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# Child's oxytocin response to mother-child interaction: The contribution of child genetics and maternal behavior

Rita Baião[a,b], Pasco Fearon[c], Jay Belsky[d], Joana Baptista[a,e], Alexandra Carneiro[f], Raquel Pinto[a], Marlene Nogueira[a], César Oliveira[g,h], Isabel Soares[a], Ana R. Mesquita[a]

[a] CIPsi, School of Psychology, University of Minho, Portugal
[b] Present address: Department of Psychiatry, University of Oxford, UK
[c] Department of Clinical, Educational and Health Psychology, UCL, UK
[d] Department of Human Ecology, University of California, Davis, USA
[e] Present address: Instituto Universitário de Lisboa (ISCTE-IUL), Lisbon, Portugal
[f] Research Centre for Human Development, Catholic University of Portugal, Portugal
[g] Chemistry Centre, University of Minho, Portugal
[h] Present address: REQUIMTE/LAQV, Porto, Portugal

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ABSTRACT

The oxytocinergic system is a primary biological system involved in regulating a child's needs for bonding and for protection from threats. It is responsive to social experiences in close relationships, though evidence across studies is not entirely consistent. Guided by previous literature, we investigated individual and environmental factors predicting and presumably affecting children's oxytocin (OT) response during mother-child interaction. by focusing on children's *OXTR* genotype, and maternal behavior, respectively. This was achieved by assessing salivary OT levels of 88 Portuguese preschoolers prior to and following a mother-child interaction task, and by genotyping children's *OXTR* SNP rs53576. Maternal interactive behavior was assessed using Ainsworth scales.

Results indicated that child genotype and mother's sensitive responsiveness interacted in predicting change in child OT concentrations from before to after the interaction. Specifically, Genotypic differences emerged under conditions of low maternal sensitive responsiveness: OT levels increased over time for children with the GG genotype when maternal sensitive responsiveness was low, but no such genotypic differences were evident when mothers were highly sensitive responsive.

Findings provide preliminary support for the notion that increased understanding of children's OT and close relationships requires consideration of both individual and environmental factors.

## 1. Introduction

The oxytocinergic system is a key biological system underlying the need for bonding and protection from threat (Insel, 2010), with recognized associations with social behavior, particularly involving social affiliation (Winslow and Insel, 2002). Indeed, it has been shown to respond to social interactions. For example, Feldman et al. (2010a) reported that mothers and fathers who provided high levels of tactile contact to their infants evinced increases in salivary oxytocin (OT) following parent–infant interaction. Of particular relevance to this inquiry is that such an increase in OT after such interaction also has been detected in children (Feldman et al., 2010a). In fact, Feldman et al. (2010b) found that infant's OT levels were positively associated with degree of parent-child affect synchrony and the infant's social engagement. The latter represents the earliest set of signals of involvement in a social interaction, and has been shown to predict future cognitive, social, and emotional growth (Marshal and Fox, 2006).

Despite the work just highlighted, research on children's OT response to close interactions, particularly in the context of the mother–infant relationship, remains limited. Thus, building on the aforementioned research, we sought to extend work on social interaction and OT levels by investigating the possibility that children vary, due to their genetic make-up, in how they respond, OT-wise, to parent-infant interaction. We focus specifically on the *OXTR* SNP rs53576 and maternal interactive behavior for reasons outlined below.

According to recent research, one individual factor that might affect OT response to social interaction is the oxytocin receptor gene (*OXTR*). The *OXTR* gene is present in a single copy in the human genome and was mapped to the locus 3p25–3p26.2 (Michelini et al., 1995). A known single-nucleotide polymorphism (SNP) on that gene is the

*E-mail address:* ana.mesquita@psi.uminho.pt (A.R. Mesquita).

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rs53576, which involves a change from guanine (G) to adenine (A) (Meyer-Lindenberg et al., 2011, Domes, Kirsch & Heinrichs, 2011). Although the biological consequences of this variation remain largely unknown, evidence suggests some mechanistic differences between carriers vs. non-carriers of the A allele. For example, the presence of the A allele is associated with less efficacious OT binding (Tost et al., 2010). Notably, however, in research with children, Parker et al. (2014) detected no differences in plasma OT levels as a function of allelic variation. The fact that this work was not undertaken in the context of social interaction may have influenced these results.

This would seem an important consideration given evidence implicating *OXTR* in psychological and behavioral functioning related to social interaction. A-carriers of the *OXTR* SNP rs53576 score lower than others on positive affect (Lucht et al., 2009), optimism and self-esteem (Saphire-Bernstein et al., 2011). And in the context of psychosocial stress exposure, A homozygous prove more responsive to social support than G-carriers, by showing similar cortisol and subjective stress responses in both support and no-support conditions (Chen, Kumsta, von Dawans et al., 2011). In line with these results, adult A-carriers prove less likely to seek social support (Kim et al., 2010). In contrast to these findings though, Parker et al. (2014) found that A-carriers scored higher on affect recognition in a sample which included children with autism spectrum disorder, unaffected siblings and unrelated neurotypical controls. Although little is known about how *OXTR* affects these social and social-cognitive processes, one plausible explanation is that *OXTR* affects OT levels, which in turn influence social behavior.

This speculation is based on evidence that the oxytocinergic system is particularly susceptible to environmental factors and forces (Brunton and Russell, 2010; Feldman, 2012). Especially important to the present inquiry is evidence that OT biology is associated with the quality of early caregiving. Animal studies indicate that the OT system affects the hypothalamic–pituitary–adrenal (HPA) axis via early caregiving experiences early in postnatal life (Hostinar et al., 2014). Indeed, the neurochemical organization of infant brain OT is shaped in early life through patterns of maternal behavior, such as licking and grooming (Kappeler and Meaney, 2010). Specifically, adult female rats that receive less maternal licking and grooming as pups subsequently exhibit decreased OT receptor binding in several brain regions (Francis et al., 2000).

In humans, adverse early caregiving environments also have been associated with lower OT concentrations in cerebrospinal fluid (Heim et al., 2008) and disruption of OT biology in regulating stress-related cortisol responses (Meinlschmidt and Heim, 2007). Studies of early social deprivation, such as institutionalization, further chronicles links between environmental care and OT. Compared with children raised in their biological families, institutionally reared children evince marginally lower levels of OT (Wismer-Fries et al., 2005). Given well-known limits of institutional caregiving environments (Bakermans-Kranenburg et al., 2011; Zeanah et al., 2009), it seems likely that a focus on social experience at the proximate rather than distal level might prove more strongly related to OT levels. It is for this reason that we investigated change in OT levels from before to after a mother-child social interaction task, while taking *OXTR* genotype and maternal behavior into account, following recommendations by Bartz, Zaki, Bolger, and Ochsner (2011). This exploratory study will follow a Gene-X-Environment (GXE) interaction approach and, given the multiplicity of possible outcomes, hypotheses are not advanced.

## 2. Experimental procedures

### 2.1. Participants

The sample consisted of 88 Portuguese preschool children and their mothers. The children were all Caucasian, aged from 40 to 76 months ($M$ = 57.70, $SD$ = 7.25); 45 (51.1%) were girls. Mothers' age ranged from 21 to 48 years ($M$ = 33.67, $SD$ = 5.43). Regarding education level, 14 mothers (15.9%) had less than nine years of education, 32 completed 9 years of education (36.4%), 28 (31.8%) completed high school, and 14 (15.8%) had a higher education degree. With respect to marital status, 18 (20.5%) of the mothers were single, 11 (12.5%) were living with their partners, 49 (55.7%) were married, 8 (9.1%) were divorced, and 2 (2.3%) were widowed.

### 2.2. Procedure

Ethical approval was obtained from University of Minho, Portuguese Ministry of Education, and National Commission for Data Protection. Following the recruitment of dyads from Portuguese preschools, the assessment was conducted either in participants' homes or preschools, depending on participants' availability. The visit started with the study description. Then, informed consent was obtained from the mothers. Mothers were then asked to join the child in an interactive task. The interaction was videotaped across three 5-minute episodes involving: (a) child play with a challenging toy under mother's guidance; (b) maternal completion of a sham questionnaire while the child has only an uninteresting toy to play with, after being instructed by the mother not to touch more interesting, but difficult-to-reach toys; and (c) mother and child engage in free play for half the period followed by mother-directed child clean-up. Child's saliva for OT concentration analysis was collected in two different time points: 1) before the mother-child interaction task, following a 10-min familiarization period with the researchers (with no contact with the mother); 2) immediately after the end of the mother-child interaction task. Finally, a separate saliva sample was collected for genetic analysis. To control for hormonal variability, data collection was done during the afternoon (between 2 p.m. and 5 p.m.).

### 2.3. Measures

#### 2.3.1. Maternal interactive behavior

Maternal behavior was assessed based on the 15-minute videotaped interaction, using Ainsworth's scales for rating maternal sensitivity and cooperation (Ainsworth et al., 1974). Sensitivity reflects the mother's ability to perceive infant signals, interpret them correctly, and react promptly and adequately in a consistent way; cooperation reflects the mother's ability to respect the child's autonomy, avoiding situations in which she might have to interrupt the child's activity or exert direct control. Each dimension was rated on a 9-point scale, with higher scores indicating more caring behavior. The videos were coded by a team of trained researchers, who were blind to the sample characteristics; 32 (36%) of them were coded in pairs. Coding achieved good interrater reliability (sensitivity: ICC = 0.93; cooperation: ICC = 0.87). In line with previous studies (Baptista et al., 2013; Juffer et al., 1997; Tharner et al., 2012), a "sensitive responsiveness" score was computed based on the two highly correlated scales ($r$ = 0.73, $p$ < .001), by averaging the two $z$ scores. In this study, the raw mean score for sensitive responsiveness was 4.75 ($SD$ = 1.57, range 1.5–7.5).

#### 2.3.2. Child's salivary OT concentrations

To assess child's OT levels, saliva samples were collected using Salivette devices (Sarstedt, Rommelsdorft, Germany). Children were instructed to place a cotton swab in the mouth and chew for a minute. Salivettes were kept chilled before being centrifuged at 4 °C at 3200 rpm for 10 min. Samples were then stored at −80 °C. An extraction step was performed to concentrate the sample, increase precision and reduce matrix interference. A strata X 33 µm polymeric reversed phase SPE sorbent was equilibrated in a 12 tubes-system containing 60 mg sorbent per tube, Phenomenex, Torrance CA, by adding 1 ml MeOH followed by 1 ml of water. Next, 0.4 ml of saliva was acidified with 0.2 ml of 1.5% trifluoroacetic acid (TFA) and centrifuged at 6000 × $g$ for 20 min at 4 °C. The supernatant was loaded onto the pre-treated strata-X tubes. The tubes were slowly washed with 1.5 ml of 0.1% TFA, and then the peptide was eluted with 1 ml of 80% acetonitrile. The

eluant was collected in a polystyrene tube and evaporated to dryness under a N2 stream. The residue was reconstituted in 250 µl of assay buffer. Determination of OT was performed using a commercial Oxytocin ELISA kit (Enzo Life Sciences, NY, USA) according to the manufacturer's instructions.

In the present study, the mean score for child's salivary OT concentrations at baseline was 23.60 pg/ml ($SD$ = 14.92); and for the post-interaction was 24.96 pg/ml ($SD$ = 23.70). An OT response variable was calculated based on the difference between the OT values post- and pre-interaction task, each of them previously log-transformed.

#### 2.3.3. Child's OXTR genotype

For genotyping, child's saliva was collected using OraGene OG-500 (DNA Genotek, Inc., Ottawa, Ontario, Canada) and stored at room temperature. Genomic DNA was isolated as instructed by the manufacturers, using the standard protocol from PrepIT L2P (DNA Genotek) and sample concentrations were assessed using Nanodrop technology. Analysis of the *OXTR* SNP rs53576 was performed using 5 ng of DNA along with the corresponding KASPar assay (LGC Genomics, UK), for a final volume of 8 µL. The thermal profile was performed as instructed by the manufacturers, in a 7500 Fast Real-Time PCR System (Applied Biosystems by Life Technology, USA). Results were validated by Sanger Sequencing of representative samples for each genotype (AA, AG or GG). Allelic frequencies were in Hardy-Weinberg Equilibrium (GG 50, GA 31, AA 7, $\chi^2$ (1) = 0.488, $p$ = 0.485). Concerning genotyping, 50 children (56.8%) were homozygous for the G allele and 31 (35.2%) were heterozygous. Minor allele (A) frequency was 0.26. Primary statistical analysis contrasted A-carriers (AA/AG) and G homozygotes (GG).

### 2.4. Statistical analysis

Descriptive data and pearson or point-biserial correlations among study variables are presented first. Next, hierarchical regression analysis was used to predict changes in child's OT response. In this analysis, child's genotype (i.e., presence vs absence of the A allele) and maternal sensitive responsiveness were entered separately in the first step, and their 2-way interaction in the second step. Finally, follow-up analysis in the form of $t$-tests were performed. For this analysis, a median split (Median = 0.23) was performed on maternal sensitive responsiveness, in order to dichotomise it into low and high scores.

## 3. Results

### 3.1. Descriptive statistics

Table 1 displays OT concentrations according to maternal sensitive responsiveness and child's genotype, and shows no group differences.

Bivariate associations of study variables are displayed on Table2. No association emerged between the child's OT response and child's sex, age, or *OXTR* genotype. Likewise, child's OT response was not associated with maternal age, level of education or sensitive responsiveness.

**Table 1**
OT concentrations according to child's genotype and maternal sensitive responsiveness.

| | Low scores maternal behavior | High scores maternal behavior | |
|---|---|---|---|
| **OT Pre** | 22.99 (14.46) | 23.54 (15.10) | $t_{(85)}$ = -.172, $p$ = .864 |
| **OT Post** | 24.30 (20.08) | 22.45 (15.66) | $t_{(86)}$ = .487, $p$ = .628 |
| | **GG** | **AG/AA** | |
| **OT Pre** | 22.86 (13.29) | 24.57 (16.98) | $t_{(86)}$ = -.530, $p$ = .598 |
| **OT Post** | 24.83 (18.99) | 25.04 (28.65) | $t_{(87)}$ = -.042, $p$ = .967 |

Note. Low and high scores based on median split for sensitive responsiveness.

**Table 2**
Correlations between study variables.

| | 1. | 2. | 3. | 4. | 5. | 6. |
|---|---|---|---|---|---|---|
| **1. Child's Sex** | – | | | | | |
| **2. Child's Age** | −.001 | – | | | | |
| **3. Child's OXTR** | −.026 | −.143 | – | | | |
| **4. Mother's Age** | −.041 | .139 | −.138 | – | | |
| **5. Maternal Educational Level** | .077 | −.042 | .018 | .150 | – | |
| **6. Maternal Sensitive Responsiveness** | −.168 | .115 | −.060 | .097 | .407** | – |
| **7. Child's OT response** | .074 | .067 | −.068 | .166 | .100 | .040 |

Note. N = 88; ** $p$ < .01. Child's Sex: 0 girls; 1 boys. Child OXTR: 0 GG; 1 AA/AG.

No group differences according to settings (home vs. preschool) were found regarding the variables of interest ($t_{(86)}$ = 1.288, $p$ = .201 for maternal behavior; $t_{(86)}$ = −0.468, $p$ = .641 for child's OT response).

### 3.2. Predicting change in OT

Table 3 presents results of a hierarchical regression analysis which included three predictors—main effects of child genotype and maternal sensitive responsiveness (step 1), followed by their interaction (step 2). Its inspection reveals that maternal sensitive responsiveness and child genotype interacted in predicting change in child OT levels ($B$ = 0.084, $SE$ = 0.037, $t$ = 2.277, $p$ = .025)—and no main effects of these predictors. Notably, similar results emerged when maternal education was included as a covariate in what became the first step of a now 3-step hierarchical regression model (i.e., no main effect of predictors; GXE interaction effect $B$ = 0.085, $SE$ = 0.037, $t$ = 2.318, $p$ = .023).

Follow-up analyses designed to illuminate the nature of the GXE interaction detected revealed that genotypic differences emerged under conditions of low maternal sensitive responsiveness ($t_{(36)}$ = 3.007, $p$ = .005). Inspection of Fig. 1 shows that for G homozygotes OT levels increased ($M$ = 0.08, $SD$ = 0.18), whereas for A carriers they decreased ($M$ = −0.10, $SD$ = 0.164). No such differences were evident when mothers were highly sensitive responsive.

## 4. Discussion

In an effort to identify individual and environmental determinants of the variation in the child's OT response during a mother-child interaction, we considered child *OXTR* genotype, maternal behavior and their interaction. Despite not being independent predictors of the child's OT change, child's *OXTR* SNP rs53576 and maternal behavior interacted to predict this outcome. Specifically, in the presence of lower quality scores of maternal sensitive responsiveness, child's OT levels tended to increase during the interaction only for the G homozygotes, and the opposite trend was found for A-carriers. Such genetic differences were not evident when mothers provided high levels of sensitive responsive care.

Regarding these two patterns of OT response to maternal behavior, the fact that, for a group of children (A-carriers) OT seemed to be lower after their interaction with less responsive mothers might be explained by the fact that such social encounters would not be experienced as pleasant, rewarding or engaging. Conversely, there was a group of children (G homozygotes) that manifested an increase in OT levels during the interaction with less responsive mothers, which is more intriguing, as we would possibly expect a lower level of engagement and pleasantness in the interaction with a mother who tends to be less sensitive and cooperative. It is, nonetheless, in agreement with the research line that considers OT as a biomarker of social distress. From this perspective, OT production is due to problematic social relationships, providing an impetus for affiliation in situations where such support is

**Table 3**
Prediction model for OT change, considering child OXTR SNP rs53576 and maternal sensitive responsiveness as predictors.

| Model; Predictors | $R^2$ ($R^2_{adj}$) | $F$ (df) | Unstandard. Coefficient | | $T$ | $p$ | 95% CI | |
|---|---|---|---|---|---|---|---|---|
| | | | $B$ | $SE$ | | | Lower | Upper |
| 1 | | | | | | | | |
| Maternal sensitive responsiveness | .015 | .652 (286) | .005 | .018 | .299 | .765 | −.030 | .041 |
| Child OXTR | (-.008) | | −.037 | .034 | −1.082 | .282 | −.105 | .031 |
| 2 | | | | | | | | |
| Maternal sensitive responsiveness | .073 (.040) | 2.184$^+$ (386) | −.024 | .022 | −1.108 | .271 | −.068 | .019 |
| Child OXTR | | | −.043 | .034 | −1.293 | .200 | −.110 | .023 |
| Maternal sensitive responsiveness X Child OXTR | | | .084 | .037 | 2.277 | .025 | .011 | .157 |

Note. N = 88; + p < 1.

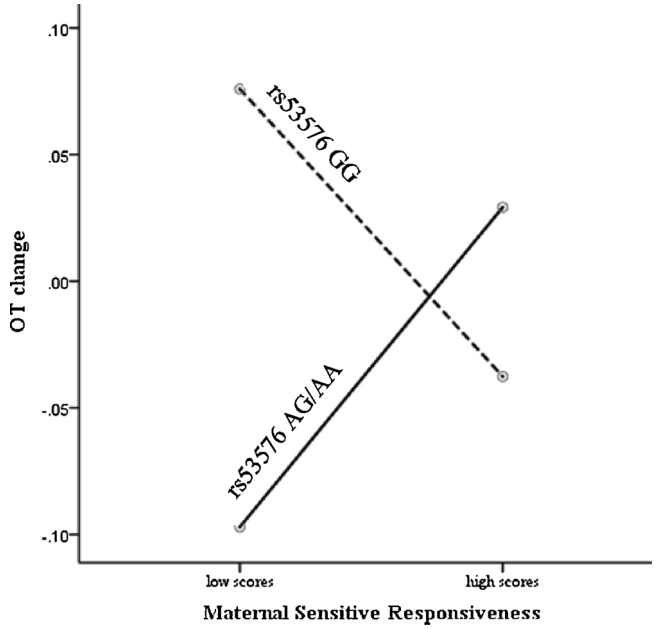


**Fig. 1.** Plot of the interaction between child OXTR SNP rs535765 (AG/AA vs GG) and maternal sensitive responsiveness in relation to child OT change (log-transformed) during an interactive task with the mother.

not present (cf. Taylor, 2006). Specifically, based on the need to maintain an adequate level of protective and rewarding social relationships, OT would be released to motivate seeking affiliative contact.

Interestingly, our results show that these different patterns of response depend on the child's genotype. This difference seems in line with previous findings showing that G-carriers are more likely to seek social support (Kim et al., 2010), and benefit more from that support (Chen et al., 2011). Such processes would seem to make this genotype more inclined to engage in affiliative efforts. G-carriers have also been shown to be more optimistic and have higher levels of self-esteem (Saphire-Bernstein et al., 2011), which is also seemingly consistent with this view.

The GXE interaction effect we detected is in line with Bartz et al. (2011), who highlighted the importance of considering an interactionist approach including individual and situational factors when investigating the oxytocinergic system. These scholars reviewed 53 studies on the social effects of OT administration, discovering that in the majority of investigations effects were person- and context-dependent.

Future research should assess other constructs related to social interaction, such as emotion regulation (Quirin et al., 2011), psychopathology (Prenoveau et al., 2013), tactile contact (Feldman et al., 2010b) or synchronous parenting (Feldman et al., 2010b). All of these constructs have previously been linked to OT. Given findings reported herein, it would also be informative to determine whether the child's attachment security affects the child's OT function in future studies.

Moreover, it would be interesting and informative to explore the seemingly paradoxical fact that high levels of OT can be associated both with relationship distress and with reduced stress responses. Taylor (2006) suggests that this may relate to different patterns of OT activation – where bursts of OT (for example, related to exogenous administration, or in response to anticipated/actual social contact) would reduce stress responses; but persistent elevated OT would associate with relationship distress. This topic should be further examined by future research.

Limitations of the present study should be taken into account. Firstly, it has a limited sample size, especially as it includes a genetic variable. Nonetheless, the allelic frequencies were in Hardy-Weinberg Equilibrium (HWE), which has been considered a potential indicator of quality (Bakermans-Kranenburg and van Ijzendoorn, 2014; Namipashaki et al., 2015). As stated by Namipashaki et al., (2015), deviations from HWE may reflect important problems, including selection bias, population stratification and genotyping errors. Nonetheless, there is still the limitation of relying on the analysis of one SNP. Authors have questioned the use of single candidate genes when investigating genotype-phenotype associations, since most human traits are complex and are likely to be influenced by mutations at multiple loci, with independent and/or interaction effects between them (i.e., epistasis) (Robinson et al., 2014). In this study, we attempted to addressed this issue by conducting research on GXE interaction. In fact, it has been argued that gene-environment interaction may undermine the ability to discern main effects of candidate genes (Robinson et al., 2014).

Another limitation, which is unavoidable in human research, is the reliance on a peripheral assessment of OT. Although the relation between central and peripheral OT is not fully understood, both animal studies (Wotjak et al., 1998; Carter et al., 2007; Ross and Young, 2009) and human research (e.g., Strathearn et al., 2009) suggest that central and peripheral activities of the OT system are likely to be coordinated. Regarding salivary OT in particular, Carter et al. (2007) demonstrated that it is a reliable biomarker of peripheral OT, showing moderate correlations between plasma and salivary OT concentrations (see also Feldman et al., 2011; Grewen et al., 2010. A recent meta-analysis of central and peripheral OT concentrations also found this link, but only for exogenous OT administration, not for OT baseline conditions (with no experimental intervention) (Valstad et al., 2017). In our study, the salivary OT measure was based on two time points of a structured interaction, and therefore it would not be considered baseline, but a measure of change following an experimental manipulation (i.e., social interaction). Nonetheless, further research comparing salivary and plasma OT in different settings and measured simultaneously is needed, as well as further studies on central and peripheral OT.

### 4.1. Conclusion

Despite the limitations, these findings are generally consistent with research indicating that the OT response/oxytocinergic function is not uniform and depends on both individual and situational factors (Bartz et al., 2010). Our results suggest an interplay between genetics and quality of care, which could be pivotal to the understanding of the OT-based foundations of social behaviour and close relationships in young children.

## Conflict of interest

The authors report no conflict of interest with regard to the submitted manuscript.

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