

# Child Maltreatment, Oxytocin, and the Physiological Bases for Social Functioning and Stress Reactivity : A Literature Review

著者(英)	Rie MIZUKI
journal or publication title	The Journal of Konan University. Faculty of Letters
volume	172
page range	173-185
year	2022-03-30
URL	<a href="http://doi.org/10.14990/00004202">http://doi.org/10.14990/00004202</a>

# Child Maltreatment, Oxytocin, and the Physiological Bases for Social Functioning and Stress Reactivity: A Literature Review

Rie Mizuki

## Introduction

Child maltreatment impedes the psychological development of children and is well documented as a serious risk factor for the long-term psychiatric and physical illnesses (Edwards, Holden, Felitti, & Anda, 2003; Felitti et al., 1998; Norman et al., 2012). Maltreatment history has been associated with disruptive and aggressive behaviors (Alink, Cicchetti, Kim, & Rogosch, 2012; Paradis & Boucher, 2010). Also, higher exposure to childhood maltreatment was associated with lower ability to presume others' emotions or internal states (Germine, Dunn, McLaughlin, & Smoller, 2015; Heleniak & McLaughlin, 2019), and consequently those who had been maltreated frequently fail to build good relationships with others and experience more stress in interacting with them (Alink et al., 2012; Hager & Runtz, 2012; Hyman, Paliwal, & Sinha, 2007; Meinschmidt & Heim, 2007). Their higher stress levels have been linked to hormonal activities (De Bellis et al., 1994; Heim et al., 2000) and autonomic nervous system (Oosterman, De Schipper, Fisher, Dozier, & Schuengel, 2010).

One of the complicated aspects of maltreatment is that interpersonal problems, which develops over years, are not only manifested as aggression, but also as subtle dysfunctional behaviors such as codependency and sexualized behaviors, which may be misinterpreted as intimacy-seeking behaviors and thus could be overlooked as 'positive' characteristics (Merrick, Litrownik, Everson, & Cox, 2008; Reyome, Ward, & Witkiewitz, 2010; Senn & Carey, 2010). Thus, identifying the underlying mechanism of impaired social functioning and coping with interpersonal stress is crucial in treating

people with maltreatment history.

Oxytocin (OT) can play a critical role in social functioning and stress coping among people with maltreatment history. OT has been originally known for its function in the process of lactation and uterine contraction (Ludwig, 1998). During the last several decades, OT has increasingly drawn public attention as a "love hormone," due to its highlighted effect on human affiliation. Particularly, the link between parent-child affiliation and the development of OT system in children has been suggested (Gordon, Martin, Feldman, & Leckman, 2011). OT's function is not limited to social behaviors; its significant involvement in stress coping and mental disorders has been also documented (Carter, 2014; Olff, 2012). Thus, the OT system may explain these three dysfunctions in social behaviors, stress coping, and mental health in people with maltreatment history, by laying down the physiological mechanism.

Based on these research findings, child maltreatment, OT system and social functioning are suggested to be inter-related in a triangular way, with possibly OT mediating between the maltreatment and social functioning. Similarly, the OT system and stress reactivity, too, can be considered to be in a triangular relationship where OT may mediate between stress reactivity and child maltreatment.

The purpose of this review is 1) to investigate the effects of OT and child maltreatment on social functioning, 2) to describe the inter-connectedness among OT, child maltreatment and stress reactivity, and 3) to identify the effects of child maltreatment on OT systems which are underlying mechanism of social functioning and stress reactivity. Due to the limited number of empirical studies examining relationships between OT concentrations and child maltreatment experiences to date, instead of

conducting a meta-analysis, issues pertaining to methodologies were analyzed to explore potential factors contributing to some of the mixed findings between OT and child maltreatment. To this end, this review is presented in three parts. In the first part, I will review studies that have investigated the link between OT system, social functioning, and child maltreatment. In the second part, I will review the research that explored the link between OT system, stress reactivity, and child maltreatment. In the third and final section, I will review the studies that look directly at the link between child maltreatment and OT concentrations, since this association may be central to uncovering the underlying mechanism of the social functioning and stress reactivity. In this third section, particular emphasis will be placed on divergent methodological issues. Thus, this review discusses the basic elements of OT's role in the link between child maltreatment and dysfunctions and how this understanding will be of use for mental health providers who share an interest in the OT system from a clinical perspective.

## Child Maltreatment, OT and Social Functioning

### OT and Social Functioning

Since maltreatment impacts both social functioning and OT system, it is important to consider how child maltreatment, social functioning and OT system are inter-related. Extended research indicates that OT system modulates the process of social functioning including social cognition and social behaviors in humans. Social cognition is the cognitive capacity to take another person's psychological perspective as well as the emotional ability to experience another's affective processes (Frith & Singer, 2008; Shamay-Tsoory, 2011). For instance, higher empathy was reported by people with higher OT levels (Barraza & Zak, 2009). Also, increased OT levels, by applying nasal spray of OT, elicited higher ability to understand others' emotions, (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001; Bartz et al., 2010; Domes, Heinrichs, Michel, Berger, & Herpertz, 2007) as well as social behaviors, such as cooperation (Declerck, Boone, & Kiyonari, 2010; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005; Zak, Kurzban, & Matzner, 2005) and generosity

(Barraza & Zak, 2009). OT is considered to increase trust in people (Zak et al., 2005).

### OT and Maltreatment Interaction

Although exogenous OT administration appeared to increase trust and prosocial behaviors in general, it did not always have the same positive effect. Parental care during early life was found to modify how OT administration increased the amount of donations; an interactional effect of early childcare and OT on social behavior was found. OT increased prosocial behavior (i.e., donations) only in people who scored low on parents' love withdrawal that is an insensitive parenting strategy of withholding affection when a child misbehaves (e.g., parent not talking to the child when feeling displeased with the child). For those with high love withdrawal, no effect of OT administration on donation was observed (Van Ijzendoorn, Huffmeijer, Alink, Bakermans-Kranenburg, & Tops, 2011). Individual differences such as early life experiences may play a role in its social functioning.

Moreover, parenting quality also serves to moderate the association between OT and interpersonal relationships in parent-child dyads. Administering OT to the father increased the infant's gaze towards their father during the experiment which simulated "parental deprivation,"<sup>1)</sup> only in the dyads with higher synchronized gaze between the father and the infant. (Weisman, Zagoory-Sharon, & Feldman, 2013). Affectionate interactions such as physical proximity, affectionate touch, and social gaze among the mother, father and infant, were predicted by parental OT levels (Gordon, Zagoory-Sharon, Leckman, & Feldman, 2010). A link from parent-child relationship during childhood to relationship quality with partner and children in young adulthood via OT levels was suggested (Feldman, Gordon, & Zagoory-Sharon, 2011; Gordon et al., 2008). The up-regulation cycle of the effect of endogenous OT and social engagement between parents and infant, i.e., the process where social engagement increased in response to the stimulus of elevated OT level, might have been set off by both mothers' and fathers' OT levels. Consequently, the up-regulation of OT could lead to more sensitive parenting and continue to influence infant's behaviors and his or her underlying OT system.

### Gene and Maltreatment Interaction

Genotypes of oxytocin receptors (OXTR) are closely related to the function of OT system. OXTRs are found in the brain (Toepfer et al., 2017) and inner organs including mammary glands (Kimura & Ivell, 1999), uterus (Kimura, Tanizawa, Mori, Brownstein, & Okayama, 1992), cardiovascular system (Gutkowska et al., 1997), and kidney (Schmidt, Jard, Dreifuss, & Tribollet, 1990) and OT is delivered to those organs through blood stream. Currently, two OXTR gene single nucleotide polymorphisms, rs2254298 and rs53576, have been studied for their association with social functioning. Each genotype of OXTR consists of two alleles (i.e., adenine (A) and guanine (G)) and the combinations of these two alleles derive three genotypes: AA, AG, and GG (Marian J. Bakermans-Kranenburg & van IJzendoorn, 2014).

While GG genotype were associated with sensitivity to others' affect, compared with A allele (Marian J Bakermans-Kranenburg & van IJzendoorn, 2008; Riem, Pieper, Out, Bakermans-Kranenburg, & van IJzendoorn, 2011), child maltreatment experiences derive differential effects on social and relational functioning. In the GG genotype, people with higher childhood emotional abuse had more supportive relationship with their partner in midlife, whereas higher emotional abuse report was related to less report of supportive relationship compared in the AA genotype (Ebbert, Infurna, Luthar, Lemery-Chalfant, & Corbin, 2019). Also, for GG carriers, childhood maltreatment was related to less perceived social support and more internalizing symptoms (Hostinar, Cicchetti, & Rogosch, 2014) and more emotional dysregulation and a disorganized attachment style (Bradley et al., 2011). The interaction between OXTR genotype and maltreatment experiences seems to play a role in social/relational functioning.

### Child Maltreatment, OT and Stress Reactivity

#### OT and Stress Reactivity

In humans, increased OT levels are also linked to social/interpersonal stress. Higher OT levels were associated with higher reports of attachment/relationship anxiety (Feldman et al., 2011; Hoge, Pollack, Kaufman, Zak, & Simon, 2008; Marazziti et al., 2006; Taylor, Sa-

phire-Bernstein, & Seeman, 2010), Social Anxiety Disorder (Hoge et al., 2008), and distress in pair-bond relationships (Taylor et al., 2010). When released in response to social stress, OT suppressed the reactivity of hypothalamic-pituitary-adrenal (HPA) axis (Meinlschmidt & Heim, 2007) as well as cardiovascular reactivity (Kubzansky, Mendes, Appleton, Block, & Adler, 2012).

#### Stress Reactivity and Parental Care

The buffering effect of OT on stress reactivity appears not to be constant and to be affected by early life experiences. When early parental separation was reported, the reduction of cortisol after OT administration was smaller, compared with those without such experiences (Meinlschmidt & Heim, 2007). The stress reactivity of maltreated participants remained elevated, which was indexed with blunted hormonal reactivity and deactivation in the limbic system, contrary to attenuated hormonal reactivity and limbic deactivation in healthy subjects (Grimm et al., 2014). The history of child maltreatment seems to play a key role in determining the direction of the OT spray effect, i.e., whether it enhances or reduces the physiological responses to social stress.

#### Mental Health and OT

Lower OT levels have been found to be associated with various psychiatric disorders, which interferes with emotional regulation and social functioning, including depression (Garcia et al., 2011), schizophrenia (Rubin et al., 2010), post-traumatic stress disorder (PTSD; Reijnen, Geuze, & Vermetten, 2017) and suicide (Jokinen et al., 2012).

Promising findings of OT administration studies on psychiatric treatment have been reported. Feifel et al. (2010) found that OT reduced positive and negative symptoms of schizophrenia. Similarly, reduction of PTSD symptoms (van Zuiden et al., 2017; Yatzkar & Klein, 2010), decreased physiological reactivity to trauma-related stimuli (Pitman, Orr, & Lasko, 1993) have been reported. Since problems with the process of fear extinction are prevalent among PTSD patients (Milad et al., 2008), the OT spray may help attenuate exaggerated fear responses which impedes fear extinction (Koch et al., 2014).

These findings suggest psychiatric disorders involv-

ing impairment with social cognition and disrupted interpersonal relationships have been connected with dysregulation of the OT system. There, higher OT levels caused by OT spray may contribute to alleviating patients' suffering by reducing their fear leading to improving their symptoms. However, these studies failed to examine the effect of child maltreatment experiences. As indicated in the section of social behavior and stress reactivity, early life experiences appear to influence the effect of OXTR genes or the effect of OT concentrations. Particularly, elevated stress reactivity after OT administration warrants careful investigation on the interaction between OT system and child maltreatment history in terms of OT application to mental health treatment. Hence, future studies need to analyze differential effects of OT administration on psychiatric symptoms according to the participants' child maltreatment history.

### Maltreatment and OT Concentrations

In understanding the dysfunctions in people who have experienced child maltreatment, it is important to elucidate how child maltreatment influences OT release in humans. Concentrations of OT in various bodily fluids, i.e., plasma, saliva, urine and cerebrospinal fluid, have been measured as an index of OT release in the brain and the values were examined to be related to the presence of child maltreatment experiences in 10 studies (Table 1). Negative associations between OT concentrations and experiences of child maltreatment were found in six studies (Bertsch, Schmidinger, Neumann, & Herpertz, 2013; Heim et al., 2009; Müller, Bertsch, Bülau, Herpertz, & Buchheim, 2019; Opacka-Juffry & Mohiyeddini, 2012; Suzuki et al., 2020; Wismer Fries, Ziegler, Kurian, Jacoris, & Pollak, 2005). OT concentrations of those with higher report of child maltreatment experiences were lower in these studies. The suppressing effect of child maltreatment on OT suggests that people tend to reduce the release of OT in the brain when they have been repeatedly exposed to maltreatment during early life.

In contrast, opposite results regarding the associations between OT concentrations and maltreatment have also been reported. In four studies, people who have a history of child maltreatment exhibited higher

OT concentrations (Bhandari et al., 2014; Mizuki & Fujiwara, 2015; Mizushima et al., 2015; Seltzer, Ziegler, Connolly, Prosofski, & Pollak, 2014). The positive associations indicate that being maltreated during childhood is likely to incite the release of OT.

Furthermore, it was found that the relationship between child maltreatment and social cognition (i.e., higher positive ratings of infant faces) was moderated by OT (Bhandari et al., 2014). This implies the development of up-regulation of OT or an increased OT response to social stress, indicating a contrary effect of child maltreatment to previous findings.

These inconsistent findings suggest the need for further research to explore the complex factors behind these varying results. It is especially critical to elucidate the mechanism in which maltreatment experiences have resulted in the opposite directions of associations with OT. Reviewing the methodologies employed in the above-mentioned studies may be a starting point to build valid evidence for the effect of child maltreatment on the development of the OT system. Thus, the various methodologies will be evaluated from three perspectives: maltreatment type, levels of severity, and accumulated effects.

### Effects of Maltreatment Types on OT

The operational definition of child maltreatment is critical when we compare and interpret findings from multiple studies. Child maltreatment is defined as an act or a failure to act by a parent or other adult legally responsible for the care of a child under 18 years of age, resulting in imminent or potential harm to a child including death, serious physical and emotional damage, sexual abuse or exploitation (World Health Organization, 2014). Based on this somewhat broad definition, a number of specific behaviors have been identified as types of child maltreatment, including physical abuse, psychological abuse, sexual abuse, physical neglect, emotional neglect, and educational neglect (Herrenkohl, 2005). While some studies operationalize maltreatment based on the presence of any child maltreatment included above, others have utilized definitions that include exposure to different types of abuse, and/or maltreatment history. In fact, the type and definition of maltreatment adopted in each study seemed rather arbitrary and heterogeneous.

Table 1 Studies that have examined the association between child maltreatment experiences and oxytocin concentrations

Correlation	Authors	Year	Sample size	Sample age (years)	Sex	Maltreatment type	Maltreatment severity	Maltreatment assessment	Maltreatment variable	OT sample
-	Heim, Young, Newport, et al.	2009	total=22	M=31.3 SD=7.8	F	EA, PA, EN, any, number of types	moderate-severe	CTQ	dichotomous	CSF
-	Opacka-Juffry & Mohiyeddini	2012	total=98	M=27.7 SD=7.9	M	EA, PA, EN, PN	N/A	ELSI	continuous	plasma
-	Wisner Fries, Ziegler, Kurian, et al.	2005	CM=18 CO=21	M=53.7* M=54.2*	12 F 12 F	neglect	N/A	adoption records	dichotomous	urine
-	Suzuki, Fujisawa, Sakakibara, et al.	2020	CM=21 TD=29	M=5.5 SD=0.4 M=4.8 SD=0.3	11 M 12 M	any	N/A	CPS records, ACE	dichotomous	saliva
-	Bertsch, Schmidinger, Neumann, et al.	2013	total=74 (BPD=34, CO=40)	M=24.4 SD=4.7	F	EA, PA, SA, EN, PN, any	N/A	CTQ	continuous	plasma
-	Muller, Bertsch, Bulau, et al.	2019	total=121	M=23.38 SD=4.4	61 F 60 M	EN	N/A	CTQ	continuous	plasma
+	Bhandari, Bakermans-Kraneburg, van der Veen, et al.	2014	total=102	M=19.86 SD=1.42	F	EA+EN	N/A	CTQ	continuous	saliva
+	Mizuki & Fujiwara	2015	total=81	M=36.2 SD=3.4	50 F 31 M	EA, PA, SA, EN, PN, number of types	low-moderate	CTQ	dichotomous	urine
+	Seltzer, Ziegler, Connolly, et al.	2014	CM=37 CO=36	M=9.0 SD=1.2 M=9.4 SD=1.2	21 F 18 F	any	N/A	CPS records, CTS	dichotomous	urine
+	Mizushima, Fujisawa, Takiguchi, et al.	2015	CM (unsettled)=15 CM (settled)=23 TD=26	M=13.1 SD=2.1 M=12.2 SD=2.9 M=12.7 SD=2.2	9 F 10 F 14 F	any	N/A	CPS records, ACE	dichotomous	saliva

Note. + : Positive association, - : Negative association, OT: Oxytocin, CM: Child Maltreatment, CO: Control, TD: Typical Development, BPD: Borderline Personality Disorder, F: Female, M: Male, CTQ: Childhood Trauma Questionnaire, ELSI: Early Life Stress Inventory, CPS: Child Protective Services, CTS: Parent-Child Conflict Tactics Scale, EA: Emotional abuse, PA: Physical abuse, SA: Sexual abuse, EN: Emotional neglect, PN: Physical neglect, Any: Any maltreatment, CSF: Cerebrospinal fluid, \*in months.

Self-report measures are one way of assessing people's maltreatment experiences during childhood. In the study of Heim et al. (2009), a self-report measure Childhood Trauma Questionnaire (CTQ; Bernstein & Fink, 1998) which taps into exposure to five maltreatment types (i.e., emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect) to assess child maltreatment history in 22 healthy women aged 18-45. The presence of any one of the five types was employed for the comparison between maltreated and non-maltreated groups and they found lower OT in the maltreated group. When comparing the presence or absence of each maltreatment type, significant negative associations were found between OT and emotional abuse, physical abuse, and emotional neglect respectively. Bertsch et al. (2013) and Müller et al. (2019) also used CTQ for maltreatment assessment. Bertsch et al. (2013) found particularly higher negative correlations with OT for emotional neglect and emotional abuse among 74 women, aged 18-36 years, with and without borderline personality disorder. In this study, OT was also found to mediate the association between child maltreatment, which was measured by CTQ total score, and the symptoms of borderline personality disorder. Müller et al. (2019) focused on emotional neglect in a population-based adult sample, aged 18-41 years, and found that higher score of emotional neglect was related to lower plasma OT, after ruling out of the effects of other maltreatment types. Another self-report measure, Early Life Stress Inventory (ELSI) with 30 items, to which 90 male participants between the age of 18 and 45 years responded with yes (=1) or no (=0), was used to assess stressful/traumatic experiences during childhood in the study of Opacka-Juffry and Mohiyeddini (2012). The scale inquired a broader range of stressful/traumatic experiences, such as victimization in crime, loss of significant people, and changes of school, in addition to experiences of child abuse and neglect. The ELSI score was negatively correlated with OT.

Court records and records of child welfare system were used as endorsement of child maltreatment history in other studies. Wismer Fries et al. (2005) defined the membership of 18 child participants with a mean age of 53.7 months to a maltreated group based

on their history of being raised in neglectful institutions abroad during early childhood and living with their adoptive families at the time of the study. The exposure to various maltreatment types, such as physical and emotional abuse, remained unknown. In the study of Suzuki et al. (2020), the participants' exposures to four types of child maltreatment (i.e., physical abuse: 19%, emotional abuse: 48%, sexual abuse: 0% and neglect: 76%) in 21 maltreated and 29 control children were assessed with the Adverse Childhood Experience (ACE) questionnaire (Felitti et al., 1998). However, the association of each type with OT was not analyzed since OT was compared between maltreated and non-maltreated group.

Thus, it is clear that the definitions of child maltreatment in these studies varied, even among the studies which used the same CTQ measure. In terms of the ELS inventory, since experiences other than child abuse and neglect were included in the scale, lower OT may not be attributed to child maltreatment, but to other uncontrollable stressful events such as long-term illness or changes in schools. Nonetheless, they showed congruent results of a negative association between child maltreatment and OT.

Several studies, however, have concluded opposite results where a positive association was found between child maltreatment and OT. In two studies that used the CTQ, Bhandari et al. (2014) created a composite of emotional maltreatment by combining scores of emotional abuse and emotional neglect and found a positive association with OT. Mizuki and Fujiwara (2015) found that only physical abuse was positively associated with urinary OT. These two studies were consistent, showing a positive relationship between child maltreatment with OT even though the types of maltreatment analyzed were different. Two other studies relied on the records of public services for maltreatment assessment and resulted in positive association with OT. Seltzer et al. (2014) defined physical abuse as maltreatment while Mizushima et al. (2015) categorized maltreated children according to the relevant records and did not specify the types of maltreatment children had experienced.

Findings by Bhandari et al. (2014) that investigated a sample of 102 healthy female college students were contradictory to the other studies using emotional mal-

treatment as described above. On the other hand, physical abuse was positively associated in two studies, one by Mizuki & Fujiwara (2015) with a community sample of 81 adults with a mean age of 36.2 who were raising children at the time, and the other by Seltzer and colleagues (2014) whose sample included 73 children, aged 8–11.5 years, with or without physical abuse history; people experienced physical abuse during childhood tended to have higher OT. The finding of a positive relationship in the study of Mizushima et al. (2015) with 79 preadolescent and adolescent children, could also reflect the effect of physical abuse, although the distributions of specific maltreatment types were assessed, but not reported. These results implied that the effect of maltreatment might differ depending on what types of maltreatment were experienced by the child.

Heterogeneity in operational definitions of child maltreatment may be inevitable as the life experiences of each sample vary from study to study while any one of the above behaviors could be regarded as child maltreatment. Therefore, inconsistent findings regarding the effect of child maltreatment on OT might be in part attributed to the heterogeneity in the assessment of types of childhood maltreatment. So, it becomes all the more crucial that researchers continue to investigate how each type of maltreatment influence OT levels by being more conscious and deliberate about which operational definition they are adopting.

#### **Assessment of Maltreatment Severity**

In addition to identifying the different types of maltreatment, different levels of severity in maltreatment have also been identified and included in OT research. Some of the above-mentioned studies that used the CTQ, included the severity of maltreatment experiences of their participants in the analysis. CTQ identifies cutoff scores for each of the five maltreatment types, and experiences of these maltreatment types can be categorized into “none,” “low,” “moderate,” or “severe” (Bernstein & Fink, 1998). For instance, Heim et al. (2009) used the cutoff scores for emotional abuse (>12), physical abuse (>9), sexual abuse (>7), emotional neglect (>14), and physical neglect (>9). Scores higher than these cutoffs were categorized as moderate-severe level exposure to respective maltreatment type which was defined as the presence of maltreatment.

In other words, participants who scored below the cutoff points above were classified into the non-maltreated group regardless of their endorsement of some maltreatment experiences. Also, in the study of Bertsch et al. (2013) correlational analysis between OT and the scores of each maltreatment type indicated that OT levels were negatively correlated correspondingly to the severity of the respective type. Most of the participants with borderline personality disorder had experienced moderate to severe maltreatment, based on the distributions of the scores of each type. Also, in the study of Müller et al. (2019), despite none or low-level emotional neglect reported by the majority of the participants based on the score distribution, the higher score of emotional maltreatment was associated with lower OT concentrations. This means that even within the less severe range, as severity of emotional maltreatment increased, OT levels decreased. Although the cutoff scores were not used in these studies, the effect of severity of different types supported the results of Heim et al. (2009).

Based on these studies with CTQ, when severity levels of maltreatment were greater, which considered to be in the moderate to severe category, OT levels were more suppressed (Bertsch et al., 2013; Heim et al., 2009; Müller et al., 2019). Suppressed OT levels were negatively associated with exposure to stressful/adverse experiences measure with ESLI or ACE questionnaire (Opacka-Juffry & Mohiyeddini, 2012; Suzuki et al., 2020). However, neither ESLI nor ACE questionnaire probed into the frequency or degree of these experiences in terms of severity. The studies of Opacka-Juffry and Mohiyeddini (2012) and Suzuki et al. (2020) could be considered to be aligned with this conceptualization, if most of the stressful/adverse events which the participants had endorsed on the ELSI or ACE questionnaire fell into moderate-severe levels. On the other hand, low severity levels of maltreatment were reported by the majority of participants in the study of Müller et al. (2019). Since Müller’s findings also indicated a negative association with OT, the possibility that higher severity could account for the suppressed OT concentrations was not supported.

Conversely, less severe maltreatment was positively associated with OT in two studies. In a study by Bhan-



dari et al. (2014), almost all participants experienced none to moderate emotional maltreatment. Positive correlation results indicated that the more severe emotional maltreatment the participants experienced, the higher the salivary OT concentrations were. Mizuki and Fujiwara (2015) used CTQ and included five maltreatment types at low and moderate level in analysis, using the cutoff score. Less severe physical abuse was positively associated with urinary OT. A dose-response relation was also found between the number of less severe maltreatment types and OT, showing a consistent incremental effect of less severe form of maltreatment, on OT concentrations.

Other studies (see Mizushima et al., 2015; Seltzer et al., 2014; Wismer Fries et al., 2005) used history of placement in orphanage, court and CPS records as the criterion for child maltreatment. For the record regarding the history in an orphanage, the severity of maltreatment, particularly physical and emotional neglect, was assumed to be fairly significant, based on the description of institutional care abroad (Human Rights Watch, 1998). Such severe neglect could explain the result of lower OT levels. Similarly, given the difficulty in investigating and substantiating child maltreatment, the cases substantiated by CPS were usually accepted as maltreatment with greater severity (Cicchetti & Barnett, 1991). Nevertheless, the efforts invested into substantiating each case may vary depending on factors other than the nature of the maltreatment, but practical factors such as the caseload of the case worker in charge (Cicchetti & Barnett, 1991). Thus, based on the lack of consistent measurement of maltreatment severity regardless of assessment methods such as self-report or use of existing records, as well as the contradictory link between child maltreatment and OT, it is critical that the severity of each maltreatment type be assessed with valid instruments in future studies, which would allow the comparison of findings across various studies that will allow researcher to understand the complex nature of OT and maltreatment.

#### **Accumulated Effect of Multiple Types of Child Maltreatment**

Co-occurrence of multiple types of maltreatment is commonly observed in research on early life experiences, and extant research documented that the accu-

mulation of different types of maltreatment have long-term impact on human health, including serious medical illnesses and mental disorders (Felitti et al., 1998; Finkelhor, Shattuck, Turner, Ormrod, & Hamby, 2011; Richmond, Elliott, Pierce, Aspelmeier, & Alexander, 2009). With regard to the measurement of severity of maltreatment, some studies did explore the cumulative effect of different types of maltreatment on OT concentrations.

Several studies examined the association between the total number of maltreatment types and OT concentrations. Heim et al. (2009) created a composite variable (i.e., 0, 1, 2, and 3 or more types) based on the number of moderate-severe maltreatment which the participants reported on CTQ. OT concentrations were compared among the groups defined by this composite. As the total number of types increased from 0 to 2, and to 3 or more, OT levels significantly declined. A cumulative suppressing effect of stressful life events on OT was also found in Opacka-Juffry and Mohiyeddini (2012); as the number of types of stressful experiences increased, OT levels decreased. The opposite direction of the effect of accumulated maltreatment types was reported. Mizuki and Fujiwara (2015) created a composite in which the count of types of less severe maltreatment was grouped into 0, 1, 2, and 3 or more. An incremental trend was found; as the count increased from 0 to 3 or more, OT levels also increased.

The findings suggest that when children are victimized with different types of maltreatment, the development of OT system may be immensely disrupted. However, contradictory associations between the number of maltreatment types and OT concentrations revealed in these studies suggest necessity of further investigations on the accumulative effects of different types of maltreatment, which integrates other dimensions such as the levels of maltreatment severity.

#### **Conclusion**

This paper reviewed studies that investigated the interactional effects of OT and child maltreatment on social functioning and stress reactivity. Also, the studies investigated the association between OT and child maltreatment were analyzed. Particularly, the operational

definitions of child maltreatment in these studies have also been explored to identify inconsistency in maltreatment type, severity and accumulated effect employed in their analysis. Then, numerous studies from non-clinical empirical investigations to clinical treatments for psychiatric disorders have been presented, expanding our understanding of the role OT plays in various contexts where social behavior and stress reactivity arise.

Social functioning, i.e., social cognition and social behavior, has been proven to be related to higher OT levels. Improvement in empathic understanding and cooperative behaviors following OT administration provides further support for the effect of OT on prosocial functioning. The formation of long-lasting affiliations, encompassing emotional interaction, social cognition, empathy, trust, and cooperation, starts even before birth. Taking an evolutionary perspective, social bonding is likely to be programmed in human genes through natural selection which maximized the survival of in-group members. In this process, OT plays a critical role in physiology and contributes to parent-child social interactions by facilitating sensitive and affectionate parenting.

Research on polymorphism of OXTR suggests a genetic effect on psychological functioning, which also interacts with early life experiences. While OT suppresses reactivity to social stress by modulating hormonal, i.e., HPA axis, and autonomic nervous system, alleviation of stress reactivity interacts with early life experiences; OT may exert opposite effects on stress reactivity depending on whether people have undergone child maltreatment during early life. Hence, OT seems to be involved in the human processes of social affiliation, by interfering with various neural and hormonal systems, such as HPA axis and autonomic nervous system. The regulation of those physiological systems is considered to modulate social functioning and reactivity to social stresses in humans.

Parenting practices during early childhood continues to impact us even in our adulthood, demonstrated by the link between peripheral OT levels and maltreatment history. Down-regulation of OT, i.e., the process where the OT release—in response to social interactions—is suppressed, may result from chronic exposure to uncertain or unsafe conditions and consequently, those with

maltreatment history remained less socially engaging or proficient. Down-regulation may be applied to lower OT in people with psychiatric disorders, many of which are characterized with social dysfunctions. On the other hand, higher OT found in people with maltreatment history may be accounted for by OT's agonistic effect which leads to its up-regulation to cope with stress as described previously. Consequently, potential use of OT in treating mental illnesses is suggested.

Given the interactional effects of OT and child maltreatment on social functioning and stress reactivity, 10 studies which examined the association between OT concentrations and experiences of child maltreatment were reviewed in order to understand the physiological basis of how people with maltreatment history adapt socially. The findings of effect of child maltreatment on OT concentrations have been inconsistent; some resulted in a negative association between the presence of child maltreatment and OT concentrations while others showed a positive association. Detailed review of each study revealed that some studies did not assess types of maltreatment, and even when they did, different types were used for the definition of maltreatment. Similar inconsistencies were also found for levels of severity of each maltreatment type. In addition to comparing the presence and absence of child maltreatment, accumulated effect of different types of maltreatment on OT concentrations was examined in some studies. Moreover, the characteristics of samples, such as age, sex, intimate relationship status, and parenting experiences, varied significantly in the studies presented in this review; replications with similar samples could allow comparison of the results, which helps elucidate other contributing factors to the inconsistent findings. Given the difficulty to capture samples with high child maltreatment histories and sensitive nature of child maltreatment assessment, continuous attempt to collect more data with various available samples is feasible nonetheless, more studies with congruent operational definition of child maltreatment, regarding type and severity level, should be conducted.

Thus, future research, firstly needs to identify the distribution of baseline OT levels to determine the range in which people's psycho-social functioning remains healthy. Secondly, research continues to investigate

what types and severity of child maltreatment is associated with OT concentrations as well as identify a pattern of such associations, such as down-regulation of OT system. Thirdly, taking into consideration the possible interaction between genetics and environment, research should also assess the genotype of OXTR and experiences of early life care when examining the association between OT levels and social/psychological functioning. Also, the effect of OT spray must be evaluated on contingent with early life experiences, especially child maltreatment, and OXTR genotypes, to help clarify to whom OT spray should be prescribed in order to stabilize its positive effects. Hopefully, it may also expand the treatment strategies, for instance, by treating issues associated with early life care before prescribing OT. In any case, based on the research described in this review, the mechanism of OT system in humans has not been fully understood and need to be further studied. Particularly, the assessment of OT level and genetics may be crucial in future research on the effect of child maltreatment with social behaviors and stress regulation in relation to OT.

【付記】本論文は、2名の文学部教員（研究指導教員を除く）による査読を経た後に人文科学研究科委員会で掲載を決定したものである。

#### Note

- 1) A stressful situation is deliberately created using the “still face” paradigm. For a review, see Adamson & Frick (2003).

#### References

- Alink, L. R., Cicchetti, D., Kim, J., & Rogosch, F. A. (2012). Longitudinal associations among child maltreatment, social functioning, and cortisol regulation. *Developmental psychology, 48*(1), 224.
- Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2008). Oxytocin receptor (OXTR) and serotonin transporter (5-HTT) genes associated with observed parenting. *Social cognitive and affective neuroscience, 3*(2), 128-134.
- Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2014). A sociability gene? Meta-analysis of oxytocin receptor genotype effects in humans. *Psychiatric Genetics, 24*(2), 45-51.
- Baron-Cohen, S., Wheelwright, S., Hill, J., Raste, Y., & Plumb, I. (2001). The “Reading the Mind in the Eyes” Test revised version: a study with normal adults, and adults with Asperger syndrome or high-functioning autism. *The Journal of Child Psychology and Psychiatry and Allied Disciplines, 42*(2), 241-251.
- Barraza, J., & Zak, P. (2009). Empathy toward strangers triggers oxytocin release and subsequent generosity. *Annals of the New York Academy of Sciences, 1167*(1), 182-189.
- Bartz, J. A., Zaki, J., Bolger, N., Hollander, E., Ludwig, N. N., Kolevzon, A., & Ochsner, K. N. (2010). Oxytocin selectively improves empathic accuracy. *Psychological Science, 21*(10), 1426-1428.
- Bernstein, D. P., & Fink, L. (1998). *Childhood trauma questionnaire: A retrospective self-report: Manual*. Bloomington, MN: NCS Pearson, Inc.
- Bertsch, K., Schmidinger, I., Neumann, I. D., & Herpertz, S. C. (2013). Reduced plasma oxytocin levels in female patients with borderline personality disorder. *Hormones and behavior, 63*(3), 424-429.
- Bhandari, R., Bakermans-Kranenburg, M. J., van der Veen, R., Parsons, C. E., Young, K. S., Grewen, K. M., . . . van IJzendoorn, M. H. (2014). Salivary oxytocin mediates the association between emotional maltreatment and responses to emotional infant faces. *Physiology & behavior, 131*, 123-128.
- Bradley, B., Westen, D., Mercer, K. B., Binder, E. B., Jovanovic, T., Crain, D., . . . Heim, C. (2011). Association between childhood maltreatment and adult emotional dysregulation in a low-income, urban, African American sample: moderation by oxytocin receptor gene. *Development and psychopathology, 23*(2), 439.
- Carter, C. S. (2014). Oxytocin pathways and the evolution of human behavior. *Annual review of psychology, 65*, 17-39.
- Cicchetti, D., & Barnett, D. (1991). Toward the development of a scientific nosology of child maltreatment.
- De Bellis, M. D., Chrousos, G. P., Dorn, L. D., Burke, L., Helmers, K., Kling, M. A., . . . Putnam, F. W. (1994). Hypothalamic-pituitary-adrenal axis dysregulation in sexually abused girls. *The Journal of Clinical Endocrinology & Metabolism, 78*(2), 249-255.
- Declerck, C. H., Boone, C., & Kiyonari, T. (2010). Oxytocin and cooperation under conditions of uncertainty: the modulating role of incentives and social information. *Hormones and behavior, 57*(3), 368-374.
- Domes, G., Heinrichs, M., Michel, A., Berger, C., & Herpertz, S. C. (2007). Oxytocin improves “mind-reading” in humans. *Biological psychiatry, 61*(6), 731-733.
- Ebbert, A. M., Infurna, F. J., Luthar, S. S., Lemery-Chalfant, K., & Corbin, W. R. (2019). Examining the link between emotional childhood abuse and social relationships in midlife: The moderating role of the oxytocin receptor gene. *Child Abuse & Neglect, 98*, 104151.
- Edwards, V. J., Holden, G. W., Felitti, V. J., & Anda, R. F. (2003). Relationship between multiple forms of childhood maltreatment and adult mental health in commu-

- nity respondents: results from the adverse childhood experiences study. *American Journal of Psychiatry*, 160 (8), 1453-1460.
- Feifel, D., Macdonald, K., Nguyen, A., Cobb, P., Warlan, H., Galangue, B., . . . Perry, W. (2010). Adjunctive intranasal oxytocin reduces symptoms in schizophrenia patients. *Biological psychiatry*, 68(7), 678-680.
- Feldman, R., Gordon, I., & Zagoory - Sharon, O. (2011). Maternal and paternal plasma, salivary, and urinary oxytocin and parent-infant synchrony: considering stress and affiliation components of human bonding. *Developmental science*, 14(4), 752-761.
- Felitti, V. J., Anda, R. F., Nordenberg, D., Williamson, D. F., Spitz, A. M., Edwards, V., . . . Marks, J. S. (1998). Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: The Adverse Childhood Experiences (ACE) Study. *American journal of preventive medicine*, 14(4), 245-258.
- Finkelhor, D., Shattuck, A., Turner, H. A., Ormrod, R., & Hamby, S. L. (2011). Polyvictimization in developmental context. *Journal of Child & Adolescent Trauma*, 4 (4), 291-300.
- Frith, C. D., & Singer, T. (2008). The role of social cognition in decision making. *Philosophical Transactions of the Royal Society B: Biological Sciences*, 363(1511), 3875-3886.
- Garcia, F. D., Coquerel, Q., Kiive, E., Déchelotte, P., Harro, J., & Fetissov, S. O. (2011). Autoantibodies reacting with vasopressin and oxytocin in relation to cortisol secretion in mild and moderate depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 35 (1), 118-125.
- Germine, L., Dunn, E. C., McLaughlin, K. A., & Smoller, J. W. (2015). Childhood adversity is associated with adult theory of mind and social affiliation, but not face processing. *PLoS One*, 10(6), e0129612.
- Gordon, I., Martin, C., Feldman, R., & Leckman, J. F. (2011). Oxytocin and social motivation. *Developmental cognitive neuroscience*, 1(4), 471-493.
- Gordon, I., Zagoory-Sharon, O., Leckman, J. F., & Feldman, R. (2010). Oxytocin, cortisol, and triadic family interactions. *Physiology & behavior*, 101(5), 679-684.
- Gordon, I., Zagoory - Sharon, O., Schneiderman, I., Leckman, J. F., Weller, A., & Feldman, R. (2008). Oxytocin and cortisol in romantically unattached young adults: associations with bonding and psychological distress. *Psychophysiology*, 45(3), 349-352.
- Grimm, S., Pestke, K., Feeser, M., Aust, S., Weigand, A., Wang, J., . . . Böker, H. (2014). Early life stress modulates oxytocin effects on limbic system during acute psychosocial stress. *Social cognitive and affective neuroscience*, 9(11), 1828-1835.
- Gutkowska, J., Jankowski, M., Lambert, C., Mukaddam, Daher, S., Zingg, H. H., & McCann, S. M. (1997). Oxytocin releases atrial natriuretic peptide by combining with oxytocin receptors in the heart. *Proceedings of the National Academy of Sciences*, 94(21), 11704-11709.
- Hager, A. D., & Runtz, M. G. (2012). Physical and psychological maltreatment in childhood and later health problems in women: An exploratory investigation of the roles of perceived stress and coping strategies. *Child Abuse & Neglect*, 36(5), 393-403.
- Heim, C., Newport, D. J., Heit, S., Graham, Y. P., Wilcox, M., Bonsall, R., . . . Nemeroff, C. B. (2000). Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. *Jama*, 284 (5), 592-597.
- Heim, C., Young, L. J., Newport, D. J., Mletzko, T., Miller, A. H., & Nemeroff, C. B. (2009). Lower CSF oxytocin concentrations in women with a history of childhood abuse. *Molecular psychiatry*, 14(10), 954-958.
- Heleniak, C., & McLaughlin, K. A. (2019). Social-cognitive mechanisms in the cycle of violence: Cognitive and affective theory of mind, and externalizing psychopathology in children and adolescents. *Development and psychopathology*, 32(2), 735-750.
- Herrenkohl, R. C. (2005). The definition of child maltreatment: From case study to construct. *Child Abuse & Neglect*, 29(5), 413-424.
- Hoge, E. A., Pollack, M. H., Kaufman, R. E., Zak, P. J., & Simon, N. M. (2008). Oxytocin levels in social anxiety disorder. *CNS neuroscience & therapeutics*, 14(3), 165-170.
- Hostinar, C. E., Cicchetti, D., & Rogosch, F. A. (2014). Oxytocin receptor gene (OXTR) polymorphism, perceived social support, and psychological symptoms in maltreated adolescents. *Development and psychopathology*, 26(2), 465.
- Human Rights Watch. (1998). *Abandoned to the state: Cruelty and neglect in Russian Orphanages*. Retrieved from New York:
- Hyman, S. M., Paliwal, P., & Sinha, R. (2007). Childhood maltreatment, perceived stress, and stress-related coping in recently abstinent cocaine dependent adults. *Psychology of addictive behaviors*, 21(2), 233.
- Jokinen, J., Chatzittofis, A., Hellström, C., Nordström, P., Uvnäs-Moberg, K., & Åsberg, M. (2012). Low CSF oxytocin reflects high intent in suicide attempters. *Psychoneuroendocrinology*, 37(4), 482-490.
- Kimura, T., & Ivell, R. (1999). The Oxytocin Receptor. In R. D. (Ed.), *Regulatory Peptides and Cognate Receptors. Results and Problems in Cell Differentiation* (Vol. vol 26, pp. 135-168). Berlin, Heidelberg: Springer.
- Kimura, T., Tanizawa, O., Mori, K., Brownstein, M. J., & Okayama, H. (1992). Structure and expression of a human oxytocin receptor. *Nature*, 356(6369), 526-529.
- Koch, S. B., van Zuiden, M., Nawijn, L., Frijling, J. L., Velt-

- man, D. J., & Olf, M. (2014). Intranasal oxytocin as strategy for medication-enhanced psychotherapy of PTSD: Salience processing and fear inhibition processes. *Psychoneuroendocrinology*, *40*, 242-256.
- Kosfeld, M., Heinrichs, M., Zak, P. J., Fischbacher, U., & Fehr, E. (2005). Oxytocin increases trust in humans. *Nature*, *435*(7042), 673-676.
- Kubzansky, L. D., Mendes, W. B., Appleton, A. A., Block, J., & Adler, G. K. (2012). A heartfelt response: oxytocin effects on response to social stress in men and women. *Biological psychology*, *90*(1), 1-9.
- Ludwig, M. (1998). Dendritic release of vasopressin and oxytocin. *Journal of neuroendocrinology*, *10*(12), 881-895.
- Müller, L. E., Bertsch, K., Bülow, K., Herpertz, S. C., & Buchheim, A. (2019). Emotional neglect in childhood shapes social dysfunctioning in adults by influencing the oxytocin and the attachment system: Results from a population-based study. *International Journal of Psychophysiology*, *136*, 73-80.
- Marazziti, D., Dell'Osso, B., Baroni, S., Mungai, F., Catena, M., Rucci, P., . . . Fabbrini, L. (2006). A relationship between oxytocin and anxiety of romantic attachment. *Clinical Practice and Epidemiology in Mental Health*, *2*(1), 1-6.
- Meinlschmidt, G., & Heim, C. (2007). Sensitivity to intranasal oxytocin in adult men with early parental separation. *Biological psychiatry*, *61*(9), 1109-1111.
- Merrick, M. T., Litrownik, A. J., Everson, M. D., & Cox, C. E. (2008). Beyond sexual abuse: The impact of other maltreatment experiences on sexualized behaviors. *Child maltreatment*, *13*(2), 122-132.
- Milad, M. R., Orr, S. P., Lasko, N. B., Chang, Y., Rauch, S. L., & Pitman, R. K. (2008). Presence and acquired origin of reduced recall for fear extinction in PTSD: results of a twin study. *Journal of Psychiatric Research*, *42*(7), 515-520.
- Mizuki, R., & Fujiwara, T. (2015). Association of oxytocin level and less severe forms of childhood maltreatment history among healthy Japanese adults involved with child care. *Frontiers in behavioral neuroscience*, *9*, 138.
- Mizushima, S. G., Fujisawa, T. X., Takiguchi, S., Kumazaki, H., Tanaka, S., & Tomoda, A. (2015). Effect of the nature of subsequent environment on oxytocin and cortisol secretion in maltreated children. *Frontiers in Psychiatry*, *6*, 173.
- Norman, R. E., Byambaa, M., De, R., Butchart, A., Scott, J., & Vos, T. (2012). The long-term health consequences of child physical abuse, emotional abuse, and neglect: a systematic review and meta-analysis. *PLoS medicine*, *9*(11), e1001349.
- Olf, M. (2012). Bonding after trauma: On the role of social support and the oxytocin system in traumatic stress. *European Journal of Psychotraumatology*, *3*(1), 18597.
- Oosterman, M., De Schipper, J. C., Fisher, P., Dozier, M., & Schuengel, C. (2010). Autonomic reactivity in relation to attachment and early adversity among foster children. *Development and psychopathology*, *22*(1), 109.
- Opacka-Juffry, J., & Mohiyeddini, C. (2012). Experience of stress in childhood negatively correlates with plasma oxytocin concentration in adult men. *Stress*, *15*(1), 1-10.
- Paradis, A., & Boucher, S. (2010). Child maltreatment history and interpersonal problems in adult couple relationships. *Journal of Aggression, Maltreatment & Trauma*, *19*(2), 138-158.
- Pitman, R. K., Orr, S. P., & Lasko, N. B. (1993). Effects of intranasal vasopressin and oxytocin on physiologic responding during personal combat imagery in Vietnam veterans with posttraumatic stress disorder. *Psychiatry research*, *48*(2), 107-117.
- Reijnen, A., Geuze, E., & Vermetten, E. (2017). Individual variation in plasma oxytocin and vasopressin levels in relation to the development of combat-related PTSD in a large military cohort. *Journal of Psychiatric Research*, *94*, 88-95.
- Reyome, N. D., Ward, K. S., & Witkiewitz, K. (2010). Psychosocial variables as mediators of the relationship between childhood history of emotional maltreatment, codependency, and self-silencing. *Journal of Aggression, Maltreatment & Trauma*, *19*(2), 159-179.
- Richmond, J. M., Elliott, A. N., Pierce, T. W., Aspelmeier, J. E., & Alexander, A. A. (2009). Polyvictimization, childhood victimization, and psychological distress in college women. *Child maltreatment*, *14*(2), 127-147.
- Riem, M. M., Pieper, S., Out, D., Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2011). Oxytocin receptor gene and depressive symptoms associated with physiological reactivity to infant crying. *Social cognitive and affective neuroscience*, *6*(3), 294-300.
- Rubin, L. H., Carter, C. S., Drogos, L., Pournajafi-Nazarloo, H., Sweeney, J. A., & Maki, P. M. (2010). Peripheral oxytocin is associated with reduced symptom severity in schizophrenia. *Schizophrenia research*, *124*(1-3), 13-21.
- Schmidt, A., Jard, S., Dreifuss, J., & Tribollet, E. (1990). Oxytocin receptors in rat kidney during development. *American Journal of Physiology-Renal Physiology*, *259*(6), F872-F881.
- Seltzer, L. J., Ziegler, T., Connolly, M. J., Prosofski, A. R., & Pollak, S. D. (2014). Stress - induced elevation of oxytocin in maltreated children: Evolution, neurodevelopment, and social behavior. *Child development*, *85*(2), 501-512.
- Senn, T. E., & Carey, M. P. (2010). Child maltreatment and women's adult sexual risk behavior: Childhood sexual abuse as a unique risk factor. *Child maltreatment*, *15*(4), 324-335.
- Shamay-Tsoory, S. G. (2011). The neural bases for empa-

- thy. *The Neuroscientist*, 17(1), 18–24.
- Suzuki, S., Fujisawa, T. X., Sakakibara, N., Fujioka, T., Takiguchi, S., & Tomoda, A. (2020). Development of social attention and oxytocin levels in maltreated children. *Scientific reports*, 10(1), 1–10.
- Taylor, S. E., Saphire-Bernstein, S., & Seeman, T. E. (2010). Are plasma oxytocin in women and plasma vasopressin in men biomarkers of distressed pair-bond relationships? *Psychological Science*, 21(1), 3–7.
- Toepfer, P., Heim, C., Entringer, S., Binder, E., Wadhwa, P., & Buss, C. (2017). Oxytocin pathways in the intergenerational transmission of maternal early life stress. *Neuroscience & Biobehavioral Reviews*, 73, 293–308.
- Van Ijzendoorn, M. H., Huffmeijer, R., Alink, L. R., Bakermans-Kranenburg, M. J., & Tops, M. (2011). The impact of oxytocin administration on charitable donating is moderated by experiences of parental love-withdrawal. *Frontiers in Psychology*, 2, 258.
- van Zuiden, M., Frijling, J. L., Nawijn, L., Koch, S. B., Gossling, J. C., Luitse, J. S., . . . Olf, M. (2017). Intranasal oxytocin to prevent posttraumatic stress disorder symptoms: a randomized controlled trial in emergency department patients. *Biological psychiatry*, 81(12), 1030–1040.
- Weisman, O., Zagoory-Sharon, O., & Feldman, R. (2013). Oxytocin administration alters HPA reactivity in the context of parent–infant interaction. *European Neuropsychopharmacology*, 23(12), 1724–1731.
- Wisner Fries, A. B., Ziegler, T. E., Kurian, J. R., Jacoris, S., & Pollak, S. D. (2005). Early experience in humans is associated with changes in neuropeptides critical for regulating social behavior. *Proceedings of the National Academy of Sciences*, 102(47), 17237–17240.
- World Health Organization. (2014). Global status report on violence prevention 2014. Retrieved from [http://www.who.int/violence\\_injury\\_prevention/violence/status\\_report/2014/en/](http://www.who.int/violence_injury_prevention/violence/status_report/2014/en/)
- Yatzkar, U., & Klein, E. (2010). P. 3.026 Intranasal oxytocin in patients with post traumatic stress disorder: a single dose, pilot double blind crossover study. *European Neuropsychopharmacology*(20), S84.
- Zak, P. J., Kurzban, R., & Matzner, W. T. (2005). Oxytocin is associated with human trustworthiness. *Hormones and behavior*, 48(5), 522–527.