifiable as a staff member due to her wearing both a uniform and identification badge. Initially the stranger apologized for the interruption and pretended to be present for the purposes of a work related reason (looking for another staff member on the first visit and checking smoke detectors on the second). Very soon after entering, the stranger noticed the infant on the floor at some distance from its mother, made a comment such as "What a lovely baby" and then moved towards the infant. Strangers had been instructed to seek neither verbal nor non-verbal permission from the mother, but to remain alert to any resistance from the parent. The stranger continued, in an ebullient, socially intrusive manner to attempt to engage the baby, aiming to elicit a number of smiles. The stranger attempted to touch the baby on the shoulder or cheek unless the mother stopped her. The stranger then apologized for the interruption and left the room. Different confederates acted as the enthusiastic stranger during session 1 and session 2. The ESP was videotaped for later coding.

A coding system was developed to assess the video footage. We coded Protectiveness of the mother (5=Active direct attempts to

stop the stranger using motor or verbal behavior, 4=Indirect attempts to stop the stranger, 3=Hypervigilant gaze towards the stranger but no attempt to stop, 2=Intermittent gaze at the stranger, 1=No or brief glances towards the stranger), and the infant's state prior and then during the paradigm, informed by Brazelton's concepts of infant state [177] (5=Distressed, 4=Fussing, 3=A combination of 5 and/or 4 and/or quiet alert, 2=Quiet alert, 1=Drowsy or asleep). To control for variance in the procedure a scale was developed to measure the Intrusiveness of the stranger (5= Extremely intrusive, 4=Intrusive, 3=Moderately intrusive, 2=Mildly intrusive, 1=Not intrusive). Finally, the presence of any External noise intrusion (4=Loud urgent, 3=Loud noticeable, 2=Background, 1=No noise intrusion) was coded.

The duration of the paradigm was defined as the time period from when the stranger uttered "What a lovely baby" to when the stranger apologized for the interruption. The entire paradigm was then watched in portions of 0.2 seconds (5 frames using DVD Player software on a Macintosh computer). For each time aliquot it was recorded whether the mother was attending to either baby/stranger or her questionnaire/the room in general. The ratio of total gaze duration

towards baby/stranger compared to looking elsewhere was calculated (For ease, this will now be referred to as "gaze duration"). The proportion of time the mother watched either the stranger, to see what she was doing to her baby, or gazed at her baby to establish how her baby was coping, was considered important when considering the effects of OT on trusting and protective behaviors. This concept is backed up by research into behavior related to potential threat. Probing the environment and visual checking are established adaptations to ensure security is maintained [178]. The ESP was coded by two independent coders who were blind to OT condition. Both were clinicians with expertise in mother-baby interactions and familiar with the concepts developed by Brazelton [177]. Training for the ESP occurred initially with non-participant video footage. Interrater reliability was established by double coding 20% of tapes (mean intraclass correlation= .91 (single measure, absolute agreement), range .82–.99).

There was no variance in the presence of external noise for either the OT or placebo conditions. For all sessions there was no noise. Average intrusiveness of the stranger in the OT condition was

M= 3.56 (*SD* 0.44); in the placebo condition mean score was M = 3.72 (*SD* 0.77) with higher values indicating more intrusiveness. In the OT condition the state of the baby prior to the ESP was M= 2.19 (*SD* 0.40); during the paradigm, baby state was M=2.06 (*SD* 0.25) with higher scores reflecting a more distressed baby. In the placebo condition, the state of the baby prior to the ESP was M= 2.75 (*SD* 1.18) whilst during the paradigm M= 2.38 (*SD* 0.89). There were no significant differences in stranger intrusiveness nor in baby state before or during the ESP in the oxytocin and placebo condition.

Results

Background variables. Order of visit (OT first, or placebo first) was not associated with mothers' behavior during the ESP. The same was true for the following background variables: baby's gender, mode of delivery, whether the mother received any treatment for her depression (including psychological treatments) and whether the mother was lactating. There was no association between the level of

agitation of the participant in either OT or placebo condition with behavior during the ESP. Similarly, there were no significant effects of either the mother's or the baby's age; the length of the pregnancy, the birth weight, the mother's income or how many years of schooling she had received (all p >.05). There was no correlation between infant age and the protective response of the mother (r = .03).

Seven participants were taking antidepressant medication. Independent samples t-tests revealed that in the placebo condition gaze duration was higher for the group taking an antidepressant (M = .69, SD = .35) than for those not taking an antidepressant (M= .28, SD = .27), $t(14) = 2.63$, p= .02. A similar but not significant trend was found for the OT condition (M = .51, SD = .42 for participants taking an antidepressant and M= .17, SD = .21 if not taking an antidepressant, t(8.4, unequal variances) = 2.01, p= .08). No differences in protectiveness between participants with and without antidepressant medication in either the OT or the placebo condition were found.

Main analysis. A multivariate repeated measures analysis of variance was performed on maternal protectiveness and gaze duration during the Enthusiastic Stranger Paradigm with condition (OT or placebo) as a within-subject factor. The overall effect of OT administration was significant, $F(2, 14) = 4.25$, $p = .036$, $\eta^2 = .38$. In the OT condition mothers were more protective of their baby in the presence of a stranger, but their gaze duration was reduced (see Table 1). Depression was not a significant covariate ($p = .48$), showing that the effect of OT was independent of level of depression at intake. Excluding the three participants taking OCP did not change the effect size either ($\eta^2 = .34$). Testing antidepressant prescription as a factor revealed a non-significant interaction with OT administration ($p = .84$), and the effect size of OT remained unchanged ($\eta^2 = .39$).

Testing any medication prescription as a between-subject factor revealed that the OT effect remained significant ($F(2, 13) = 4.00$, $p = .04$) without a main effect for medication ($F(2, 13) = 2.13$, $p = .16$ or an interaction effect with OT condition ($F(2, 13) = 0.09$, $p = .92$. In sum, the effect of OT on ESP behavior remained significant

after controlling for depressive symptoms, use of OCP, use of antidepressants or any prescribed medication.

Table 1

	OT condition	Placebo condition
Maternal Protectiveness	2.44	2.19
Gaze Duration	0.32	0.45

Mean scores for maternal protectiveness and gaze duration in OT and placebo conditions.

Discussion

It is important to note that this is a pilot study and we present findings which we hope will initiate further research into this highly relevant clinical topic. Mothers with a diagnosis of postnatal depression were more protective in their response to an intrusive stranger after OT administration, but their gaze duration was decreased. This finding is similar to results from animal studies; maternal aggression in the presence of an intruder is enhanced by

intraventricular injection of OT in rodents [179]. To our knowledge, no similar human research had been completed yet, thus this pilot provides an important beginning to understanding the role of OT in maternal protectiveness.

The decrease in mothers' gaze duration after OT administration may seem in contrast with their increased protectiveness. This finding could be explained by the greater activation of mothers in the OT condition. Gaze duration reflected only visual monitoring of the baby and stranger, whereas the scale for protective response included motor and verbal behaviors to prevent the stranger intruding. We found that in the OT condition mothers were more active physically or verbally to protect their baby from social intrusion. Other hypotheses for our findings should be considered. It may be that OT had effects other than protectiveness to explain the decrease in gaze duration. Perhaps there was an effect upon behavior given that participants were challenged with two competing demands at the time of the ESP. They were expected to complete a questionnaire at the same time that the stranger entered. Future studies could remove the requirement for depressed

participants to attend to two tasks at once to clarify this point. The main strength of this study is the methodology employed. The double-blind design and the use of an observed rather than self- report measure adds validity maternal protectiveness assessment. The within-subject design requires fewer research participants to yield sufficient statistical power, ethically the correct methodology when considering exposing depressed mothers to a potentially stressful experience. The within subject design also controls for most confounders. Potential confounders including the state of the baby, the presence of external noise disturbing participants, and whether participants were taking the OCP or antidepressants were all taken into account. Finally, participants were from a clinical population, enhancing our knowledge of a common, debilitating condition which effects capacity to parent, postnatal depression [1, 164]. Clinical studies exploring the effects of OT upon behavioral and social outcomes are rarer than those with student or community samples but represent an important contribution to understanding these conditions and potentially alleviating some related symptoms [180].

One limitation of our pilot is the lack of comparative data from a non-clinical sample. Future research should use larger samples and consider using non depressed controls. Another limitation in our design was the small numbers of participants, which precluded us from sub-classifying depressed groups. A clinically important issue in a depressed cohort is the presence or absence of negative childhood experiences such as abuse and neglect. Some studies have commenced teasing out this question by discovering that subgroups with borderline personality disorder or negative childhood experiences have differential receptiveness to the effects of OT [101, 102, 104, 180]. The finding is that for those with negative childhood experiences, the effects of OT may be either reduced or absent. One proposed mechanism for this reduction in effect is that the early adverse experience may cause epigenetic changes to genes such as the OT receptor gene [180]. It may be that our sample had experienced high rates of early adversity as is common in those with PND [144]. Future larger studies should include a measure of childhood trauma, including neglect. This would help us better understand the variance in child protection risk levels within a depressed population. It is also

vital that future studies explore the ESP using non-clinical samples. This would establish the level of protective behavior that a community sample would show towards their infant.

Clinicians and child protection services alike are interested in maximizing the quality of parenting in depressed populations. Our finding in a pilot sample is an important beginning, but there are many future areas to explore. Repeating this study with community samples, alternate clinical samples (those with anxiety, psychotic or substance use disorders) and a larger depressed cohort sub-grouped into previously traumatized or not, are examples of future directions. Future research could also establish if mothers' protective response changes with infant age, or with alterations to the style of stranger used such as non-uniformed or male strangers. Exploring if there is a gender difference between mothers' and fathers' responses, biological and non-biological parents and primary carer status compared with other important attachment figure would also be interesting.

Conclusion

In conclusion, this is the first pilot study exploring the effects of intranasal OT administration upon the protective behaviors of mothers with postnatal depression towards their infants in the presence of a socially intrusive stranger. We found that the protective response increased, in line with the 'tend and defend' effects of oxytocin in animal and human models[124, 161]. Future research should be developed to further explore this important topic of relevance to clinical, community and child protection populations.

4

The effects of intranasal oxytocin administration on sensitive caregiving in mothers with postnatal depression.

Beth L. Mah
Marinus H. Van IJzendoorn
Dorothee Out
Roger Smith
Marian J. Bakermans-Kranenburg

Submitted for Publication

Abstract

Postnatal depression (PND) is common and negatively affects the mother–infant relationship; oxytocin (OT) has been found to have positive effects on parenting, although negative childhood environments and psychiatric disorders may reduce positive effects of OT administration. Thus, we explored the role of OT in the provision of sensitive caregiving by mothers diagnosed with PND.

A within-subject, randomized controlled double-blind design was used to test the effects of nasal administration of OT or placebo on sensitive caregiving. The outcome measures were perceptual and caregiving responses to prerecorded cry sounds (cry paradigm), as well as observed maternal sensitivity during mother-infant interaction.

We found that in the OT condition mothers with PND were more likely to rate an infant cry as more urgent and they were more likely to indicate they would chose a harsh caregiving strategy in response. There was no effect of OT on maternal sensitive interaction with their own baby. Further research is required prior to consideration of OT administration in depressed mothers of infants.

Introduction

Infants signal their needs to elicit adequate caregiving in numerous ways, and the percentage of time that a caregiver is attuned to the infant's signals has been found to be a powerful predictor of infant socio-emotional development [181]. Infants are able to use a varying repertoire of cues to achieve caregiving, changing their tactic if one strategy fails to achieve the desired result [181]. Ainsworth contributed much to our knowledge in this area, recognizing the importance that for a sensitive response to infant signals caregivers need to accurately perceive and interpret an infant's signal, and respond appropriately to it [182]. Together, these capacities have been labeled Sensitivity. Mothers vary in their caregiving sensitivity, and those who display high maternal sensitivity are more likely to have an infant with a secure attachment and better academic outcomes [116, 183-185]. The current study explores the role of OT in the provision of sensitive caregiving by mothers diagnosed with PND, using a within-subject, randomized controlled double-blind design with nasal administration of OT or placebo.

Sometimes an infant cue is not enough to provoke a needed response. One common situation where this occurs is when a mother has a diagnosis of PND. Arguably two of the most important sensory modalities a caregiver uses to perceive the needs of an infant are the visual perception of the infant's facial expression and the auditory perception of infant vocalizations including crying. Depressed mothers are less likely to accurately identify infants' happy facial expressions [186] and they have a decreased neural response to positive infant signals, such as smiling [5], compared with non-depressed controls. Various features of a newborn's cry communicate to the caregiver the state of the baby, and the urgency of its need for care. Infants born with various medical complications signal their distress with a higher pitched cry compared with well newborns [187, 188]. Observation of caregiver response indicates that in general greater soothing efforts are elicited by higher pitched infant cries [189], however, depressed mothers are less likely to perceive the saliency of higher pitched infants cries [6].

In terms of maternal ability to interpret infant communications, depressed mothers have been found to generally

perceive their infants as more difficult [54, 57], interpret the bond shared as more negative [68], have poorer perceptions of their infants' adaptability [190] and have lower reflective capacity when considering the meaning of their infants' communication [191]. Finally, PND affects the parental response to the infant negatively. At the most serious end of a spectrum of caregiving, depressed mothers are more likely to neglect or use aggressive parenting styles [192], and their infants' mortality rates are higher [8] than those of non-depressed controls. Other important aspects of caregiving are also affected. Depressed mothers have been found to show less positive engagement [54], to have poorer interactions [193], and to be less responsive [57], less attuned [194], less sensitive, and more intrusive with their infants [195]. They also have infants with higher rates of attachment insecurity [195].

The relationship between plasma OT level and aspects of parenting have been studied in community populations. It has been found that plasma OT level during pregnancy and during the postnatal period is positively associated with sensitive parenting [13, 84]. Parental plasma OT level raises during contact with their infant

generally [85] but more marked increases occur for parents who show greater sensitivity of parenting [85]. It seems that other parental aspects contribute to differing levels of OT increase after contact with an infant. Mothers who have high levels of affectionate contact with their babies and fathers who are highly stimulating in their play have the greater OT rise after contact [14]. Mothers' temperaments influence the OT rise; those sensitive to emotion and less schedule driven have greater plasma OT increases than mothers with different temperamental styles [92]. Finally, in terms of adult attachment classification, mothers classified as secure have the greatest plasma OT rise in response to contact with their baby than those whom are classified as non-secure [91].

The link between OT and depression remains unclear. Correlational studies have found lower serum levels of OT in depressed in-patients [196]. Conversely, higher OT levels have been found in adults with major depression [197, 198]. However, correlational research specific to mothers with depression is sparse. Lower plasma OT level during mid-pregnancy predicts a risk for the subsequent development of PND [19, 98]. Outcomes for children

have also been measured when considering the link between OT and PND. By the age of six, children whose mothers were chronically depressed were four times more likely to be diagnosed with an axis I disorder. They also had lower empathy and social skills than control peers. Interestingly, when salivary OT levels were measured in both the children and their chronically depressed mother, levels were lower than controls [2].

Considering the literature exploring associations between OT administration and parenting behaviors, in a community sample, the administration of intranasal OT showed positive impact on parenting behaviors. Fathers displayed greater responsive structuring and were less hostile in the OT condition compared to the placebo condition when interacting with their young children [15]. In a study of non-parents, testing responses to a newborn cry sound, administration of intranasal OT resulted in lower amygdala activation and presumably lower anxiety whilst simultaneously increasing activation in empathy related regions [122]. In another community study of non-parents the effects of OT were explored in association with childhood experiences. Participants were asked to squeeze a hand-grip

dynamometer to a previously learned mid-point, after hearing infant cry sounds. Intranasal OT decreased excessive use of handgrip force but only in those who had not experienced harsh discipline [102]. In psychiatric clinical samples there is a trend of diminished OT effectiveness for subjects diagnosed with various conditions associated with untoward childhood experiences [180]. Thus exploring the effects of OT administration on parenting in mothers with a diagnosis of PND is important.

In a previous report on the current sample administration of intranasal OT caused lower self-reported mood in depressed mothers but at the same time they rated the relationship with their infants as more positive compared with a placebo nasal spray [33]. Given the importance of sensitive parenting and concerns that PND decreases sensitive responsiveness, we tested the following two hypotheses: (1) We expect that the administration of intranasal OT enhances a depressed mother's ability to perceive the urgency of cry sounds, and enhances her intention to choose a sensitive care giving strategy after presentation of cry stimuli; (2) we expect that intranasal OT administration results in improvements in maternal sensitivity in

mothers with PND as observed in interaction with her own young infant. Given the previously documented moderating effect of childhood experiences [101, 102, 180], we explore whether the effects are stronger for mothers with non-abusive backgrounds compared to mothers with childhood experiences of physical abuse.

Method

Procedure

Twenty five mothers (mean age 28.24 years, *SD* = 5.93, range 19-38) participated in the double-blind, placebo-controlled, within-subject design. All participants received intranasal OT and placebo on separate visits to investigate the effects of OT on response to infant crying and the interaction with their child. The participants were recruited from various health agencies, and all had a diagnosis of PND. Infants participating in the study were aged between 3 and 12 months (mean age 6.22 months, *SD* = 2.44). Stenlake Compounding Chemist (Bondi, Australia) produced both the OT and placebo, bottling the two in identical containers for double blind purposes. Roughly half the participants received OT during the first visit.

Randomisation was conducted using block design and participants were stratified according to whether they were prescribed anti-depressant medication or not. The master file was held by Stenlake pharmacy until completion of the trial. The study protocol was approved by the Hunter New England Human Research Ethics Committee. All mothers gave written informed consent before their participation. This informed consent included their infant.

The day before initial attendance, each participant was telephoned and completed the Edinburgh Post Natal Depression Scale (EPNDS [99]) to establish that symptoms were current, with a cutoff score of 12. On arrival a single dose of 24 IU OT or placebo nasal spray was administered. Forty-five minutes later participants completed a video-taped play session to measure Maternal Sensitivity [182]. During the waiting time between intranasal spray and play session, on the first visit, the mothers provided written demographic and pregnancy/delivery related information. They also completed a self-report questionnaire to establish occurrence of child abuse and neglect during their past (Conflict Tactic Scales: Parent-Child Version [152]. The play sessions lasted 10 minutes and included five minutes

each of playing with and without toys. Mothers were given the instruction to 'play with their infant as they normally would at home', knowing they were being videotaped. Immediately following the play session the Cry Paradigm [175], a computer based rating of audio-taped newborn cries, was administered.

Participants underwent both the OT and the placebo conditions with an interval of one week in a balanced within-subject design. Both sessions took place within a clinical setting for families with young children (the Parent and Infant Mental Health Service, Wallsend, NSW, Australia).

Participants

Participants with a range of social demographic factors were included in this study (see Table 1). Income levels, educational levels, age of mother and cohabitation status were all broadly represented. Three participants were using oral contraceptives (OCP).

Table 1

Participant characteristics

	Mean	SD	Percent
Gestational age (weeks)	38.25	3.92	
Birth Weight (kg)	3.1	0.97	
Delivery: NVD[a] (vs. Cesarian)			81.3
Gender: Female			55.6
Feeding: Breast fed (vs. bottle fed)			37.5
Family Status: cohabitation (vs. single)			68.8
Annual Household income:			12.5
>AUD$[b]100,000			
<AUD$20,000			31.3
Years of Higher Education	5.28	0.89	
Aboriginal			6.25
Receiving Depression Rx			62.5

[a]NVD= Normal Vaginal Delivery

[b]AUD$=Australian Dollars

[c]Rx=Treatment

Measures

Edinburgh Post Natal Depression Scale (EPNDS) [99]. This 10-item self-report screening tool to identify depression has a sensitivity of 86% and a specificity of 78% when used with a cutoff score of 12 [99]. A score of 12 or higher was required for inclusion into the study. Coding occurred using the directions as established by Cox et al. [99]. Scores ranged from 12 to 29 (mean 16.96, *SD* 3.41) on the first visit. Internal consistency was moderate (α=0.62). Data inspection revealed a single outlier, which was winsorized by replacing the outlying score with a score just above the next highest value (with $z < 3.29$) [151].

Conflict Tactic Scales: Parent Child Version [152]. The Parent Child version of this scale was developed from a self-report instrument to measure conflict within adult relationships, the Conflict Tactic Scales. Numerous investigators have used the adaptation to establish rates of child abuse [152]. Following the CTS guidelines, participants indicated on an 8-point rating scale the frequency of occurrence of a parental strategy in the year that they turned thirteen. An example of

a prompt is "My mother threw or knocked me down". The 22 items were coded according to the directions given in Straus [152], producing scores in the following categories: Non-violent discipline (deemed to be an optimal parenting strategy in the face of conflict), Psychological aggression, Physical aggression (separated into three levels of severity- minor corporal punishment, severe physical abuse and extreme physical abuse), and Neglect. In our sample, 'severe physical abuse' was spread most evenly with almost half the participants ever having experienced this form of abuse. Because of low variance for the other categories, these scales were not included in the analyses.

Maternal Sensitivity and Non-Intrusiveness Scales [182]. The measure consists of two 9-point rating scales (sensitivity and non-intrusiveness) describing a continuum of maternal interactive behaviors. For the sensitivity scale, a low score corresponds to low maternal sensitivity, when a mother shows extremely limited affective attunement and doesn't seem to consider or recognize her infant as experiencing its own internal state. A high score is given to a mother

who attends closely to the emotional cues given by her baby and responds in a way that maximizes the baby's optimal level of arousal. Using the non-intrusiveness scale a low score is given to a very intrusive mother, such as frequent interference with the baby's interests, wishes and mood. The mother behaves as though she has no respect or awareness that the baby is a separate, autonomous person. A high score is given if the mother cooperates with the activities her baby is interested in, and when needing to shift activities, this mother invites or diverts the baby, scaffolding a mood change. The video footage of the play sessions were coded independently by two trained observers, who were unaware of the condition of the mothers (OT or placebo). Intercoder reliability for sensitivity was .87, for (non-) intrusiveness it was .74 (intraclass correlation, single measure, absolute agreement, $n = 10$). We used one observer's ratings of all first visit play sessions and the other's ratings of all second visit play sessions.

Cry Paradigm. The cry paradigm was administered on a laptop using E-Prime software (Version 1.1; Psychology Software Tools, Inc., PA,

USA). Previously recorded/digitally enhanced infant cry sounds were used, details of which are described by Out et al. [175]. The peak fundamental frequency of the original cry was 515 ± 15 Hz. This was subsequently digitally increased to produce two new cry sounds with overall peak frequencies of 714.5 Hz and 895.8 Hz respectively. Higher fundamental frequencies are generally perceived as more urgent and associated with increased infant arousal [44]. The three cry sounds are referred to as the 500, 700 and 900 Hz cries. Participants listened to the presented sounds at a constant volume via Sennheiser HD 280 Pro headphones. After a trial to familiarize the participant with the equipment, cry stimuli were presented in three cycles; each cycle consisted of the three frequency stimuli. The order of presentation was random within each cycle.

Accompanying each cry sound were questions for the participant to answer, organized into two sections. Four questions pertained to the perception of the cry sound assessing the domains of arousal, aversion, sickness and urgency, as in Out et. al [175]. These domains were rated by use of a 5-point rating scale (e.g.: How urgent do you think this cry is? A score of 1 indicated “not urgent” whereas a

score of 5 indicated “urgent”). As in our sample sickness showed modest item-total correlation we created a scale for Urgency based on arousal, aversion and urgency for each of the fundamental frequencies, with reliabilities reflected by Cronbach’s alphas ranging from .75 to .96 (mean .87). Nine questions pertained to the participants intended caregiving response (How likely is it that you would pick this baby up? A score of 1 indicated it “not likely”, a score of 5 indicated that it was “likely” the participant would pick up the baby in response to hearing such a cry). Caregiving response questions enquired about parenting behaviors; these were grouped into positive (to cuddle, feed, pick up the baby, focus on something else [reversed], wait and see [reversed]), and harsh (to speak firmly, shock, give the baby something to cry about) choices. We added two harsh caregiving items to the original scale used in Out et. Al. [175] to improve reliability and validity of the scale, as it might be of particular interest in our clinical sample. Cronbach’s alphas for intended caregiving responses to cry sounds with the three different fundamental frequencies during the two sessions separately ranged

from .69 to .84 (mean .77) for positive caregiving and from .77 to .98 (mean .93) for harsh caregiving.

Results

Background variables. The following background variables were not associated with mothers' sensitive behavior or cry paradigm outcomes: baby's age, baby's gender, baby's birth weight, duration of gestation, mode of delivery, and whether the mother was lactating. There were also no significant associations between maternal sensitivity or cry paradigm results and how many years of schooling the mother had received, maternal age, and whether she was taking antidepressant medication or not. Income was positively associated with observed sensitivity in the OT condition ($p = .02$), so the analyses for sensitivity were controlled for income. Similarly, the analysis on intended positive caregiving at 900 Hz was controlled for level of depression (EPNDS score at the first visit) to take the positive correlation between the two variables ($p = .04$) into account.

Maternal sensitivity and intrusiveness. A multivariate repeated measures of variance was performed on the sensitivity and non-

intrusiveness scales as dependent variables with condition (OT or placebo) as a within subject factor. The results were not significant (p = .36, η^2 = .04 for maternal sensitivity and p = .45, η^2 = .02 for non-intrusiveness). Income was not a significant covariate, and childhood severe physical abuse did not moderate the effect.

Perception of cry sounds. A multivariate repeated measures of variance with perception as a dependent variable and condition (OT or placebo) as a within-subject factor showed a significant effect of condition for the perception of the 500 Hz cry (F(1,24) = 4.97, p = .04, η^2= .17). Mothers rated the infant cry as more urgent in the OT condition as compared to the placebo condition. Experiences of physical abuse during childhood did not moderate the effect. OT did not significantly affect the perception of the 700 Hz cry or the 900 Hz sound and experiences of physical abuse during childhood did not moderate results for these frequencies either.

Intended care giving. For intended positive caregiving, we did not find an effect of OT for the 500 Hz cry sound, F(1,24) = 0.32, p = .58, η^2= .01. For harsh caregiving however, mothers were more likely to be harsh in the OT condition, F(1,24) = 5.60, p = .03, η^2= .19

(see Figure 1). Results were not moderated by a history of childhood physical abuse. For the other fundamental frequencies (700 Hz and 900 Hz) no effects of OT administration were found. Again findings were not moderated by childhood physical abuse and EPNDS score was not a significant covariate.

Figure 1

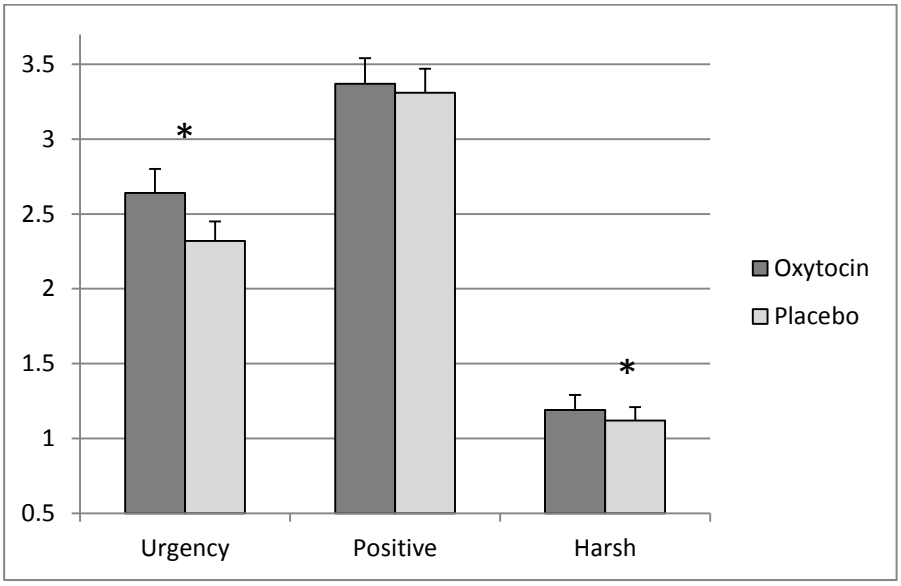


Fig. 1 The effect of oxytocin on cry perception and intended caregiving at 500 Hz (mean, SE). Urgency – perceived urgency of cry, Positive – intended positive caregiving, Harsh – intended harsh caregiving. *$p < .05$.

Discussion

We found that in the OT condition, mothers with a diagnosis of PND rated a naturalistic newborn cry as more urgent than in the placebo condition. We also found that in the OT condition subjects in this clinical sample were more likely to choose a harsh caregiving strategy in response to the 500 Hz cry sound. There was no effect of OT on observed maternal sensitivity.

The combination of perceiving a cry as more urgent but choosing a harsh strategy might indicate that OT enhances a depressed mother's already negative cognitive processes, as has been found previously. In studies on non-clinical subjects, OT seemed to increase the salience of emotional states [104, 122, 135, 199]. In this clinical sample, mothers were more likely to describe their babies as more difficult and reported a lower mood in the OT condition [96] compared to the placebo condition. Of our findings, the most salient was the significant increase in a harsh caregiving choice when asked how the mother imagined she would respond to a cry. Again, other published studies may help us to understand this finding. OT has been found to increase 'non-cooperation' when a partner is

considered a threat in studies using games to assess trust and cooperation in community adults[180]. It may be that a depressed mother is more likely to view a crying infant as some form of threat, even if just to her emotional well-being .

Also worthy of consideration is the fact that in our study there were only significant findings for one of the fundamental frequencies tested, 500 Hz. The influence of genetic factors and cry pitch was investigated using the cry paradigm in a community sample [175] with the same cry sounds. Significant findings showed that adults were more likely to choose a sensitive intended caregiving strategy for the higher pitched cries and when they perceived the cry as more urgent. The 500 Hz cry was a naturalistic recording and both the 700 Hz and the 900 Hz cry were digitally altered to achieve higher pitched cry sounds with identical temporal structure in order to study the effects of cry pitch on adults' perception and caregiving responses. Future research should also use naturalistic high pitched cry recordings to answer the question whether OT has effects in depressed mothers when responding to naturalistic high pitched cry sounds or only at lower pitches.

OT administration did not impact on maternal sensitivity in our clinically depressed sample. What is interesting to consider is the different findings from our study compared to a very similar study using a community sample of fathers [15]. In Naber et. al significant improvements in parent child interactions were found in a smaller sample of seventeen fathers in a within subject, randomized placebo controlled design using an identical OT dose and duration of administration to outcome measure. Based on the effect size reported in the Naber et al. study, the power to find a significant effect in our sample was 78% for an expected positive effect of OT administration on parenting sensitivity. The absence of a significant effect on sensitivity in our sample adds some weight to the current trend found in two recent meta-analytic studies that OT effects are often diminished or absent in clinical samples [180, 199]. One mechanism proposed by Bakermans-Kranenburg et. al. was that early environmental factors which may predispose an individual to depression may cause changes to the OT system by methylation of associated genes [180]. Future research could explore this idea further.

Contrary to our hypotheses, the presence of severe physical abuse during the childhoods' of our participants did not moderate the OT effect in the outcome measures studied. Previous studies finding differential susceptibility to the effects of OT have used various measures of childhood adversity [101, 102, 180]. Bakermans-Kranenburg et. al used the same measure as in the current study, but an alternate subscale, that of harsh discipline [102]. In our sample the most evenly represented domain was severe physical abuse. We were unable to determine if harsh discipline was a potential moderating factor due to the low variance of scores on this construct in our sample. Thus, a more direct comparison using the same subscale as Bakermans-Kranenburg et al. could not be undertaken. Other limitations of our study should also be considered. Our outcome measure of self-reported intended caregiving response could be improved by using observational methods in future studies. Under-reporting of intended harsh caregiving strategies may have occurred due to social desirability [164].

Strengths of our study include its sound research design. Using a within-subject design increases the power without having to

expose a larger number of clinically depressed participants to a hormonal manipulation, an ethically important consideration – although negative side-effects have not been reported so far [200].

In conclusion, this study found that OT has effects on the perception of urgency and on the choice of a parenting strategy in response to infant cry sounds in a sample of mothers with a diagnosis of PND. We found no effect of OT on maternal sensitivity. The finding of increased intended harsh caregiving is important and we should fully explore this association prior to using OT as a pharmacotherapy to enhance parental capacity, especially in a depressed population, as we may induce an iatrogenic effect.

5

General Discussion

Research exploring the role of oxytocin in parenting behavior, had its genesis in animal research. An increase in plasma oxytocin after cervical stimulation in ewes resulted in non-rejecting maternal behavior towards alien lambs even after selective bonding with their own lambs had occurred. The same stimulation also led to commencement of maternal behavior in cycling ewes [201]. Oxytocin plasma concentrations in reproductively naïve male prairie voles, after twenty minute exposure to a pup, increased [202]. Female prairie voles given oxytocin improved their alloparenting behavior [203].

Findings from animal models prompted research in the field of human behavioral science. In humans, intravenous oxytocin has been delivered to a population with a diagnosis of autism, with central effects being found [204, 205]. More commonly, administration of oxytocin via the intranasal route has occurred to ascertain its effect on numerous social outcome measures (e.g., [15, 124, 199]). However, questions remain unanswered regarding the pharmacokinetics involved. The oxytocin molecule doesn't easily cross the blood brain

barrier [206], but has been shown to reach the brain in animal studies [207], with an uptake ratio of about 2% [208] and produce central effects in humans, [122, 123, 206, 209] such as the down regulation of amygdala activation, when delivered intranasally. What remains unknown is the mechanism of this action. Various pathways have been postulated, such as direct diffusion from nasal cavity to cerebrospinal fluid [210] or an indirect peripheral mechanism [206].

Accepting this mechanistic black-box, this thesis broadly explored the associations between oxytocin, maternal sensitivity, maternal protectiveness and postnatal depression in humans. Oxytocin is a neuropeptide produced centrally (but not exclusively) in the paraventricular and supra optic nuclei. It acts in many physiological processes including delivery [9] and breastfeeding [10], it aids social affiliative processes [11] and is involved in parenting behaviors [12] including bonding [119]. Maternal or parental sensitivity is a construct incorporating the ability of a caregiver to accurately perceive and interpret an infant's signal and then the skill

and motivation to choose and carry out an appropriate caregiving response [182]. Mothers vary in their caregiving sensitivity, and those who display high maternal sensitivity are more likely to have an infant with a secure attachment and better academic outcomes [116, 183-185]. Maternal protectiveness, or maternal aggression, as it is referred to in animal literature, is considered an essential component of adequate parenting [165]. This aspect of parenting has been far less focused upon in human studies, however similarities between human mothers' protectiveness of their infants and animal maternal aggression has been commented on [166]. Postnatal depression is a high incidence psychiatric disorder [1] and results in many negative outcomes for the infant [2, 195].

Initially a comprehensive introduction to the topic is provided (Chapter 1). A systematic review was carried out with the aim to understand associations in the following three topic areas: i) postnatal depression and its impact upon parenting, ii) oxytocin and parenting and iii) postnatal depression and oxytocin. This review sought to answer four related questions. Does depression affect the quality of

parenting? Do interventions in a depressed cohort improve parenting? What is the effect of oxytocin on parenting in a community sample? What effects, if any, has oxytocin on postnatal depression?

Chapter 2 considers the effect of administration of oxytocin to a group of mothers with postnatal depression on their mood, Expressed Emotions and verbal fluency. Chapter 3 explores how mothers with postnatal depression behave with respect to their level of protectiveness towards their infant after intranasal oxytocin administration. Chapter 4 reports on study findings which sought to confirm our hypothesis that oxytocin administration to a sample with postnatal depression would improve aspects of sensitive parenting especially if the mother had experienced a supportive childhood. The findings will now be discussed in greater detail.

Mood, Expressed Emotion and Executive Function

The overall hypothesis for this thesis was that oxytocin provided to a sample of mothers with postnatal depression would result in increased caregiving sensitivity. We aimed to break down

aspects of sensitive parenting into relevant components. This chapter explores the mothers' mood, her representations or interpretations of her infant and her executive or frontal lobe function. We considered all these aspects important for caregiving as a sensitive mother has to be in a mood state conducive to response, she needs the ability to both attend to her infant and plan an adequate response and she needs to interpret her infant's communicated need. Twenty-five mothers with postnatal depression with infants under the age of one, participated in a randomized, double-blind, placebo-controlled within-subject clinical study. They received 24IU of oxytocin alternating with placebo approximately one week apart in random order, forty-five minutes prior to completing outcome measures. The diagnosis of depression was initially made by clinical interview but severity and currency of symptoms were established by use of the Edinburgh Postnatal Depression Scale [99], immediately prior to laboratory sessions. The outcome measures were the Self-Assessment Manikin to measure mood [149], the Five Minute Speech Sample which measures Expressed Emotion [130], and the Controlled Oral Word Association Test to examine executive function [150]. In the

oxytocin condition mothers reported feeling sadder. They more often initially described their babies as difficult but reported that the quality of their relationship with their infant was more positive. There were no significant findings when measuring performance on the Controlled Oral Word Association Test for the oxytocin compared to the placebo condition.

This chapter also considers whether there are differential effects of oxytocin, as other studies have found [102, 104, 146], depending upon the quality of childhood the participant experienced. We measured rates of childhood trauma using the Conflict Tactic Scales: Parent and Child Version [148, 152]. We did not find a moderating effect of a childhood history of severe physical abuse on any of the outcome measures.

Maternal Protectiveness

Chapter 3 explores the effects upon maternal protectiveness of intranasal administration of oxytocin in mothers with a diagnosis of postnatal depression. Successful parenting requires parental behaviors that ensure infant survival such as protection from predators. In animal studies, oxytocin has been associated with

maternal aggression to protect offspring [163]. This chapter presents the first findings exploring this topic with human participants (to the best of our knowledge). It is particularly important to consider this in a clinical population as mothers with a diagnosis of postnatal depression are at higher risk of neglecting their infants [164].

Mothers with a diagnosis of postnatal depression received 24IU intranasal oxytocin during one visit and placebo spray on an alternate visit approximately one week apart. Fifty-five minutes later maternal protective behavior toward their infant was measured in the presence of a socially intrusive stranger in a novel procedure; the enthusiastic stranger paradigm. In the oxytocin condition depressed mothers' protective response was increased. This protective response included motor and verbal behaviors to prevent the stranger approaching the infant. Interestingly, in the oxytocin condition, the proportion of time that participants visually monitored the stranger's approach to the infant compared to attending to a questionnaire or gazing around the room was reduced. Pearson's correlation between maternal protectiveness and gaze duration was $r = .66$, $p = .01$. This

seeming discrepant finding will be further discussed in the section considering future directions.

Maternal Sensitivity

In chapter 5 findings are presented exploring the sensitive caregiving of depressed mothers towards their under-one-year-old infants in two ways. Infants signal their needs to elicit adequate caregiving in numerous ways, and the percentage of time that a caregiver is attuned has been found to be a powerful predictor of infant socio-emotional development [181]. Caregivers monitor the needs of their infants using many sensory modalities but two common methods include the visual perception of an infant's facial expression and the auditory perception of the sounds an infant utters. It has been found that depressed mothers are less accurate in both these forms of interpreting the communication cues of an infant [6, 186].

We predicted that in the oxytocin condition depressed mothers would provide more sensitive care to their infant and that this effect would be moderated by the presence of a sub-optimal childhood as found in other studies [101, 102, 180]. As indicated two different outcome measures were used to explore this topic. Perceptual and

caregiving responses to pre-recorded cry sounds (the cry paradigm as described by Out et. al [175]) were collected and analysed in addition to observed, video-taped maternal sensitivity [182] during mother-infant interaction.

In the oxytocin condition mothers with a diagnosis of postnatal depression were more likely to rate an infant cry as more urgent but were also more likely to indicate that they would chose a harsh caregiving strategy in response to the crying. There was no effect of oxytocin administration on maternal sensitive interaction with their baby. The presence of a history of severe physical abuse during childhood did not moderate these findings.

Limitations and future directions

Considering the effects of intranasal oxytocin administration in a clinical cohort is important especially given findings of other researchers of the differential effects of this neuropeptide on different populations [180]. Future studies could expand upon the initial findings presented in this thesis.

One limitation of reporting separately upon subgroups of related outcome measures is that possible associations between effects

were not reported upon. In our sample of mothers, in the OT condition, there was a correlation between the quality of relationship a mother reported and how sensitive and non-intrusive she was observed to be. In the placebo condition, we found an association between how positively a mother initially described her baby and both her protectiveness and the proportion of time spent gazing towards stranger and infant when intruded upon. What is interesting is that such an association was absent in the OT condition. Given our other finding that in the OT condition mothers were more protective but spent less time gazing at their baby, it would be prudent to embark on further research on the associations between maternal representations of her infant, her sensitivity and the way in which she behaves in the enthusiastic stranger paradigm prior to using OT as a treatment in a clinical sample.

The effect of administered oxytocin upon mood needs to be further explored. It is very important to establish if our finding that oxytocin administration results in lower mood can be replicated in a larger cohort and whether this finding holds true for a general adult population with depression. Depression as a clinical construct is

likely to include many sub-sets of symptomatology and individuals [211]. Aspects of participants that future studies could measure and consider include the presence of adverse childhood experiences, premorbid personality and those with differing core symptoms in line with previous findings [92, 104, 146]. This may provide us with a clearer indication of whether particular sub-groups of depressed individuals respond better, or conversely worse to administered oxytocin.

Arguably the most important aspect of interpretation of an infant's cues, the representation a parent has of their infant or the 'Expressed Emotion' is its stability or variability over time. This thesis explored this construct at one specific moment in the mother's experience of parenting. Future studies could explore the effect of oxytocin upon perception of an infant's needs or interpretation of how difficult an infant is over time, such as how long a single administration of oxytocin sustains an improvement in parental representation. Another aspect to consider is what the effect upon the parent-infant relationship is with any change in parental representation.

The effect of oxytocin upon one aspect of executive function was also considered in this thesis. Parental sensitivity requires the parent to attend to the baby's signal, interpret the cue, then plan and carry out an appropriate response [182]. Future research could explore the effect of oxytocin on different executive function outcome measures, especially those requiring the participant to attend whilst there are competing demands, as would be common for parents in a naturalistic setting.

Given established animal literature of the role of oxytocin in maternal aggression [165], future studies could further explore this in humans, using both community and high risk samples. The 'enthusiastic stranger paradigm', developed for use in the study described in this thesis, should be used in a normative sample to establish rates of protectiveness in this setting, both in the oxytocin and placebo conditions. Alternative applications of the paradigm could be considered, such as the use of male, or potentially less trusted strangers, such as those not wearing an identifiable uniform. Other high risk samples could be considered, especially those of interest to child protection agencies, such as substance abusing

parents, parents with a psychotic illness or those with personality disorders [104]. Future studies could also attempt to better understand our finding that depressed mothers were more protective of their infant but they gazed towards their infant for a shorter duration. Further coding of 'gaze' could be developed so that perhaps gaze towards infant and stranger could be separated, although this would require sophisticated filming techniques. An attempt could also be made to rate the emotional quality of the gaze, differentiating anxious from affectionate or interested visual monitoring. Lastly, our finding may have been due to the fact that our participants were asked to complete a competing task. Future studies could design an experiment without this requirement and see whether the results replicate.

Our finding that in the oxytocin condition, depressed mothers were more likely to choose a harsh caregiving strategy in response to a pre-recorded infant cry sound is a particularly concerning result. This finding could motivate future research, replicating with larger numbers of depressed mothers, sub-classifying depressed mothers to establish if there is a differential effect such as childhood trauma to

explain this finding. In a larger sample it could be tested if the group with lower mood were more likely to use a harsh strategy or if this was a general oxytocin effect.

Finally further studies could consider the role of administered oxytocin in parental sensitivity. It would be very interesting to establish if fathers' sensitivity was enhanced in at least two contexts, those with depression in the postnatal period as well as those whose spouses are depressed [58]. Different clinical populations could be considered too, in particular those with anxiety disorders, psychotic illness, or personality disorder. Of course the effect of oxytocin on psychiatric symptom severity should also be observed/established in these groups concurrently [96].

Previous research has commented upon the effects on salience effects of administered oxytocin [104, 123, 135]. It seems that oxytocin may enhance the predominant emotional state of an individual. This idea may help to explain some of our discrepant results. Depressed mood may be worsened, a crying baby may increase the agitation and thus result in the choice of a harsher caregiving strategy and more focus may be given to how difficult a

baby is perceived to be, if the mother is already depressed, when oxytocin is administered.

In addition to various postulated pathways for intranasally administered oxytocin to result in central effects, concerns have been raised regarding the lack of standardisation between research studies with respect to intranasal administration. Guastella et. al. published guidelines on the use of intranasal administration of oxytocin after we had completed our experiment [15]. They noted that one limitation in this area of research is the capacity to control dosing and absorption. To this end they make numerous recommendations to standardize research approach to increase comparability between studies. Examples of recommendations include the exclusion of participants with septal deviation or a history of nasal congestion; reporting of details of the nasal spray formulation including its pH; the use of an enhancer; a concentrated dose and instructions to participants to ensure maximum delivery to olfactory epithelium, located in a specific area of the nasal passage [15]. These recommendations should be followed in future.

Conclusion

The current thesis provides insight into associations between oxytocin, sensitive parenting and maternal protectiveness in a cohort of mothers with a diagnosis of postnatal depression. The current findings alert us to the need for further research prior to consideration of clinical application of intranasal oxytocin administration to mothers with postnatal depression in an attempt to improve aspects of their parenting. This thesis demonstrated that there are a number of positive outcomes of using oxytocin in this clinical population. In the oxytocin condition, depressed mothers report that the quality of the relationship with their baby is better, they are more protective of their infant in the face of a socially intrusive stranger, and they rate a pre-recorded infant cry sound as more urgent. However, these findings need to be considered in concert with the negative results: In the oxytocin condition, depressed mothers report feeling sadder, they rate their babies as more difficult, and they indicate that are more likely to choose a harsh caregiving strategy in response to a pre-recorded infant cry sound.

These findings have obvious psychiatric and child protection implications. The presence of a maternal diagnosis of postnatal depression increases the risk of child abuse [7, 144]. This increased risk has been established for participants not exposed to oxytocin administration. Administration of oxytocin via the intranasal route has been found to increase salivary levels for at least seven hours [174]. We have clear ethical and moral obligations to both research participants and psychiatric patients, to conduct further research to explore the effect of oxytocin on ongoing mood and ability to parent in a non-abusive way, for a population with postnatal depression. It is clear that we would wish to avoid the iatrogenic clinical and parenting effects of worsening an already depressed mother's mood or inducing harsh parental behavior.

In conclusion this thesis provides important insights into the effects of oxytocin on parenting related outcome measures in a cohort of clinically depressed mothers. More research should be embarked upon prior to advocacy of the use of oxytocin in mothers with a diagnosis of postnatal depression.

References

1. O'Hara, M.W. and A.M. Swain, *Rates and risk of postpartum depression-a meta-analysis.* International Review of Psychiatry, 1996. **8**(1): p. 37.
2. Apter-Levy, Y., et al., *Impact of Maternal Depression Across the First 6 Years of Life on the Child's Mental Health, Social Engagement, and Empathy: The Moderating Role of Oxytocin.* American Journal of Psychiatry, 2013. **Vol.170**(10): p. 1161-1168.
3. Murray, L. and P.J. Cooper, *The impact of postpartum depression on child development.* International Review of Psychiatry, 1996. **8**(1): p. 55.
4. Arteche, A., et al., *The effects of postnatal maternal depression and anxiety on the processing of infant faces.* Journal of Affective Disorders, 2011. **133**(1-2): p. 197-203.
5. Wonch, K.E., et al., *The neural correlates of maternal responsiveness to infant cues in mothers with and without postpartum depression.* Biological Psychiatry, 2012. **71**(8): p. 310S-311S.
6. Schuetze, P. and P.S. Zeskind, *Relations between women's depressive symptoms and perceptions of infant distress signals varying in pitch.* Infancy, 2001. **2**(4): p. 483-499.
7. Sagami, A., M. Kayama, and E. Senoo, *The relationship between postpartum depression and abusive parenting behavior of Japanese mothers: a survey of mothers with a child less than one year old.* Bulletin of the Menninger Clinic, 2004. **68**(2): p. 174-87.
8. Chen, Y.H., S.Y. Tsai, and H.C. Lin, *Increased mortality risk among offspring of mothers with postnatal depression: a nationwide population-based study in Taiwan.* Psychological Medicine, 2011. **41**(11): p. 2287-2296.
9. Chard, T., *An introduction to radioimmunoassay and related techniques*. 4 ed. 1990, Amsterdam: Elsevier.

10. Carter, C.S., et al., *Oxytocin: Behavioral Associations and Potential as a Salivary Biomarker.* Annals of the New York Academy of Sciences, 2007. **1098**(1): p. 312-322.
11. Meyer-Lindberg, A., et al., *Oxytocin and vasopressin in the human brain: social neuropeptides for translational medicine.* Nature, 2011. **12**(September): p. 525-538.
12. Galbaly, M., et al., *The role of oxytocin in mother-infant relations: A systemic review of human studies.* Harvard Review of Psychiatry, 2011. **19**(1): p. 1-14.
13. Feldman, R., et al., *Evidence for a Neuroendocrinological Foundation of Human Affiliation: Plasma Oxytocin Levels Across Pregnancy and the Postpartum Period Predict Mother-Infant Bonding.* Psychological Science (Wiley-Blackwell), 2007. **18**(11): p. 965-970.
14. Feldman, R., et al., *Natural variations in maternal and paternal care are associated with systematic changes in oxytocin following parent–infant contact.* Psychoneuroendocrinology, 2010. **35**(8): p. 1133-1141.
15. Naber, F., et al., *Intranasal oxytocin increases fathers' observed responsiveness during play with their children: A double-blind within-subject experiment.* Psychoneuroendocrinology, 2010. **35**(10): p. 1583-1586.
16. Purba, J.S., et al., *Increased number of vasopressin and oxytocin expressing neurons in the paraventricular nucleus of the hypothalamus in depression.* Archives of General Psychiatry, 1996. **53**(2): p. 137-143.
17. Meynen, G., et al., *Hypothalamic oxytocin mRNA expression and melancholic depression.* Molecular Psychiatry, 2007. **12**(2): p. 118-119.
18. Gordon, I., et al., *Oxytocin and cortisol in romantically unattached young adults: Associations with bonding and psychological distress.* Developmental Psychobiology, 2008. **50**(7): p. 728.
19. Skrundz, M., et al., *Plasma oxytocin concentration during pregnancy is associated with development of postpartum depression* Neuropsychopharmacology, 2011. **36**: p. 1886-1893.

20. Liu, J.C.J., R.A. McErlean, and M.R. Dadds, *Are We There Yet? The Clinical Potential of Intranasal Oxytocin in Psychiatry.* Current Psychiatry Reviews, 2012. **8**(1): p. 37-48.
21. Mah, B.L., et al., *Oxytocin in postnatally depressed mothers: its influence on mood and expressed emotion.* Prog Neuropsychopharmacol Biol Psychiatry, 2013. **40**: p. 267-72.
22. Kirsch, P., et al., *Oxytocin modulates neural circuitry for social cognition and fear in humans.* Journal of Neuroscience Methods, 2005. **25**(49): p. 11489-11493.
23. Rockliff, H., et al., *Effects of intranasal oxytocin on 'Compassion Focused Imagery'.* Emotion, 2011. **11**(6): p. 1388-1396.
24. Labuschagne, I., et al., *Oxytocin attenuates amygdala reactivity to fear in generalized anxiety disorder.* Neuropsychopharmacology, 2010. **35**: p. 2403-2413.
25. Molyneaux, E., et al., *Obestiy and Mental Disorders During pregnancy and Postpartum: A Systematic Review and Meta-analysis.* Obstetrics and Gynecology, 2014. **123**(4): p. 857-867.
26. Delahaije, D.H.J., et al., *Anxiety and depression following preeclampsia or hemolysis, elevated liver enzymes, and low platelets syndrome. A systematic review.* Acta Obstetricia et Gynecologica Scandinavica, 2013. **92**(7): p. 746-761.
27. Bryn, M.A. and S. Penckofer, *Antenatal Depression and Gestational Diabetes: A review of Maternal and Fetal Outcomes.* Nursing for Women's Health, 2013. **17**(1): p. 22-33.
28. Davis, K. and S. Dimidjian, *The Relationship Between Physical Activity and Mood Across the Perinatal Period: A Review of Naturalistic and Clinical Research to Guide Future Investigation of Physical Activity-Based Interventions for Perinatal Depression.* Clinical Psychology: Science and Practice, 2012. **19**(1): p. 27-48.
29. Ross, L.E., et al., *Risk for postpartum depression associated with assisted reproductive technologies and multiple births.* Human Reproduction Update, 2011. **17**(1): p. 96-106.
30. Daley, A.J., C. MacArthur, and H. Winter, *The Role of Exercise in Treating Postpartum Depression: A Review of the*

Literature. Journal of Midwifery and Women's Health, 2007. **52**(1): p. 56-62.
31. Kleiber, B. and S. Dimidjian, *Postpartum Depression Among Adolescent Mothers: A Comprehensive Review of Prevalence, Course, Correlates, Consequences and Interventions.* Clinical Psychology: Science and Practice, 2014. **21**(1): p. 48-66.
32. Clare, C.A. and J. Yeh, *Postpartum Depression in Special Populations: A Review.* Obstetrical and Gynecological Survey, 2012. **67**(5): p. 313-323.
33. Gulamani, S.S., et al., *A Review of Postpartum Depression, Preterm Birth, and Culture.* Journal of Perinatal and Neonatal Nursing, 2013. **27**(1): p. 52-59.
34. Villegas, L., et al., *Postpartum Depression Among Rural Women From Developed and Developing Countries: A Systematic Review.* Journal of Rural Health, 2011. **27**(3): p. 278-288.
35. Qui, j. and Z. Xiao, *Reproductive-related depression in women: A review of two decades of research in China.* Asia-Pacific Psychiatry, 2010. **2**(1): p. 19-25.
36. Cox, J., *Review: Preventing and treating postpartum depression in women- a municipality model.* Journal of Research in Nursing, 2012. **17**(2): p. 157-158.
37. Freed, R.D., et al., *Enhancing Maternal Depression Recogntion in Health Care Settings: A Review of Strategies to Improve Detection, Reduce Barriers, and Reach Mothers in Need.* Families, Systems and Health, 2012. **30**(1): p. 1-18.
38. Vliegen, N., S. Casalin, and P. Luyten, *The Course of Postpartum Depression: A Review of Longitudinal Studies.* Harvard Review of Psychiatry, 2014. **22**(1): p. 1-22.
39. Ng, R.C., et al., *Pharmacologic Treatment for Postpartum Depression: A Systematic Review.* Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy, 2010. **30**(9): p. 928-941.
40. Hewitt, C.E. and S.M. Gilbody, *Is it clinically and cost effective to screen for postnatal depression : a systematic review of controlled clinincal trials and economic evidence.* British Journal of Obstetrics and Gynaecology: An

Internationsl Journal of Obstetrics and Gynaecology, 2009. **116**(8): p. 1019-1027.
41. Hendicks, K. and J. Liu, *Childbearing Depression and Childhood Aggression: Literature Review.* American Journal of Maternal Child Nursing, 2012. **37**(4): p. 253-261.
42. Misri, S. and K. Kendrick, *Perinatal Depression, Fetal Bonding, and Mother-Child Attachment: A Review of the Literature.* Current Pediatric Reviews, 2008. **4**(2): p. 66-70.
43. Veening, J.G.a.b. and B.a. Olivier, *Intranasal administration of oxytocin: Behavioral and clinical effects, a review.* Neuroscience & Biobehavioral Reviews, 2013. **37**(8): p. 1445-1465.
44. MacDonald, K.M.D. and T.M.R.N. MacDonald, *The Peptide That Binds: A Systematic Review of Oxytocin and its Prosocial Effects in Humans.* Harvard Review of Psychiatry January/February, 2010. **18**(1): p. 1-21.
45. Gaustella, A.J. and C. MacLeod, *A critical review of the influence of oxytocin nasal spray on social cognition in humans: Evidence and future directions.* Hormones & Behavior, 2012. **61**(3): p. 410-418.
46. Viero, C., et al., *REVIEW: Oxytocin: Crossing the Bridge between Basic Science and Pharmacotherapy.* CNS: Neuroscience & Therapeutics, 2010. **16**(5): p. e138-e156.
47. De Dreu, C.K.W., *Oxytocin modulates cooperation within and competition between groups: An integrative review and research agenda.* Hormones & Behavior, 2012. **61**(3): p. 419-428.
48. Galbally, M.M.M.P.M.F., et al., *The Role of Oxytocin in Mother-Infant Relations: A Systematic Review of Human Studies.* Harvard Review of Psychiatry, 2011. **19**(1): p. 1-14.
49. Cochran, D.M.M.D.P., et al., *The Role of Oxytocin in Psychiatric Disorders: A Review of Biological and Therapeutic Research Findings.* Harvard Review of Psychiatry September/October, 2013. **21**(5): p. 219-247.
50. Maguire, S., et al., *Oxytocin and Anorexia Nervosa: A Review of the Emerging Literature.* European Eating Disorders Review, 2013. **21**(6): p. 475-478.

51. Stavropoulos, K.K.M. and L.J. Carver, *Research Review: Social motivation and oxytocin in autism - implications for joint attention development and intervention.* Journal of Child Psychology & Psychiatry, 2013. **54**(6): p. 603-618.
52. MacDonald, K. and D. Feifel, *Oxytocin in schizophrenia: a review of evidence for its therapeutic effects.* Acta Neuropsychiatrica, 2012. **24**(3): p. 130-146.
53. Alder, E. and J. Truman, *Counselling for postnatal depression in the voluntary sector.* Psychology and Psychotherapy: Theory, Research and Practice, 2002. **75**(Pt 2): p. 207-20.
54. Campbell, S.B., et al., *Course and correlates of postpartum depression during the transition to parenthood.* Development and Psychopathology, 1992. **4**(1): p. 29-47.
55. Chabrol, H., N. Bron, and J. LeCamus, *Mother-infant and father-infant interactions in postpartum depression.* Infant Behavior & Development, 1996. **19**(1): p. 149-152.
56. Crockenberg, S.C. and E.M. Leerkes, *Parental acceptance, postpartum depression, and maternal sensitivity: mediating and moderating processes.* Journal of Family Psychology, 2003. **17**(1): p. 80-93.
57. Forman, D.R., et al., *Effective treatment for postpartum depression is not sufficient to improve the developing mother-child relationship.* Development and Psychopathology, 2007. **19**(2): p. 585-602.
58. Goodman, J.H., *Influences of maternal postpartum depression on fathers and on father-infant interaction.* Infant Mental Health Journal, 2008. **29**(6): p. 624-643.
59. Goodman, S.H., et al., *Treatment of postpartum depression in mothers: secondary benefits to the infants.* Infant Mental Health Journal, 2008. **29**(5): p. 492-513.
60. Hasselmann, M.H., G.L. Werneck, and C.V. Silva, *Symptoms of postpartum depression and early interruption of exclusive breastfeeding in the first two months of life.* Cadernos de saude publica, 2008. **24 Suppl 2**: p. S341-52.
61. Herrera, E., N. Reissland, and J. Shepherd, *Maternal touch and maternal child-directed speech: effects of depressed mood in the postnatal period.* Journal of Affective Disorders, 2004. **81**(1): p. 29-39.

62. Horowitz, J.A., et al., *Promoting responsiveness between mothers with depressive symptoms and their infants.* Journal of Nursing Scholarship, 2001. **33**(4): p. 323-9.
63. Horowitz, J.A., et al., *Nurse home visits improve maternal/infant interaction and decrease severity of postpartum depression.* Journal of Obstetric, Gynecologic, & Neonatal Nursing, 2013. **42**(3): p. 287-300.
64. Loh, C.-C. and P. Vostanis, *Perceived mother-infant relationship difficulties in postnatal depression.* Infant and Child Development, 2004. **13**(2): p. 159-171.
65. Murray, L., et al., *Controlled trial of the short- and long-term effect of psychological treatment of post-partum depression: 2. Impact on the mother-child relationship and child outcome.* British Journal of Psychiatry, 2003. **182**: p. 420-427.
66. Murray, L., A. Fiori-Cowley, and R. Hooper, *The impact of postnatal depression and associated adversity on early mother-infant interactions and later infant outcome.* Child Development, 1996. **67**: p. 2512-2526.
67. Milgrom, J., *Parenting stress and postnatal depression.* Stress Medicine, 1996. **12**(3): p. 177-186.
68. Noorlander, Y., V. Bergink, and M.P. van den Berg, *Perceived and observed mother-child interaction at time of hospitalization and release in postpartum depression and psychosis.* Archives of Womens Mental Health, 2008. **11**(1): p. 49-56.
69. Onozawa, K., et al., *Infant massage improves mother-infant interaction for mothers with postnatal depression.* Journal of Affective Disorders, 2001. **63**(1-3): p. 201-207.
70. Paris, R., R.E. Bolton, and E. Spielman, *Evaluating a home-based dyadic intervention: Changes in postpartum depression, maternal perceptions and mother-infant interactions.* Infant Mental Health Journal, 2011. **32**(3): p. 319-338.
71. Paris, R., R.E. Bolton, and M.K. Weinberg, *Postpartum depression, suicidality, and mother-infant interactions.* Archives of Womens Mental Health, 2009. **12**(5): p. 309-21.
72. Paulson, J.F., S. Dauber, and J.A. Leiferman, *Individual and combined effects of postpartum depression in mothers and*

fathers on parenting behavior. Pediatrics, 2006. **118**(2): p. 659-68.
73. Pritchard, M.A., et al., *Six-week postnatal depression predicts parenting stress profiles in mothers of preterm children.* Journal of Reproductive and Infant Psychology, 2012. **30**(3): p. 303-311.
74. Puckering, C., et al., *Mellow Babies: A group intervention for infants and mothers experiencing postnatal depression.* Counselling Psychology Review, 2010. **25**(1): p. 28-38.
75. Reissland, N., J. Shepherd, and E. Herrera, *The pitch of maternal voice: a comparison of mothers suffering from depressed mood and non-depressed mothers reading books to their infants.* Journal of Child Psychology and Psychiatry and Allied Disciplines, 2003. **44**(2): p. 255-61.
76. Seimyr, L., et al., *In the shadow of maternal depressed mood: experiences of parenthood during the first year after childbirth.* Journal of Psychosomatic Obstetrics and Gynaecology, 2004. **25**(1): p. 23-34.
77. Smith, J.C., A. Cumming, and S. Xeros-Constantinides, *A decade of parent and infant relationship support group therapy programs.* International Journal of Group Psychotherapy, 2010. **60**(1): p. 59-89.
78. Stanley, C., L. Murray, and A. Stein, *The effect of postnatal depression on mother-infant interaction, infant response to the Still-face perturbation, and performance on an Instrumental Learning task.* Development and Psychopathology, 2004. **16**(1): p. 1-18.
79. Stein, A., et al., *The relationship between post-natal depression and mother-child interaction.* British Journal of Psychiatry, 1991. **158**: p. 46-52.
80. Væver, M.S., et al., *Measuring spatial proximity in mother-infant interaction: a kinematic approach for an examination of the effects of maternal postpartum depression.* Infant Behavior & Development, 2013. **36**(3): p. 427-31.
81. Wan, M.W., et al., *Attitudes and adjustment to the parental role in mothers following treatment for postnatal depression.* Journal of Affective Disorders, 2011. **131**(1-3): p. 284-92.

82. Weinberg, M.K., et al., *Effects of maternal depression and panic disorder on mother-infant interactive behavior in the face-to-face still-face paradigm.* Infant Mental Health Journal, 2008. **29**(5): p. 472-491.
83. Zajicek-Farber, M.L., *Postnatal Depression and Infant Health Practices Among High-Risk Women.* Journal of Child and Family Studies, 2009. **18**(2): p. 236-245.
84. Feldman, R., I. Gordon, and O. Zagoory-Sharon, *Maternal and paternal plasma, salivary, and urinary oxytocin and parent-infant synchrony: considering stress and affiliation components of human bonding.* Developmental Science, 2011. **14**(4): p. 752-761.
85. Feldman, R., I. Gordon, and O. Zagoory-Sharon, *The cross-generation transmission of oxytocin in humans.* Hormones and Behavior, 2010. **58**(4): p. 669-676.
86. Feldman, R., et al., *Sensitive Parenting Is Associated with Plasma Oxytocin and Polymorphisms in the OXTR and CD38 Genes.* Biological Psychiatry, 2012. **72**(3): p. 175-181.
87. Gordon, I., et al., *Oxytocin, cortisol, and triadic family interactions.* Physiology & Behavior, 2010. **101**(5): p. 679-684.
88. Gordon, I., et al., *Oxytocin and the Development of Parenting in Humans.* Biological Psychiatry, 2010. **68**(4): p. 377-382.
89. Gordon, I., et al., *Prolactin, Oxytocin, and the development of paternal behavior across the first six months of fatherhood.* Hormones and Behavior, 2010. **58**(3): p. 513-518.
90. Naber, F., et al., *Brief Report: Oxytocin Enhances Paternal Sensitivity to a Child with Autism: A Double-Blind Within-Subject Experiment with Intranasally Administered Oxytocin.* Journal of Autism & Developmental Disorders, 2013. **43**(1): p. 224-229.
91. Strathearn, L., et al., *Adult Attachment Predicts Maternal Brain and Oxytocin Response to Infant Cues.* Neuropsychopharmacology, 2009 **34**: p. 2655-2666.
92. Strathearn, L., et al., *Maternal oxytocin response during mother–infant interaction: Associations with adult temperament.* Hormones and Behavior, 2012. **61**(3): p. 429-435.

93. Weisman, O., O. Zagoory-Sharon, and R. Feldman, *Oxytocin Administration to Parent Enhances Infant Physiological and Behavioral Readiness for Social Engagement.* Biological Psychiatry, 2012. **72**(12): p. 982-989.
94. McCullough, M.E., P.S. Churchland, and A.J. Mendez, *Problems with measuring peripheral oxytocin: Can the data on oxytocin and human behavior be trusted?* Neuroscience and Biobehavioral Reviews, 2013 **37**: p. 1485– 1492.
95. Hinshaw, K., et al., *A randomised controlled trial of early versus delayed oxytocin augmentation to treat primary dysfunctional labour in nulliparous women.* BJOG: An International Journal of Obstetrics & Gynaecology, 2008. **115**(10): p. 1289-1296.
96. Mah, B.L., et al., *Oxytocin in postnatally depressed mothers: Its influence on mood and expressed emotion.* Progress in Neuro-Psychopharmacology & Biological Psychiatry, 2013. **40**: p. 267-272.
97. Skrundz, M., et al., *Plasma Oxytocin Concentration during Pregnancy is associated with Development of Postpartum Depression* Neuropsychopharmacology, 2011. **36**(9): p. 1886-1893.
98. Stuebe, A.M., K. Grewen, and S. Meltzer-Brody, *Association Between Maternal Mood and Oxytocin Response to Breastfeeding.* Journal of Women's Health, 2013. **22**(4): p. 352-361.
99. Cox, J.L., J.M. Holden, and R. Sagovsky, *Detection of postnatal depression: development of the 10-item Edinburgh Postnatal Depression Scale.* British Journal of Psychiatry, 1987. **15**: p. 782-786.
100. Gibson, J., et al., *A systematicc review of studies validating the Edinburgh Postnatal Depression Scale in antepartum and postpartum women.* Acta Psychiatrica Scandinavica, 2009. **119**(5): p. 350-364.
101. van IJzendoorn, M.H., et al., *The impact of oxytocin administration on charitable donating is moderated by experiences of parental love-withdrawal.* . Frontiers in Psychology, 2011. **2**(258): p. 1-8.

102. Bakermans-Kranenburg, M.J., et al., *Oxytocin decreases handgrip force in reaction to infant crying in females without harsh parenting experiences.* Social Cognitive and Affective Neuroscience, 2012. **7** (8): p. 951-957.
103. Riem, M.M.E., et al., *Does intranasal oxytocin promote prosocial behavior to an excluded fellow player? A randomized controlled trial with Cyberball.* Psychoneuroendocrinology, 2013. **38**(8): p. 1418-1425.
104. Bartz, J., et al., *Oxytocin can hinder trust and cooperation in borderline personality disorder.* Social Cognitive and Affective Neuroscience, 2011. **6**(5): p. 556-563.
105. Bakermans-Kranenburg, M.J. and M.H. van IJzendoorn, *A sociability gene? Meta-analysis of oxytocin receptor genotype effects in humans.* Psychiatric Genetics, 2014. **24**(2): p. 45-51.
106. Ditzen, B., et al., *Intranasal Oxytocin Increases Positive Communication and Reduces Cortisol Levels During Couple Conflict.* Biological Psychiatry, 2009. **65**: p. 728-731.
107. Heinrichs, M., et al., *Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress.* Biological Psychiatry, 2003. **54**(12): p. 1389-1398.
108. Weisman, O., O. Zagoory-Sharon, and R. Feldman, *Oxytocin administration alters HPA reactivity in the context of parent–infant interaction.* European Neuropsychopharmacology, 2013. **23**: p. 1724–1731.
109. Weisman, O., O. Zagoory-Sharon, and R. Feldman, *Oxytocin administration, salivary testosterone, and father–infant social behavior.* Progress in Neuro-Psychopharmacology & Biological Psychiatry, 2014. **49**: p. 47-52.
110. Marazziti, D., et al., *A link between oxytocin and serotonin in humans: Supporting evidence from peripheral markers.* European Neuropsychopharmacology, 2012. **22**: p. 578–583.
111. Lee, R., et al., *Plasma oxytocin in response to pharmaco-challenge to D-fenfluramine and placebo in healthy men.* Psychiatry Research, 2003. **30**: p. 129–136.
112. Cicchetti, D. and F.A. Rogosch, *Gene by Environment Interaction and Resilience: Effects of Child Maltreatment and Serotonin, Corticotropin Releasing Hormone, Dopamine, and*

Oxytocin Genes. Developmental Psychopathology, 2012. **24**(2): p. 411–427.
113. Montag, C., et al., *Interaction of 5-HTTLPR and a Variation on the Oxytocin Receptor Gene Influences Negative Emotionality.* Biological Psychiatry, 2011. **69**(6): p. 601–603.
114. Montag, C. and M. Reuter, *Disentangling the molecular genetic basis of personality: From monoamines to neuropeptides.* Neuroscience and Biobehavioral Reviews, 2014. **43**: p. 228–239.
115. Stein, A., et al., *Maternal cognitions and mother-infant interaction in postnatal depression and generalized anxiety disorder.* Journal of Abnormal Psychology, 2012.
116. Campbell, S.B., et al., *Trajectories of maternal depressive symptoms, maternal sensitivity, and children's functioning at school entry.* Developmental Psychology, 2007. **43**(5): p. 1202-1215.
117. Pedersen, C.A. and A.J. Prange, *Induction of maternal behavior in virgin rats after intracerebroventricular administration of oxytocin.* Proceedings of the National Academy of Sciences of the United States of America, 1979. **76**(12): p. 6661-6665.
118. van Leengoed, E., E. Kerker, and H. Swanson, *Inhibition of post-partum maternal behaviour in the rat by infecting an oxytocin antagonist into the cerebral ventricles.* Journal of Endocrinology, 1987. **112**(2): p. 275-282.
119. Feldman, R., et al., *Evidence for a neuroendocrinological foundation of human affiliation: Plasma oxytocin levels across pregnancy and the postpartum period predict mother-infant bonding.* Psychological Science, 2007. **18**(11): p. 965-970.
120. Feldman, R., et al., *Natural variations in maternal and paternal care are associated with systemic changes in oxytocin following parent-infant contact.* Psychoneuroendocrinology, 2010. **I35**(8): p. 1133-1141.
121. Strathearn, L., et al., *Adult attachment predicts matenal brain and oxytocin response to infant cues.* Neuropsychopharmacology, 2009. **34**(13): p. 2655-66.
122. Riem, M.M.E., et al., *Oxytocin modulates amygdala, insula, and inferior frontal gyrus responses to infant crying: A*

randomized controlled trial. Biological Psychiatry, 2011. **70**(3): p. 291-297.
123. Riem, M.M.E., et al., *No laughing matter: Intranasal oxytocin administration changes functional brain connectivity during exposure to infant laughter.* Neuropsychopharmacology, 2012. **37**(5): p. 1257-1266.
124. De Dreu, C.K.W., et al., *The neuropeptide oxytocin regulates parochial altruism in intergroup conflict among humans.* Science 2010. **328**: p. 1408-1411.
125. Guastella, A.J., P.B. Mitchell, and M.R. Dadds, *Oxytocin increases gaze to the eye region of human faces.* Biological Psychiatry, 2008. **63**(1): p. 3-5.
126. Domes, G., et al., *Oxytocin improves "mind-reading" in humans.* Biological Psychiatry, 2007. **61**(6): p. 731-733.
127. Brown, G.W., J.L.T. Birley, and J.K. Wing, *Influence of family life on the course of schizophrenic disorders: A replication.* British Journal of Psychiatry, 1972. **121**.
128. Lenior, M.E., D.H. Linszen, and M.A.J. Dingemans, *The association between parental expressed emotion and psychotic relapse: applying a quantitative measure for expressed emotion.* International Clinical Psychopharmacology, 1998. **13 Supplement**(1): p. S81-S88.
129. Hooley, J.M. and H.A. Parker, *Measuring expressed emotion: An evaluation of the shortcuts.* Journal of Family Psychology, 2006. **20**(3): p. 386-396.
130. Magaña, A.B., et al., *A brief method for assessing expressed emotion in relatives of psychiatric patients.* Psychiatry Research, 1986. **17**(3): p. 203-212.
131. Hale, W.W., III, et al., *How does longitudinally measured maternal expressed emotion affect internalizing and externalizing symptoms of adolescents from the general community?* Journal of Child Psychology and Psychiatry and Allied Disciplines, 2011. **52**(11): p. 1174-1183.
132. Jacobsen, T., E. Hibbs, and U. Ziegenhain, *Maternal expressed emotion related to attachment disorganization in early childhood: A preliminary report.* Journal of Child Psychology and Psychiatry and Allied Disciplines, 2000. **41**(7): p. 899-906.

133. Bolton, C., et al., *Expressed emotion, attributions and depression in mothers of children with problem behaviour.* Journal of Child Psychology & Psychiatry & Allied Disciplines, 2003. **44**(2): p. 242-254.
134. Gibb, B.E., et al., *Children's inferential styles, 5-HTTLPR genotype and maternal expressed emotion-criticism: An integrated model for the intergenerational transmission of depression.* Journal of Abnormal Psychology, 2009. **118**(4): p. 734-745.
135. Alvares, G.A., I.B. Hickie, and A.J. Guastella, *Acute effects of intranasal oxytocin on subjective and behavioral responses to social rejection.* Experimental & Clinical Psychopharmacology, 2010. **18**(4): p. 316-321.
136. Cardoso, C., et al., *Coping style moderates the effect of intranasal oxytocin on the mood response to interpersonal stress.* Experimental & Clinical Psychopharmacology, 2011.
137. Ferrier, B.M., D.J. Kennet, and M.C. Devlin, *Influence of oxytocin on human memory processes.* Life Sciences, 1980. **27**(24): p. 2311-2317.
138. Kennett, D.J., M.C. Devlin, and B.M. Ferrier, *Influence of oxytocin on human memory processes: Validation by a control study.* Life Sciences, 1982. **31**(3): p. 273-275.
139. Silber, M.r., et al., *Temporary peripartal impairment in memory and attention and its possible relation to oxytocin concentration.* Life Sciences, 1990. **47**(1): p. 57-65.
140. Benton, A.L., K.D. Hamsher, and A.B. Sivan, *Multilingual aphasia examination. Manual of instructions*. 3 ed. 2000, Iowa City: AJA Associates.
141. Van IJzendoorn, M.H., M.J. Bakermans-Kranenburg, and J. Mesman, *Dopamine system genes associated with parenting in the context of daily hassles.* Genes, Brain and Behavior, 2008. **7**(4): p. 403-410.
142. Van Londen, L., et al., *Neuropsychological performance and plasma cortisol, arginine vasopressin and oxytocin in patients with major depression.* Psychological Medicine, 1998. **28**(2): p. 275-284.

143. Douglas, K.M.P., et al., *Neuropsychological changes and treatment response in severe depression.* British Journal of Psychiatry, 2011. **198**(2): p. 115-122.
144. Ammermann, R.T., et al., *PTSD in depressed mothers in home visitation.* Psychological Trauma, 2012. **4**(2): p. 186-195.
145. Bakermans-Kranenburg, M.J., et al., *Oxytocin decreases handgrip force in reaction to infant crying in females without harsh parenting experiences.* Social Cognitive and Affective Neuroscience, 2011.
146. Huffmeijer, R., et al., *Love withdrawal is related to heightened processing of faces with emotional expressions and incongruent emotional feedback: Evidence from ERPs.* Biological Psychology, 2011. **86**: p. 307-313.
147. Huffmeijer, R., et al., *Salivary levels of oxytocin remain elevated for more than two hours after intranasal oxytocin administration.* Neuroendocrinology Letters, 2012. **33**: p. 21-25.
148. Straus, M.A., et al., *The revised conflict tactics scales (CTS2): Development and preliminary psychometric data.* Journal of Family Issues, 1996. **17**: p. 283-316.
149. Bradley, M.M. and P.J. Lang, *Measuring emotion: The self-assessment manikin and the semantic differential.* Journal of Behavior Therapy and Experimental Psychiatry, 1994. **25**(1): p. 49-59.
150. Benton, A.L. and K.S. Hamsher, *Multilingual aphasia examination manual*. 1976, Iowa City, IA: University of Iowa.
151. Tabachnick, B.G. and L.S. Fidell, *Using multivariate statistics*. Fifth Edition ed. 2007, Boston, MA: Pearsons Education, Inc.
152. Straus, M.A., S.L. Hamby, and W.L. Warren, *The conflict tactics scales handbook. Revised conflict tactic scales (CTS2). CTS:parent-child version (CTSPC)*. 2003, Los Angeles, CA: Western Psychological Services.
153. Backs, R.W., S.P. da Silva, and K. Han, *A comparison of younger and older adults' Self-Assessment Manikin ratings of affective pictures*. Experimental Aging Research, 2005. **31**: p. 421-440.

154. Gallo, I.S., et al., *Strategic automation of emotion regulation.* Journal of Personality and Social Psychology, 2009. **96**(1): p. 11-31.
155. Hillman, C., K.S. Rosengren, and D.P. Smith, *Emotion and motivated behavior: postural adjustments to affective picture viewing.* Biological Psychology, 2004. **66**: p. 51-62.
156. Bradley, M.M., et al., *Rembering pictures: Pleasure and arousal in memory.* Journal of Experimental psychology, 1992. **18**(2): p. 379-390.
157. Casado, Y., et al., *Emotional processing in obsessive-compulsive disorder.* Journal of Anxiety Disorders, 2011. **25**: p. 1068-1071.
158. Terhaar, J., et al., *Increased sensitivity to heat pain after sad mood induction in female patients with major depression.* European Journal of Pain, 2010. **14**: p. 559-563.
159. Moe`, A. and M. Sarlo, *Who finds neutral pictures pleasant and relaxing?* International Journal of Psychology, 2011. **46**(2): p. 97-105.
160. Sloan, D.M. and A.R. Sandt, *Depressed mood and emotional responding.* Biological Psychology, 2010. **84**: p. 368-374.
161. Carter, C.S., *Neuroendocrine Perspectives on Social Attachment and Love.* Psychoneuroendocrinology, 1998. **23**(8): p. 779-818.
162. Bos, P.A., et al., *Acute effects of steroid hormones and neuropeptides on human social–emotional behavior: A review of single administration studies.* Frontiers in Neuroendocrinology, 2012. **33**(1): p. 17-35.
163. Bosch, O.J., et al., *Brain Oxytocin Correlates with Maternal Aggression: Link to Anxiety.* J. Neurosci., 2005. **25**(29): p. 6807-6815.
164. Kotch, J.B., et al., *Predicting child maltreatment in the first 4 years of life from characteristics assessed in the neonatal period.* Child Abuse and Neglect, 1999. **23**(4): p. 305-319.
165. Rosenblatt, J., E. Factor, and A. Mayer, *Relationship between maternal aggression and maternal care in the rat.* Aggressive Behavior, 1994. **20**: p. 243-255.
166. Hrdy, S., *Mother Nature: Natural Selection and the Female of the Species*. 1999, London: Chatto and Windus.

167. Deschamps, S., B. Woodside, and C.D. Walker, *Pups presence eliminates the stress hyporesponsiveness of early lactating females to a psychological stress representing a threat to the pups.* Journal of Neuroendocrinology, 2003. **15**: p. 486–497.
168. Kiel, E.J. and K.A. Buss, *Associations among Context-Specific Maternal Protective Behavior, Toddler Fearful Temperament, and Maternal Accuracy and Goals.* Social Development, 2012 **21**(4): p. 742–760.
169. Stein, D., et al., *Parent-child bonding and family functioning in depressed children and children at high risk and low risk for future depression.* Journal of the American Academy of Child and Adolescent Psychiatry, 2000. **39**(11): p. 1387-95.
170. Oshino, S., et al., *Influences of parental rearing on the personality traits of healthy Japanese.* Comprehensive Psychiatry, 2007. **48**(5): p. 465-469.
171. Kiel, E.J. and K.A. Buss, *Prospective Relations among Fearful Temperament, Protective Parenting, and Social Withdrawal: The Role of Maternal Accuracy in a Moderated Mediation Framework.* Journal of Abnormal Child Psychology, 2011. **39**(7): p. 953-966.
172. Nephew, B.C., et al., *Enhanced Maternal Aggression and Associated Changes in Neuropeptide Gene Expression in Multiparous Rats.* Behavioral Neuroscience, 2009. **123**(5): p. 949-957.
173. Skrundz, M., et al., *Plasma oxytocin concentration during pregnancy is associated with development of postpartum depression.* Neuropsychopharmacology, 2011. **36**(9): p. 1886-1893.
174. van IJzendoorn, M.H., et al., *Elevated Salivary Levels of Oxytocin Persist More than 7 h after Intranasal Administration.* Frontiers in Neuroscience, 2012. **6**(174): p. 1-6.
175. Out, D., et al., *Intended sensitive and harsh caregiving responses to infant crying: The role of cry pitch and perceived urgency in an adult twin sample.* Child Abuse and Neglect, 2010. **34**: p. 863-873.

176. Australian Bureau of Statistics, *Australian demographic statistics*. 2010: Canberra.
177. Brazelton, T.B. and J.K. Nugent, *Neonatal Behavioral Assessment Scale*. 3 ed. Clinics in Developmental Medicine No. 137, ed. M.C.O. Bax. 1995, London: Cambridge University Press.
178. Woody, E.Z. and H. Szechtman, *A biological security motivation system for potential threats: are there implications for policy-making?* Frontiers in Human Neuroscience, 2013. **9**(7).
179. Pedersen, C.A., *Biological aspects of social bonding and the roots of human violence.* Annals of the New York Academy of Sciences, 2004. **1036**: p. 106-127.
180. Bakermans-Kranenburg, M.J. and M.H. van IJzendoorn, *Sniffing around oxytocin: review and meta-analyses of trials in healthy and clinical groups with implications for pharmacotherapy.* Translational Psychiatry, 2013. **3**: p. e258.
181. Tronick, E., *Neurobehavioral and Social-Emotional Development of Infants and Children*. 2007, New York: W.W. Norton and Co.
182. Ainsworth, M.D.S., et al., *Patterns of attachment. A Psychological Study of the Strange Situation.Maternal Sensitivity Scale*. 1978, Hillsdale, NJ: Lawrence Erlbaum.
183. NICHD, E.C.C.R.N., *Child-Care and Family Predictors of Preschool Attachment and Stability From Infancy.* Developmental Psychology, 2001. **37**(6): p. 847-862.
184. Bakermans-Kranenburg, M.J., M.H. van Ijzendoorn, and F. Juffer, *Less Is More: Meta-Analyses of Sensitivity and Attachment Interventions in Early Childhood.* Psychological Bulletin, 2003. **129**(2): p. 195-215.
185. De Wolff, M.S. and M.H. van Ijzendoorn, *Sensitivity and attachment: A meta-analysis on parental antecedents of infant attachment.* Child Development, 1997. **68**(4): p. 571.
186. Arteche, A., et al., *The effects of postnatal maternal depression and anxiety on the processing of infant faces.* Journal of Affective Disorders, 2011. **133**: p. 197-203.
187. Zeskind, P.S. and B.M. Lester, *Acoustic features and auditory perceptions of the cries of newborns with prenatal and*

perinatal complications. Child Development, 1978. **49**: p. 580-589.
188. Michelsson, K., P. Sirvio, and O. Wasz-Hockert, *Sound spectographic cry analysis of infants with bacterial meningitis.* Developmental Medicine and Child Neurology, 1977. **19**: p. 309-315.
189. Zeskind, P.S. and V. Collins, *Pitch of infant crying and caregiver responses in a natural setting.* Infant Behavior and Development, 1987. **10**: p. 501-504.
190. Clark, R., A. Tluczek, and A. Wenzel, *Psychotherapy for postpartum depression: A preliminary report.* American Journal of Orthopsychiatry, 2003. **73**(4): p. 441-454.
191. Vik, K. and 26., *Postnatal depression, mother-infant interaction and video interaction guidance.* European Psychiatry, 2011. **26**.
192. Sagami, A., M. Kayama, and E. Senoo, *The relationship between postpartum depression and abusive parenting behavior of Japanese mothers: a survey of mothers with a child less than one year old.* Bulletin of the Menninger Clinic, 2004. **68**(2): p. 174-187.
193. Clark, R., *Theoretical basis, development, structure and efficacy of the mother-infant therapy group model of treatment for postpartum depression.* Archives of Women's Mental Health, 2011. **14**: p. S14.
194. Reissland, N., J. Shepherd, and E. Herrera, *The pitch of maternal voice: a comparison of mothers suffering from depressed mood and non-depressed mothers reading books to their infants.* Journal of Child Psychology & Psychiatry, 2003. **44**(2): p. 255-261.
195. Cooper, P.J., et al., *Improving quality of mother-infant relationship and infant attachment in socioeconomically deprived community in South Africa: randomised controlled trial.* British Medical Journal, 2009. **338**: p. b974.
196. Ozsoy, S., E. Esel, and M. Kula, *Serum oxytocin levels in patients with depression and the effects of gender and antidepressant treatment.* Psychiatry Research, 2009. **169**(3): p. 249-252.

197. Parker, K.J., et al., *Preliminary evidence that plasma oxytocin levels are elevated in major depression.* Psychiatry Research, 2010. **178**(2): p. 359-362.
198. Holt-Lunstad, J., W. Birmingham, and K.C. Light, *The influence of depressive symptomatology and perceived stress on plasma and salivary oxytocin before, during and after a support enhancement intervention.* Psychoneuroendocrinology, 2011. **36**(8): p. 1249-1256.
199. Cochran, D.M., et al., *The role of oxytocin in psychiatric disorders: A review of biological and therapeutic research findings.* Harvard Review of Psychiatry, 2013. **21**(5): p. 219-247.
200. MacDonald, K.S., et al., *Oxytocin improves social cognition in depressed patients with high attachment anxiety.* Biological Psychiatry, 2011. **69**(9): p. 279S-280S.
201. Keverne, E.B., et al., *Vaginal stimulation: an important determinant of maternal bonding in sheep.* Science, 1983. **219**(4580): p. 81-83.
202. Kenkel, W.M., et al., *Neuroendocrine and behavioral responses to an infant in male Prairie Voles.* Journal of Neuroendcrinology, 2012. **24**: p. 874-886.
203. Bales, K.L., et al., *Oxytocin has dose-dependent developmental effect on pair-bonding and alloparental care in female prairie voles.* Hormones and Behavior, 2007. **52**: p. 274-279.
204. Hollander, E., et al., *Oxytocin infusion reduces repetitive behaviours in adults with autistic and Asperger's disorders.* Neuropsychopharmacology, 2003. **28**: p. 193-198.
205. Hollander, E., et al., *Oxytocin increases retention of social cognition in autism.* . Biological Psychiatry, 2007. **61**: p. 498-503.
206. Evans, S.L., et al., *Intranasal oxytocin effects on social cognition: A critique.* Brain Research, 2013. **In Press**.
207. Neumann, I.D., et al., *Increased brain and plasma oxytocin after nasal and peripheral administration in rats and mice.* Psychoneuroendocrinology, 2013. **38**(10): p. 1985-1993.
208. Ermisch, A., et al., *On the blood-brain barrier to peptides: accumulation of labelled vasopressin, DesGlyNH2-*

vasopressin and oxytocin by brain regions. Endocrinol Exp., 1985. **19**(1): p. 29-37.
209. Baumgartner, T., et al., *Oxytocin Shapes the Neural Circuitry of Trust and Trust Adaptation in Humans.* Neuron, 2008. **58**(4): p. 639-650.
210. Guastella, A.J., et al., *Recommendations for the standardisation of oxytocin nasal administration and guidelines for its reporting in human research.* Psychoneuroendocrinology, 2013. **38**(5): p. 612-625.
211. Forgeard, M.J.C., et al., *Beyond Depression: Towards a Process-Based Approach to Research, Diagnosis, and Treatment.* Clinical Psychology (New York), 2011. **18**(4): p. 275-299.

Samenvatting (Summary in Dutch)

Dit proefschrift richt zich op de invloed van oxytocine op ouderschap van moeders met een diagnose van postnatale depressie. Het eerste hoofdstuk is een algemene inleiding op het overkoepelende thema van postnatale depressie, oxytocine en ouderschap. In dit hoofdstuk staat een systematische review beschreven van onderzoek naar drie onderling verwante thema's: 1) het effect van postnatale depressie op de kwaliteit van ouderschap, 2) relaties tussen oxytocine en ouderschap, en 3) de relatie tussen oxytocine en postnatale depressie. Aan de hand van de review wordt geprobeerd een antwoord te geven op vier vragen: Is depressie van invloed op opvoedingskwaliteit? Zijn interventies in een depressieve populatie effectief in het verbeteren van de opvoedingskwaliteit? Wat is het effect van oxytocine op opvoedingsgedrag in niet-klinische groepen? Wat zijn de effecten van oxytocine op postnatale depressie?

De review laat zien dat moeders met postnatale depressie meer opvoedingsstress rapporteren dan moeders zonder postnatale

depressie, dat zij zich minder competent voelen en minder in staat om opvoedingsproblemen het hoofd te bieden. Hun houding ten opzichte van hun kinderen is in vergelijking met niet-depressieve moeders ook negatiever. In termen van opvoedingsgedrag stoppen moeders met postnatale depressie eerder met borstvoeding geven, en zijn ze minder dan niet-depressieve moeders gericht op activiteiten die de gezondheid en de ontwikkeling van hun kind stimuleren. De meerderheid van de experimentele studies laat positieve effecten zien van psychologische interventies voor moeders met postnatale depressie op de kwaliteit van de moeder - kind interactie. De review lijkt er ook op te wijzen dat oxytocine een aanvullende rol kan spelen in het verbeteren van de kwaliteit van de ouder-kind interactie. Resultaten voor de relatie tussen oxytocine en postnatale depressie waren echter inconsistent. Lagere oxytocineniveaus in plasma hangen samen met een meer depressieve symptomen, maar de toediening van oxytocine resulteert in hogere depressiescores.

In een empirische studie hebben we de effecten van de toediening van oxytocine bij een groep moeders met postnatale

depressie onderzocht. We deden dat met een gerandomiseerd, dubbel-blind, within-subject design, waarbij de participanten via een neusspray één maal oxytocine en één maal een placebo-oplossing kregen toegediend, met een tussenliggende periode van ongeveer een week. Vijfentwintig depressieve moeders met kinderen jonger dan een jaar namen deel aan deze studie. Moeders werden geworven via een psychiatrie-instelling voor ambulante perinatale zorg in Newcastle, Australië. Deelnemende moeders ontvingen ofwel 24IU oxytocine ofwel een placebo in willekeurige volgorde: de ene helft van de moeders kreeg oxytocine bij het eerste bezoek en placebo bij het tweede bezoek, de andere helft van de moeders kreeg de placebo bij het eerste bezoek en oxytocine bij het tweede bezoek. De volgende drie hoofdstukken rapporteren over de bevindingen van dit gerandomiseerde experiment.

Hoofdstuk 2 beschrijft het effect van toediening van oxytocine op de stemming van de moeders, op hun 'expressed emotions' (dat wil zeggen de manier waarop zij over hun kind praten), en op hun verbale vaardigheid. In de oxytocineconditie

hadden moeders met postnatale depressie nog meer depressieve klachten, en ze beschreven hun baby's als moeilijker, maar niettemin meldden ze dat de kwaliteit van de relatie met hun kind goed was, beter dan wanneer zij die beoordeelden in de placebo conditie.

In Hoofdstuk 3 staat de vraag centraal hoe moeders met postnatale depressie zich gedragen als het gaat om beschermend gedrag ten opzichte van hun kind. We ontwikkelden daartoe een nieuwe procedure, de Enthusiastic Stranger Paradigm. In deze procedure worden beschermende reacties uitgelokt door het optreden van een opdringerige onbekende persoon die actief met de baby probeert te interacteren. We vonden dat moeders met een diagnose van postnatale depressie na oxytocinetoediening meer beschermend voor hun kind waren dan in de placeboconditie.

Hoofdstuk 4 betreft bevindingen van de experimentele studie met betrekking tot sensitief opvoedingsgedrag. We hadden verwacht dat toediening van oxytocine aan moeders met een postnatale depressie sensitief ouderschap zou verbeteren, vooral als

de moeder in haar eigen jeugd goede ondersteuning van haar ouders had ervaren (er zijn namelijk aanwijzingen in de literatuur dat vroege ervaringen het effect van oxytocine kunnen modereren). We vonden dat in de oxytocineconditie moeders met postnatale depressie het geluid van een huilende baby als meer urgent ervoeren dan in de placeboconditie. Ze gaven dan echter ook vaker aan een hardhandige aanpak te zullen toepassen in reactie op zulk huilen. Er was geen effect van oxytocine op moeders' geobserveerde sensitieve responsiviteit in de interactie met hun kind tijdens spel met en zonder speelgoed.

In het laatste hoofdstuk wordt gereflecteerd op de bevindingen van deze studie, en worden die in een bredere context geplaatst. Dit proefschrift over oxytocine, ouderschap, en postnatale depressie laat aan de ene kant zien dat oxytocine van belang is voor het bredere psychiatrische veld. Sommige aspecten van opvoedingsattituden en –gedrag werden positief beïnvloed door de toediening van oxytocine bij moeders met een diagnose van postnatale depressie. Aan de andere kant waren er ook iatrogene

effecten, en het is daarom te vroeg om oxytocine met groot enthousiasme binnen te halen als remedie voor het bevorderen van positieve ouder-kind interactie bij moeders met postnatale depressie.

Dankwoord (Acknowledgements)

Completing a body of work such as a dissertation is not done in isolation and there are many individuals to acknowledge and thank. Many staff members from both the Faculty of Child and Family Studies, Leiden, Netherlands and the Mothers and Babies Research Centre, Newcastle, Australia welcomed me and offered various help, warmly. My thanks go to many colleagues at my work place, Hunter New England Mental Health Service for supporting my research in numerous ways. Finally to many family members and friends, I wish to deeply acknowledge your contribution, both to this piece of work and my life in general. In particular, my two exquisite daughters, thank you for putting up with a busy and stressed mum particularly at a time in our lives that was not the easiest. Your enthusiastic cheering was perfect. To all of you, my sincere thanks.

Curriculum Vitae

Dr. Beth Lynette Mah was born in Lower Hutt, New Zealand on the 5th of June 1966. In 1995, she received a Bachelor of Medicine with Honours from the University of Newcastle, Australia. During her postgraduate studies Dr Mah achieved both a Fellowship of the Royal Australian and New Zealand College of Psychiatrists and a Certificate in Child and Adolescent Psychiatry in 2007. In 2011 she embarked upon a PhD at the University of Leiden. Her topic was postnatal depression, oxytocin and maternal sensitivity. Dr Mah continues to do clinical work in the field of Infant, Child and Adolescent Psychiatry at various sites in New South Wales, Australia.