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Oxytocin Receptors (OXTR) and Early Parental Care: An Interaction That Modulates Psychiatric Disorders

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Abstract

Oxytocin plays an important role in the modulation of social behavior in both typical and atypical contexts. Also, the quality of early parental care sets the foundation for long-term psychosocial development. Here, we review studies that investigated how oxytocin receptor (OXTR) interacts with early parental care experiences to influence the development of psychiatric disorders. Using Pubmed, Scopus and PsycInfo databases, we utilized the keyword “OXTR” before subsequently searching for specific OXTR single nucleotide polymorphisms (SNPs), generating a list of 598 studies in total. The papers were catalogued in a database and filtered for gene-environment interaction, psychiatric disorders and involvement of parental care. In particular, rs53576 and rs2254298 were found to be significantly involved in gene-environment interactions that modulated risk for psychopathology and the following psychiatric disorders: disruptive behavior, depression, anxiety, eating disorder and borderline personality disorder. These results illustrate the importance of OXTR in mediating the impact of parental care on the emergence of psychopathology.

Keywords: gene-environment interaction, OXTR, parental bonding, rs2254298, rs53576, psychiatric disorders

Introduction

1.1 Oxytocin and Biological Functions, Affiliation and Social behavior

The oxytocin receptor (OXTR) gene is a protein that works as a receptor for the widely expressed oxytocin, which acts both as hormone and neurotransmitter. OXTR encodes 389 amino acids and it is present as a single copy in the human genome mapped to the gene locus 3p25–3p26.2. The gene spans 19.2 kb on chromosome 3, and contains 3 introns and 4 exons (International HapMap Consortium et al., 2007). It is well known that the oxytocin system exerts its effects on biological functions, in both humans and animals, such as on reproduction, parturition and breastfeeding (Xu et al. 2017; Ilicic et al. 2017; Mandelli and Serretti 2013), metabolism and body weight regulation (Blevins & Baskin, 2015; Klockars et. al., 2015; Ho & Blevins, 2013;), and recently, on the mechanisms behind eating disorders (Arase et al.,2017; Bush et al. 2017; Smearman et al., 2016; Kim et al., 2015). However, its effects are not just restricted to biological processes. There are many implications of OXTR regulation on complex social behaviors like parenting (Bendesky et al. 2017; Leerkes et al. 2017, Bush et al. 2017; Esposito et al., 2016; Senese et al., 2016; Smearman et al., 2016; Unternaehrer et al., 2015; Klahr et al., 2015; Feldman et al., 2013; Kryski et al. 2014) affiliative behavior (Hygen et al. 2017; Feldman et al., 2016; Smearman et al., 2016; Mileva-Seitz et al., 2013; Bakermans-Kranenburg & van Ijzendoorn, 2008), construction of interpersonal bonds (McInnis et al. 2017; Denes 2015; Kumsta & Heinrichs, 2013; Krueger et al., 2012; Pouli et al., 2012; Chen et al., 2011; Kogan et al., 2011; Bartz et al., 2011; Insel & Young, 2001; Feldman et al., 2012; Rodrigues et al., 2009), romantic relationships (Walum et al., 2012; Schneiderman et al., 2014; Sturge-Apple et al., 2012; Chang et al., 2013) and responses to stressful social situations (Cristóbal-Narváez et al. 2017; Chen et al. 2017; Bonassi et al. 2017; Unternaehrer et al. 2012; Feldman et al., 2012; Rodrigues et al., 2009; Heinrichs et al., 2009; Domes et al., 2007; Kirsch et al., 2005).

1.2 Oxytocin Receptor (OXTR) Single Nucleotide Polymorphisms (SNPs)

Researchers have begun to demonstrate that people tend to inherit genetic predispositions to a certain disorder rather than inherit the disorder itself. Thus, the vulnerability lies within the phenomenon of gene expressions (Schroeder et al., 2010; Murgatroyd et al., 2009; Poelmans et al., 2013). Within the introns and exons of OXTR encoding gene, it is possible to extract information about over 5000 single nucleotide polymorphisms (SNPs), which are essentially variations of genic material, on charge of a nucleotide (International HapMap Consortium et al., 2007). Even though SNPs are located in the intronic region of the gene that encodes for OXTR, with no effects on OXTR

functionality per se, some studies revealed that polymorphisms are related to biological differences in plasma levels of oxytocin (Feldman et al., 2012; Luo et al., 2012; Yamasue, 2013). Intronic OXTR gene polymorphisms might have regulatory functions (Smearman, Yu, et al., 2016), causing altered splicing or affecting the transcription or methylation of adjacent genomic regions (Cooper, 2010). The growing evidence that associates this neurohormone to a list of individual susceptibility is "tickling" the interest of many (Ebstein et al., 2009; Jacob et al., 2007; Lerer et al., 2008; Liu et al., 2010; Meyer-Lindenberg & Tost, 2012; Wermter, Kamp-Becker, et al., 2010; S. Wu et al., 2005; Yrigollen et al., 2008; Guastella et al. 2012; Gregory et al., 2009). As a result, the set of SNPs that are being investigated continues to widen (LoParo & Waldman, 2015; Yamasue, 2013; Lerer et al., 2008). Many variations have already been explored, not only within SNPs, but also in haploid genotypes (or haplotypes), which are groups of genes inherited together (Beitchman et al., 2012; Lerer et al., 2008; Lucht et al., 2009; N. Wu, Li, & Su, 2012). In some studies, OXTR rs1042778 and rs237887 are investigated together, suggesting that this couple might be involved in regulatory mechanisms of social stress (Kumsta & Heinrichs, 2013), and pair bonding behaviors (Walum et al., 2012). In this review, we will be discussing primarily about SNPs, considering them singly. The following figure (Figure 1) shows where the different SNPs presented in this review are located inside the OXTR gene.

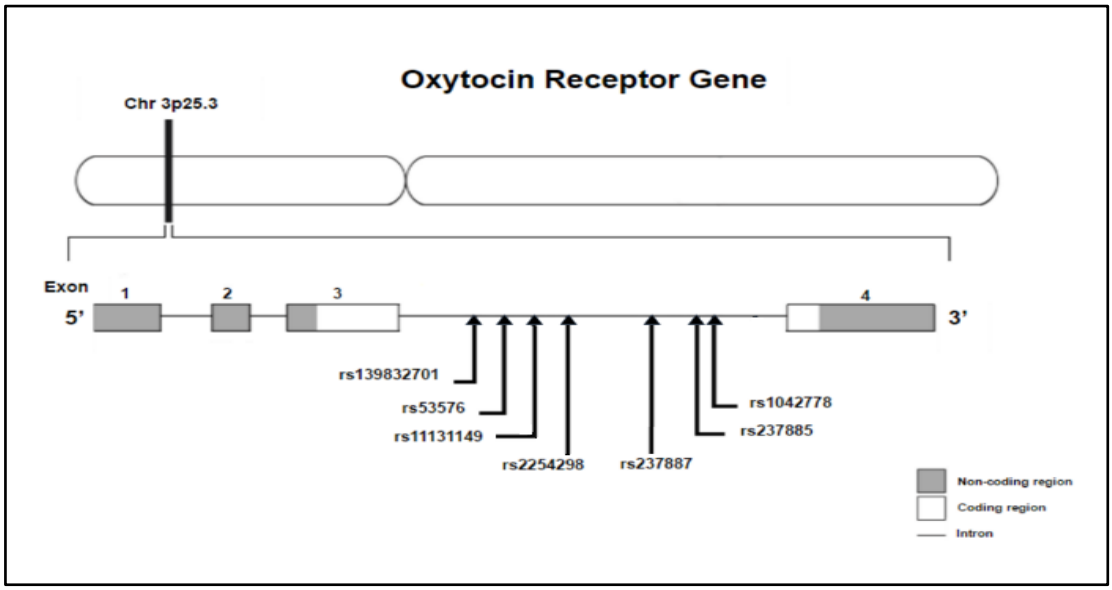

Figure 1. The OXTR gene encodes 389 amino acids and is present as a single copy in the human genome mapped to the gene locus 3p25–3p26.2. The gene spans 17 kb and contains 3 introns and 4 exons. The relative locations of seven OXTR SNPs of interest on a pre-mature mRNA transcript, are depicted here: rs139832701, rs53576, rs2254298, rs237887, rs237885, rs1042778 and rs11131149. These SNPs were previously found to contribute to the development of psychiatric disorders. rs139832701 (G/T) has a chromosomal base-pair (Chr. bp) location of 8773124. rs53576 (G/A) has a chr. bp location of of 8762685, while rs11131149 (G/A) is located at chr. bp 8761165. rs2254298 (G/A) has a chr. bp location of 8760542. Further downstream, rs237887 (G/A) has a chr. bp of 8755356, while rs237885 (G/T) has a chr. bp of 8753857. Nearer to exon 4, rs1042778 (G/T) is located at chr. bp 8752859.

1.3 General Functions of OXTR SNPs

Several studies showed that the gap between genotype (SNPs) and phenotype (social behavior) might be bridged by OXTR activity in the brain (Wade et al.,, 2015; Yamasue, 2013), especially in areas such as the amygdala, dorsal anterior cingulate gyrus and hypothalamus (Inoue et al., 2010; Tost et al., 2010; Yamasue, 2013), that are largely involved in social cognition and cognitive development (Carter, 2014). Some known downstream mechanisms of OXTR include fostering of stem cell differentiation or inhibiting programmed cell death (Carter, 2014; Gutkowska & Jankowski, 2012; Leuner et al., 2012). Thus, variability in, and expression of, OXTR SNPs might produce consequential effects on structural and functional neuroanatomy through modulation of OXT activity (Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012).

In 2012, Brüne suggested that the A allele of the OXTR rs2254298 polymorphism might be involved in plasticity processes, increasing resilience in dealing with a stressful environment, especially during early life stages (Brüne, 2012). In fact, it is possible to find evidence in the literature that links rs2254298 polymorphisms with biological differences, such as lower plasma levels of OXT in GG carriers (Feldman et al., 2012), while A carriers show increased volume of the amygdala (Ebstein et al. 2012; Meyer-Lindenberg and Tost 2012; Bethlehem et al. 2013); Furman et al., 2011; Inoue et al., 1994) and decreased volume of the hypothalamus (Tost et al., 2011). Many studies have elucidated the influence of OXTR rs2254298 over social skills and cognition (Kalyoncu et al. 2017; King 2016; Micali et al., 2016; Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012; Brüne, 2012; Feldman et al., 2012; Bickart et al., 2011; Furman et al., 2011), anxiety and depression (Gottschalk and Domschke 2017; Costa et al. 2017; Smearman et al., 2016; Costa et al., 2009; Thompson et al., 2011; Chen and Johnson 2011; Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012; Kawamura et al., 2010), eating disorders (e.g., bulimia nervosa) (Kim et al., 2015; Acevedo et al., 2015; Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012), parenting (Senese et al., 2016), and autism (Hernandez et al. 2017; Klein et al. 2017; Yang et al. 2017; Zhang et al. 2017; Warrier et al. 2015; Wu et al., 2005; Liu et al., 2010; Kinney et al., 2008; Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012). Generally, it seems that the A variant of this polymorphism confers a greater susceptibility to environmentally unfavorable conditions (e.g., prenatal contingencies) (Reiner et al. 2016; van Roekel et al. 2013; Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012; Ronald et al., 2010), leading to an autistic phenotype, or otherwise to higher sociability.

Similar to the previous SNP, GG carriers of rs53576 have been found to be linked to greater adult emotional dysregulation (Bradley et al., 2011), depressive symptoms in people who experienced childhood maltreatment and negative environmental conditions (McQuaid et al., 2013; Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012), and psychopathology, such as eating disorders (Smearman et al., 2016; Kim et al., 2015; Acevedo et al., 2015) and depression (Adrian et al., 2015; Hostinar et al., 2014; Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012; Thompson et al., 2014; McQuaid et al., 2013; Bradley et al., 2011; Saphire-Bernstein et al., 2011); some results are still inconsistent though (Tollenaar et al. 2017). With regard to parenting attitudes, Senese and colleagues found more positive implicit association to infant faces in G homozygous carriers than in A carriers (Senese et al., 2016), while in 2008, Bakermans-Kranenburg and van Ijzendoorn showed that people with the A allele variation of this SNP displayed lower parental sensitivity (Bakermans-Kranenburg & van Ijzendoorn, 2008). Generally, many studies suggested that in early life stages, rs53576 might reflect a sensitivity to familial environment, parental warmth and perceived social support, and this SNP was associated with a reduced ability to benefit from social support (Mileva-Seitz et al. 2016; Kryski et al. 2014; Hostinar et al., 2014; Chen et al., 2011; Kim et al., 2010) and resilience to stressful situations (Bonassi et al. 2017; Myers et al. 2014; Bradley et al., 2013; Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012; Rodrigues et al., 2009), leading sometimes to mental health issues in adulthood (McInnis et al., 2015; Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012; Bradley et al., 2011; McQuaid et al., 2013; Hostinar et al., 2014; Belsky & Pluess, 2009). These findings suggest that G carriers are more sensitive to the surroundings, both in favorable or negative contexts. This elevated susceptibility to the environment may affect neural plasticity in mechanisms involving the oxytocin system (Lin et al., 2012).

With regard to children and adolescents with behavioral dysregulation (Sakai et al., 2012) or callous-unemotional traits (Beitchman et al., 2012), rs237885 had a higher association than other SNPs or haplotypes; it is not possible to assert, so far, that this variation is strictly correlated to aggressive behavior, since the result might be the effect of a whole haplotype. In 2014, Myers et al. were the first authors to publish a study about association between exposure to stress in early life stages and increased risk for anxiety and depression. They found a significant correlation between individuals with the OXTR rs139832701 variant, who were also exposed to stress, and more severe symptoms of anxiety, depression and stress (Myers et al., 2014). Similar to others SNPs, this genotype variant was found to confer a higher sensitivity to environmental stress, thus increasing the probability of developing symptoms of anxiety and a depressive temperament. So far, this is the only research done on this specific variation.

A parallel idea that has been gaining recognition relates to the epigenetic modification of OXTR, which occurs by DNA methylation. This process varies from one individual to another, and results in

differences in gene transcription. While implications on specific social behaviors are still unknown, we came across studies reporting some results at an epigenetic level. Those that investigated on psychiatric disorders (Chen et al. 2017; Gouin et al. 2017; Smearman, et al., 2016; Unternaehrer et al., 2015; Cecil et al., 2014) found alteration in brain areas that are influenced by OXTR functionality. Specific results will be further discussed in this review. As have been explained so far, there are many OXTR SNPs and there is a considerable amount of literature about them. In our review, we focused on OXTR SNPs rs2254298 and rs53576, recapitulating recent findings to further understand the clinical implications of OXTR variations. We looked at the latest studies to uncover possible future directions that could overcome the limitations of past research.

2. Method

We decided to use Pubmed, Scopus and PsycInfo databases to browse for articles on the oxytocin receptor system. Firstly, we gathered all the papers that were generated by the keyword “OXTR”. Then, we made two new searches using the Boolean operator “OR” for different SNPs: first we included rs53576, rs2254298 and rs2268493, and then we added rs237092, rs6133010 and rs237885. This search resulted in a long list of papers (n=598), which was organized in a database and subsequently filtered according with the PRISMA guidelines as represented in Figure 2. We selected which articles to study based on these fixed criteria: the SNPs that were discussed (rs53576, rs2254298, rs2268493, rs237902, rs6133010, rs237885), whether the sample was human or animal species, if there was a gene-environment interaction, if parental care was involved in the research and lastly, if and which psychiatric disorders were presented. After having catalogued all 598 papers, we filtered them and developed 5 different lists: a general one including papers on OXTR SNPs rs53576 and/or rs2254298 (241 papers), since these are the SNPs of interest, and gene-environment interaction (119 papers), a second one filtering the database by OXTR, presence of psychiatric disorder, interaction between gene and environment, and involvement of parental care (30 papers). In order to better understand and parse out the contribution of the authors in each field, we searched, among the papers on OXTR, for the ones integrating gene-environment interaction and psychiatric disorders (55 papers), the ones combining gene-environment interaction and parental care (66 papers in total, 51 of whom referred to a human sample) and those involving psychiatric disorders and parental care (34 papers). In the following paragraphs we will discuss these topics, starting from a more general point of view then focusing on increasingly specific issues.

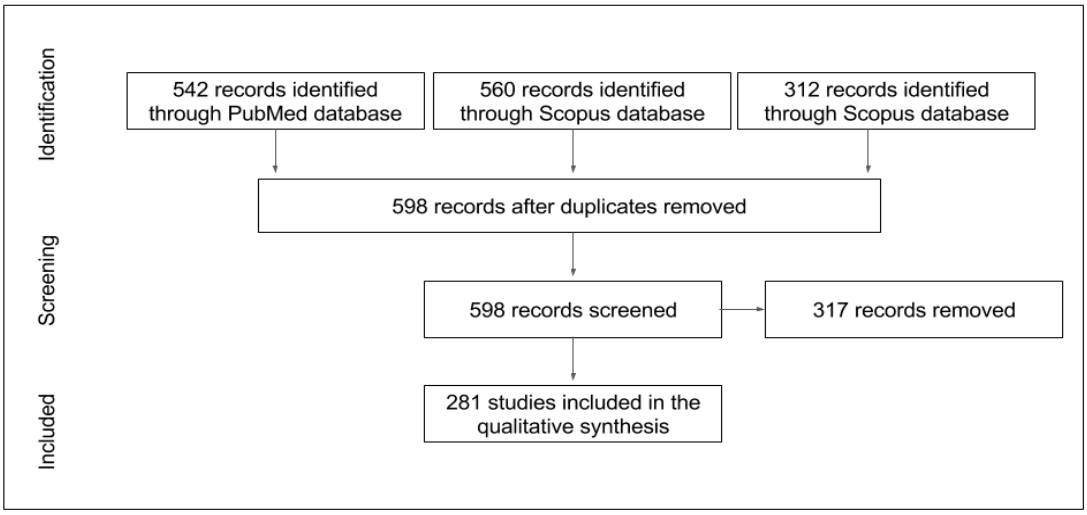

Figure 2. PRIMA flow criteria for inclusion.

3. OXTR and Parental Care: Modulation of Psychiatric Disorders

3.1 Overview

Amidst an expanding interest in the interaction of oxytocin with environmental factors, one particular area that has been receiving greater attention is parental care. Adults' emotional response to infant cues has been shown to predict later attachment style and security (Reiner et al. 2016; Denes 2015; Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012; Leerkes et al., 2011; Chen & Johnson 2011), shape resilience against the adverse effects of stressors (Sippel et al. 2017; Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012; Cohen & Wills, 1985; Thoits, 2011) and have long-term consequences (Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012; Joosen et al., 2012; Leerkes et al., 2011; McElwain & Booth-LaForce, 2006). Given the enduring impact that parenting has been found to exert on lifelong development, parental care remains a topic of focus in gene-by-environment studies that involve the "social hormone", oxytocin.

Early environmental factors leave enduring consequences in their wake. Over the past few decades, a robust link has been drawn between adversities, which occurred during childhood and subsequent mental health issues in adulthood (Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012; Paolucci et al., 2001). This relationship has been shown to persist due to a fundamental dysregulation of emotion processing systems and stress response pathways upon being exposed to early adverse experiences (Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012; Paolucci et al., 2001; Repetti et al., 2002, mediated partly by oxytocin (Heinrichs & Domes, 2008). Variation in OXTR modulates sensitivity to social contexts (Kumsta & Heinrichs, 2013), such that those with variants that render them more vulnerable to adverse social factors are more

differentially susceptible to developing symptoms of psychopathology (Anderson et al. 2017; Belsky et al., 2009; Brüne, 2012). For instance, OXTR variants have been found to differentially affect responses of youth to parental behavior, and moderate the effects of early parental care (Bonassi et al. 2017; Esposito et al. 2016). Amongst adolescent youth, OXTR rs53576 G/G homozygotes were found to be most responsive to parental support and intervention (Smearman, et al., 2016). Male A-carriers of this polymorphism with a history of paternal overprotection have been shown to be more susceptible to social distress, exhibiting greater increases in heart rate and nose temperature changes, than those with G/G genotype (Esposito et al., 2016). Since early adverse experiences often manifest in the context of inadequate parental care, studies on gene-by-environment interactions between OXTR and parental care represents a crucial area of research that could strengthen the framework of how gene and environment jointly contribute to etiologies underlying psychological disorders (Wermter et al., 2010).

3.2 Risk for Psychopathology

3.2.1 Information-processing biases

Recently, (Burkhouse et al., 2016) discovered that children with the OXTR rs53576 G/G genotype, when raised by mothers with a history of major depressive disorder (MDD), showed a higher propensity to detect sad faces and diminished sensitivity in detecting happy faces, as compared to those raised by nondepressed mothers. Deficits in emotion recognition were not evident amongst A-carriers, and surfaced amongst children with G/G genotype only upon exposure to maternal depression. These findings suggest that individuals with G/G genotypes, who are more affected by their social environments (Merrill et al. 2017; McQuaid et al., 2013; Pollak, 2003), which in this context is the quality of parental care, are more likely to develop a preferential processing of recurring subtle cues of sadness. Sensitivity to these cues potentially allowed children of depressed mothers to adapt their behaviors according to their mothers' emotional states. However, these information-processing biases risk developing into maladaptive deficits that have been shown to be associated with a myriad of psychopathologies (Gottschalk % Domschke 2017; Bittencourt Jacondino et al. 2014; Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012; Golarai et al., 2006; Edwards et al., 2002).

3.2.2 Cross-generational Transfer of Psychiatric Predisposition

A family-based approach in examining OXTR revealed that rs2254298 G/G genotypes were markedly overrepresented in families with maternal depression and were associated with lower

concentrations of salivary oxytocin (Apter-Levy et al., 2013; Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012). Dysregulation of oxytocin functioning in depressed mothers was evident by the genetic risk (rs2254298 G/G genotypes) and lower salivary oxytocin that they borne. Fathers from these families possess lower peripheral oxytocin (Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012; Feldman et al., 2010), which resulted in children who were raised in low-oxytocin conditions and who received inadequate parental care (Furman et al., 2011). Depressed mothers with a single A-allele, however, exhibited higher oxytocin levels and predicted children's' positive social development. This study demonstrates the cross-generational transfer of predispositions to psychiatric susceptibility, involving both a genetic risk and detrimental parental caregiving behavior.

3.2.3 Emotional Dysregulation and Insecure Attachment

Oxytocin interacts with parental care to modulate a fundamental cornerstone of human social development: parent-infant bond and subsequent adult attachment. High plasma oxytocin levels correlated with longer parent-infant gaze synchrony (Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012; Feldman et al., 2011; Feldman et al., 2012). Both maternal and paternal peripheral oxytocin levels shape the infant's oxytocin profile (Feldman et al., 2013; Bales & Perkeybile, 2012), and social reciprocity in multiple affiliative attachments were found to be synergistically contributed by parents' oxytocin levels and early parenting practices (Cruwys et al., 2014; Feldman et al., 2013). Early life adversities, in the form of abusive parental care, lead to sociocognitive deficits that present a risk for psychopathology (Anda et al., 2006; De Pauw & Mervielde, 2010; R. F. Krueger et al., 2002), and trigger the concurrent initiation of fear and attachment responses (Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012; Anda et al., 2006; Moriceau et al., 2010, 2009). Additionally, the continual importance of OXTR in influencing attachment security across the span of development has been illustrated (Bradley et al., 2011; Raby et al., 2013). Indeed, the OXTR variant rs53576 was found to interact with the severity of childhood maltreatment to predict deficits in adult emotional regulation and attachment security (Bradley et al., 2011). Amongst individuals with OXTR rs53576 G/G genotype, but not in A-carriers, insecure childhood attachment also predicted alexithymia in adulthood, higher mentalizing-related brain activity and an increased amygdalial grey matter volume (Schneider-Hassloff et al., 2016), while secure infant attachment reliably predicted general and romantic attachment security in adulthood (Raby et al., 2013; Bradley et al., 2011). In a dose-dependent manner (Bradley et al., 2011; Anda et al., 2006), an increasing number of categories of childhood maltreatment was associated with significantly more emotional dysregulation and attachment insecurity in G/G homozygotes than in A-carriers. In line with the differential susceptibility hypothesis,

the G/G genotype of rs53576 possesses a malleable characteristic (Tost et al., 2010), in that it promotes resilience in enriching environments but poses a risk under stressful or adverse circumstances (H. S. Kim et al., 2010).

3.2.4 Internalizing Symptoms

While some individuals develop psychopathological symptoms upon experiencing childhood maltreatment, others display extraordinary resilience. To investigate this differential effect, a study by (Hostinar et al., 2014) examined the interaction between OXTR rs53576 and maltreatment. A gene-by-environment interaction was illustrated by how the same objective measures of maltreatment (category, brutality of abuse or duration), generated significantly greater internalizing symptoms in G/G homozygotes as compared to A-carriers. Those with the G/G genotype could have also been more sensitive to adverse social occurrences (McQuaid et al., 2013; Pollak, 2003), leading them to consistently report the perception of lower social support than A-carriers. G/G homozygotes have been found to be more attuned to salient social stimuli (Kogan et al., 2011; Tost et al., 2010). However, in an abusive environment where anger and aggression are frequently displayed by parents, such an empathic trait might subject G/G homozygotes to greater distress (Rodrigues et al., 2009). Internalizing symptoms might inhibit these individuals from forming healthy adult relationships, making them more susceptible to psychopathology (Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012; Bolger et al., 1998; Rodrigues et al., 2009; Rogosch et al., 1995).

3.2.5 Childhood Maltreatment and Resilience

Interaction between OXTR and poor parental care has been made evident especially in studies of maltreatment. Severe childhood maltreatment has been shown to interact with OXTR rs53576, subjecting G/G homozygotes, but not A-carriers, to a greater risk of emotional dysregulation and a more pronounced disorganized attachment style in adulthood (Bradley et al., 2011). Early emotional abuse was associated with higher salivary oxytocin levels and was found to indirectly modulate processing of infant expressions (Bhandari et al., 2014). A study on harsh parenting, by (Brody et al., 2016; Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012), revealed that difficult temperament in pre-adolescence forecasted harsher parenting behavior which resulted in poorer physical health, only when both parents and child were A-carriers. In addition to long-term behavioral consequences, maltreatment interacted with OXTR rs53576 genotype to modulate structural brain changes. In G/G homozygotes, but not in A-carriers, gray matter volume of the bilateral ventral striatum has been found to be negatively correlated with severity of childhood maltreatment (Dannlowski et al., 2016). An epigenetic imprint of poor parental care has also been illustrated by an association between low maternal care during childhood and enhanced DNA methylation in an OXTR sequence in blood cells in adulthood (Unternaehrer et al., 2015). On the

opposite spectrum of risks imposed by maltreatment, OXTR also modulates resilience to stressors. For instance, the protective effect of a positive childhood family environment was found to be associated with higher resilient coping methods amongst those with OXTR rs53576 G/G and A/G genotypes (Bradley et al., 2013). Similarly, lower cortisol response to stressors were found amongst G-carriers only if they were given social support (Chen et al., 2011).

3.3 Disorders of Disruptive Behaviors

A moderately heritable disorder (Rhee & Waldman, 2002), conduct disorder (CD), is characteristically identified in youth with low social competence (Brotman et al., 2008; Drugli et al., 2007; Rhee & Waldman, 2002), who disregard the rights' of others and exhibit blatant disobedience towards legal or societal rules. (Sakai et al., 2012) examined OXTR variants from family-based probands of youth diagnosed with substance abuse. However, OXTR variants failed to distinguish between families of patients with and without CD. In a related study, Cecil and collaborators investigated the interaction between parental care and methylation of DNA, near the OXTR gene locus, in modulating callous-unemotional traits (CU) (Cecil et al., 2014). CU is characterized by a deficit in prosocial emotions, such as empathy or guilt, and is associated with CD (Dandreaux & Frick, 2009; Rowe et al., 2010), and psychopathy (Frick & Viding, 2009). Higher methylation has been shown to be associated with lower oxytocin levels (Dadds et al., 2014), which has subsequently been correlated with low prosocial behaviors (Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012; Insel, 2010; Kumsta et al., 2013). Amongst adolescents with low internalizing symptoms, the study found higher prenatal parental risk (e.g. delinquent conduct, psychopathology) to be associated with higher OXTR methylation at birth. Although it remains to be elucidated whether the relationship between prenatal parental risk and OXTR is causal or correlational (Johannes et al., 2009; Richards, 2006), such an interaction nonetheless plays a contributing role in the development of CU and CD. Lastly, strong comorbid relationships have been previously found between oppositional defiant disorder (ODD) and affective disorders (Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012; Angold et al., 1999). Employing a Bayesian mixture modeling technique, Adrian and colleagues found that this comorbidity was not modulated by an interaction between OXTR and family support (Adrian et al., 2015).

3.4 Depression

Development of depressive disorders has been shown to be greatly influenced by early parent-child relationships (Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012; Salzinger et al., 2002). OXTR has also been found to modulate interactions between unsupportive parent-child affiliations, coping styles and severe symptoms of depression (McInnis et al., 2015).

The moderating role of OXTR was particularly illustrated by how OXTR rs53576 A-carriers were more inclined to adopt disadvantageous emotion-focused coping styles (Matheson & Anisman, 2003; van Roekel et al., 2013) when exposed to negative social environments. Such coping strategies were found to be linked to greater symptoms of depression. In a related study, youth's OXTR genotype was also found to moderate the interaction between maternal depression in early childhood and subsequent youth depression (Thompson et al., 2014). Findings showed that youth who were OXTR rs53576 A-carriers, whose mothers had depression during the youth's childhood, were found to possess greater depressive symptoms at 15 years of age.

Aside from the child's OXTR genotype, (Aupperle et al., 2016) have also discovered that parental OXTR is associated with adolescents' response to maternal praise and criticism. Similar to previous studies (Beesdo et al., 2009; Guyer et al., 2008; Monk et al., 2008), increased depressive symptoms was found to be associated with greater activation of the right amygdala in response to criticism. However, an intriguing finding was that adolescents whose parents were OXTR rs53576 A-carriers, as compared to G/G homozygotes, were associated with significantly reduced right amygdalial activation in response to criticism, and increased activation during receipt of praise. Since the A-allele has been found to contribute to decreased parenting responsiveness (Bakermans-Kranenburg & van Ijzendoorn, 2008), this phenomenon might be explained by how less sensitive maternal behaviors trigger an adaptive neural response pattern within the adolescent's amygdala.

Lastly, early-life stressors represent a critical factor in the development of depression (Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012; Bradley et al., 2011; Preacher et al., 2007). In a study by McQuaid, childhood maltreatment was correlated with greater symptoms of depression, with OXTR occupying a moderating role. In conditions of severe maltreatment, only G-carriers of OXTR rs53576 exhibited greater symptoms of depression, as compared to A/A homozygotes (McQuaid et al., 2013), in line with findings in literature (Bradley et al., 2011; Preacher et al., 2007). Additionally, for G-carriers, a breach of trust (i.e. neglect, abuse) was found to be a more pertinent factor in mediating childhood stressors with depression, echoing previous findings which showed that enhanced social sensitivity conferred by the G-allele renders an individual more vulnerable in adverse environments (Belsky et al., 2009). In a similar study on childhood distress, (Myers et al., 2014) discovered that early life maltreatment interacts with a rare OXTR variant, rs139832701, to produce symptoms of depression. In one epigenetic study, (Smearman et al., 2016) demonstrated that greater levels of DNA methylation at cg00385883 were associated with symptoms of depression if individuals experienced a history of childhood maltreatment. While previous literature has focused on the role of genes in determining the risk of depression, (Kimmel et al., 2016) found evidence of childhood abuse interacting with postpartum depression to regulate levels OXTR DNA methylation in the CpGs region.

3.5 Anxiety Disorders

Early childhood experiences presided by tumultuous parent-child interactions often lead to adverse psychological consequences (Gouin et al. 2017; Repetti et al., 2002). A recent study by Schneider-Hassloff and colleagues led to the finding of an OXTR-CAS-sex interaction for anxiety, where childhood attachment insecurity was correlated with greater anxiety levels amongst female G/G homozygotes, but not in males or A-carriers (Schneider-Hassloff et al., 2016). Sex-specific effects of the oxytocin system have been previously reported (Bethlehem et al., 2013; Carter, 2007; Gimpl & Fahrenholz, 2001), and oxytocin has been shown to govern pair-bonding more significantly in females than in males (Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012; C. Carter, 2007; C. S. Carter et al., 2009). Epigenetics has also elucidated gene-by-environment mechanisms associated with anxiety (Gottschalk and Domschke 2017). Recently, (Smearman et al., 2016) discovered that, amongst G-carriers, higher levels of methylation at cg11589699 was correlated with greater symptoms of depression and anxiety.

3.6 Eating Disorders

In the past decade, increasingly more studies have unveiled the role of oxytocin in conferring genetic predispositions to eating behaviors (Bethlehem et al., 2013; Sabatier et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012; Leng et al., 2008). Employing a gene-by-environment framework, (Micali et al., 2016) investigated the interaction of two OXTR polymorphisms, rs53576 and rs2254298, with the quality of maternal care received. Similar to previous studies, they showed that the A-allele of rs53576 possesses a protective effect as it was inversely correlated with eating disorders, and the G/G genotype was associated with binging and purging behaviors (Kim et al., 2015). A/A genotype of rs2254298, on the other hand, was found to be associated with restrictive eating habits. Most interestingly, they found that A/A or A/G genotypes of OXTR rs2254298 interacted with inadequate maternal care to jointly increase the risk of purging and binge eating behaviors.

3.7 Borderline Personality Disorder

Socially dysfunctional relationships have been established to be the hallmark of borderline personality disorders (BPD) (Stanley & Siever, 2010; Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012; Clarkin et al., 2007). Examining the role of OXTR in propagating

this condition, it has been found that OXTR rs53576 moderated the relationship between quality of intimate family relationships and BPD (Sharp and Kim 2015; Hammen et al., 2015; Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012). In line with the differential susceptibility model, A-carriers exhibited BPD symptoms to a greater extent only in disharmonious family settings with poor child-parent relationships, and low levels of BPD symptoms were seen when individuals were in supportive family environments. Conversely, amongst G/G homozygotes, no correlation was evident between symptoms of BPD and harsh family conditions (Zhang et al. 2017).

3.8 Autism Spectrum Disorder (ASD)

Numerous studies have demonstrated an association between autism spectrum disorder (ASD) and OXTR gene polymorphisms (Horvath et al. 2001; Zhang et al. 2017; Warrier et al. 2015; Bakermans-Kranenburg & van Ijzendoorn, 2014; LoParo & Waldman, 2015; Di Napoli et al. 2014; Yrigollen et al., 2008; Horvath et al., 2001). With respect to OXTR rs53576, this variant has been linked to vulnerability in developing the autistic phenotype (Connelly, & Morris, 2012; Tost et al., 2010; Wang et al., 2013; Liu et al., 2010). It has also been found to influence prosociality (Yamasue, 2013; Kogan et al., 2011; Tost et al., 2010) and affiliative behaviours (Zhang et al., 2017; Bakermans-Kranenburg & van Ijzendoorn, 2014; LoParo & Waldman, 2015), which are social competencies that are impaired in persons with autism. A strong association between rs2254298 and ASD has been elucidated by studies across multiple populations (LoParo & Waldman, 2015; Liu et al., 2010; S. Wu et al., 2005). Similarly, rs2268493 has been shown to correlate with the development of autism (Di Napoli et al., 2014; Yrigollen et al., 2008), while rs11131149 has been recognized as a possible marker involved in deficiencies in Theory of Mind (ToM) (Wade et al., 2015; Wade et al., 2014; Wu and Su 2014; Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012). An undeveloped ToM confers individuals with difficulty in understanding that people have their own thoughts, beliefs and emotions, which places these individuals at risk of developing autism (Liu et al., 2010; M. Wade et al., 2014). These consistent findings linking OXTR SNPs to ASD represent some semblance of success in uncovering potential candidate polymorphisms that underpin autism. However, due to differences in methodological procedures and sample characteristics, studies involving gene-and-environment interaction of these genetic variants showed inconsistent results (Horvath et al., 2001).

4. Conclusions / Future Research

The interaction between oxytocin and parental care clearly holds an imperative role in continually shaping our socio-emotional trajectories, differentially protecting us from or imperiling us to psychological perturbation, depending on the unique interplay of OXTR variants and parental care experiences that one has been exposed to. Sifting through the different articles, it is possible to interpret how oxytocin functions as a bridge that links gene, environment and behavior across the entire lifetime, starting from very early experiences. In the last section, we reported wide-ranging evidence illustrating how oxytocin and parental care interacted to increase the probability of developing mental disorders, especially those involving an impairment of social functioning. Inconsistency among available results might be due to the complex system of regulatory mechanisms of this neurohormone, since there are genetic variants in the promoter region that have yet to be identified, thus studied individually (Ebstein et al., 2012). Environmental measures, such as retrospective questionnaires, and individual variability, are certainly caveats to the research methodology, and they present a challenge to be overcome in future studies. Technological advancements are providing novel ways to collect data on individual behaviors and social interactions, like smartphones, that allow researchers to gather an enormous amount of human behavioral data with a breadth and depth that was previously inconceivable. These devices are able to continuously collect data such as location, movement, and physiological parameters (Lane et al., 2010; Miller, 2012). In the last few years, several works have started to use smartphone activity data in order to detect and predict mood states (LiKamWa et al., 2013), and daily stress levels (Bogomolov et al., 2014; LiKamWa et al., 2013). These technologies also allow researchers to invite participants to complete brief psychological and social questionnaires offered on a daily, weekly, or monthly basis. Recently, some large-studies were designed to measure human behaviors and interactions using multiple sources of data (Aharony et al., 2011; Centellegher et al., 2016; Eagle & Pentland, 2005; Stopczynski et al., 2014). For example, the Mobile Territorial Lab (MTL) living lab study has been observing the lives of more than 100 parents through multiple sources (e.g. smartphones, questionnaires, experience sampling probes, etc.) for more than three years. Further researches may clarify how to leverage these devices to gather rich environmental measures that can be associated to genetic and physiological assessments. Moreover, with the growing interest in epigenetic processes, another relevant gear in gene-environment interactions includes how life experiences can alter molecular transcription and affect socio-cognitive development (Kundakovic et al., 2015). In this context, parental care might become a significant topic of interest in developmental and behavioral neuroscience (Bethlehem et al., 2013; Ebstein et al., 2012; Meyer-Lindenberg & Tost, 2012; Kumsta et al., 2013; Kundakovic et al., 2015; van IJzendoorn et al., 2011), but despite the general consensus of the findings some discrepancies are still present (Leerkes et al. 2017; Tollenaar et al. 2017).

Focusing on the environment may enlighten new ways of rehabilitating psychiatric disorders. This prolific body of knowledge has also started to meet the pharmacological field, with experimental administrations of intranasal oxytocin currently underway (Feng et al., 2015; Marsh et al., 2012). Presently, the implication of this area of study in clinical practice looks encouraging, especially with respect to psychopathologies that involve severe social impairment, such as autism, schizophrenia and depression. While the focus of this review has been on psychiatric disorders, it is indisputable that this field transcends beyond unraveling the etiologies of disorders, and may also uncover new clues to better understand the mechanisms underlying parenthood, or simply improving the wellbeing of everyday life.

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