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

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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 paternal 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

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>SD</th>
<th>Percent</th>
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<tbody>
<tr>
<td>Gestational age</td>
<td>38.25</td>
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<tr>
<td>Birth Weight (kg)</td>
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<tr>
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<tr>
<td>Gender: Female</td>
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<td>55.6</td>
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<tr>
<td>Feeding: Breast fed (vs. bottle fed)</td>
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<td></td>
<td>37.5</td>
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<tr>
<td>Family Status: cohabitation (vs. single)</td>
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<td></td>
<td>68.8</td>
</tr>
<tr>
<td>Annual Household income:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;AUD(^b)$100,000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;AUD$20,000</td>
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<td></td>
<td>31.3</td>
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<tr>
<td>Aboriginal(^d)</td>
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<td></td>
<td>6.25</td>
</tr>
<tr>
<td>Receiving Depression Rx</td>
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<td></td>
<td>62.5</td>
</tr>
</tbody>
</table>

\(^a\)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, $t(8.4, \text{unequal variances}) = 2.01, p = .08$). 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

<table>
<thead>
<tr>
<th></th>
<th>OT condition</th>
<th>Placebo condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Protectiveness</td>
<td>2.44</td>
<td>2.19</td>
</tr>
<tr>
<td>Gaze Duration</td>
<td>0.32</td>
<td>0.45</td>
</tr>
</tbody>
</table>

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.