Hormones and Behavior 108 (2019) 84–93

Contents lists available at ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh

Review article

Genetic and epigenetic regulatory mechanisms of the oxytocin receptor gene (*OXTR*) and the (clinical) implications for social behavior☆

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ARTICLE INFO

Keywords:
OXTR
Oxytocin
Social behavior
ASD
SNPs
Epigenetic regulation

ABSTRACT

Oxytocin and the oxytocin receptor (*OXTR*) play an important role in a large variety of social behaviors. The oxytocinergic system interacts with environmental cues and is highly dependent on interindividual factors. Deficits in this system have been linked to mental disorders associated with social impairments, such as autism spectrum disorder (ASD). This review focuses on the modulation of social behavior by alterations in two domains of the oxytocinergic system. We discuss genetic and epigenetic regulatory mechanisms and alterations in these mechanisms that were found to have clinical implications for ASD. We propose possible explanations how these alterations affect the biological pathways underlying the aberrant social behavior and point out avenues for future research. We advocate the need for integration studies that combine multiple measures covering a broad range of social behaviors and link these to genetic and epigenetic profiles.

1. Introduction

Oxytocin is a nonapeptide that is synthesized in the hypothalamus and released into the bloodstream via the posterior pituitary (Lerer et al., 2008). It is a key moderator of a broad range of social behaviors, both within and between species (Donaldson and Young, 2008; Neumann, 2002), such as parent-child bonding, mating, pair-bond formation and attachment (Bartz and Hollander, 2006).

Intranasal administration of oxytocin has been shown to alter the processing of and reactions to social stimuli. Initial studies suggested an enhancement of 'prosociality', supported by increased eye gaze to human faces (Guastella et al., 2008), affective empathy (Hurlemann et al., 2010), and the ability to derive the mental state of others (Domes et al., 2007a), although there is evidence that denies the latter (Radke and de Bruijn, 2015). Oxytocin administration studies have investigated acute effects on autism spectrum disorder (ASD) in children and adults, a developmental disorder characterized by impairments in social interaction and communication with a restricted repertoire of interests and activities (American Psychiatric Association, 2013). Oxytocin yielded beneficial effects on social cognition (Bartz and Hollander, 2006), such as an increased ability of deriving mental states of others (Guastella et al., 2010) as well as reduced repetitive behaviors (Hollander, 2003).

Contrary to the beneficial acute effects of oxytocin on ASD, long term administration had divergent outcomes. Over the course of 12 weeks, twice daily administration of oxytocin led to improvement in measures of social function, social cognition, repetitive behaviors and anxiety (Anagnostou et al., 2014). In a similar experiment, with the same dosage and administration frequency, Guastella et al. (2015) did not find any long term effects on social responsiveness, social cognition and repetitive behaviors. Longitudinal oxytocin administration studies in ASD have produced inconclusive results (Anagnostou et al., 2014; Dadds et al., 2014). What accounts for these mixed results could be differences in dosage, study duration, age, small sample sizes, and developmental stages and therefore results should be interpreted with caution (Young and Barrett, 2015). Functional imaging studies applying intranasal oxytocin to children and adults with ASD found increased activity in the striatum, nucleus accumbens, left posterior superior temporal sulcus and left premotor cortex for socially relevant stimuli and decreased activity for nonsocial stimuli (Gordon et al., 2013). Additionally, the amygdala has been suggested as an important region through which oxytocin modulates its effect on social cognition. Intranasal oxytocin increased activation in the left amygdala during social information processing in individuals with ASD (Domes et al., 2014).

In line with its anxiolytic effects in animals and humans (Heinrichs et al., 2003; McCarthy et al., 1996), oxytocin attenuates amygdala

☆ This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
No conflict of interest.

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https://doi.org/10.1016/j.yhbeh.2018.03.002
Received 13 April 2017; Received in revised form 16 February 2018; Accepted 1 March 2018
Available online 12 March 2018
0018-506X/

Table 1
SNPS affecting brain structure.

Study	SNPs	Sample size	Ethnicity	Sex	Findings
Tost et al. (2010)	Rs53576A	212	Caucasian	103m, 109f	Decreased hypothalamus Right amygdala increase
Furman et al. (2011)	Rs2254298G	51	American adolescents	51f	Decreased bil. amygdala Small dACC
Inoue et al. (2010)	Rs2254298A	208	Japanese adults	143m, 65f	Larger bil. amygdala
Marusak et al. (2015)	Rs2254298A	55	American	21m, 34f	Larger bil. amygdala
Saito et al. (2014)	Rs2254298A	135	Japanese adults	79m, 56f	Decreased right insula in males.
Tost et al. (2011)	Rs2254298A	212	Caucasian	103m, 109f	Decreased hypothalamus
Yamasue et al. (2011)	Rs2254298A	208	Japanese adults	Not reported	Decreased hypothalamus and dACC

Bil.: bilateral, dACC: dorsal anterior cingulate cortex.

responses to emotional stimuli in healthy individuals (Domes et al., 2007b; Kirsch et al., 2005; Radke et al., 2017). As one of the main brain regions with a high density of oxytocin receptors (*OXTR*), the amygdala is to a great extent influenced by oxytocin (Huber et al., 2005).

The effects of oxytocin are mediated by binding to the oxytocin receptor, a class I G protein coupled receptor with seven transmembrane domains (Gimpl and Fahrenholz, 2001). As oxytocin receptor distribution is species specific, one has to keep a critical eye when using animal models to get insight into the human *OXTR* system. Oxytocin receptors in the rat brain are distributed in regions including forebrain regions, amygdala, hippocampus, bed nucleus of the stria terminalis, ventrolateral septum, paraventricular nucleus (PVN) and the supraoptic nucleus of the hypothalamus (Windle et al., 2004). In macaque monkeys, oxytocin receptors are mostly limited to the nucleus basalis of Meynert, pedunculopontine tegmental nucleus, superior colliculus, trapezoid body and the ventromedial hypothalamus (Freeman et al., 2014). The distribution in the human brain has not been fully investigated. Using autoradiography to localize oxytocin receptors in human brain tissue is problematic due to high affinity of the radioligand to both oxytocin receptors as vasopressin 1a receptors (Freeman et al., 2017).

The *OXTR* gene is located on chromosome 3p25 and contains three introns and four exons (Simmons et al., 1995; Inoue et al., 1994). The exact position of the *OXTR* is chr3:8,750,408–8,769,617 and spans 19,210 base pairs (bp) (UCSC Genome Browser: Kent et al., 2002). This is the position of the *OXTR* on the forward strand, although the coding gene is located on the reverse strand. Single nucleotide polymorphisms (SNPs) in and epigenetic regulatory mechanisms on the *OXTR* gene can have a major impact on social functioning. Several studies found links between certain SNPs and ASD (Wu et al., 2005; Wermter et al., 2010), deficits in empathy (Rodrigues et al., 2009), and in attachment (Costa et al., 2009).

The aim of the current review is to elucidate how the biological regulatory mechanisms of the oxytocinergic system affect social behavior. Here we use social behavior as an umbrella term to indicate a large range of behaviors that involve an interaction between individuals. We discuss a combination of variations in the *OXTR* gene and epigenetic regulatory mechanisms of the *OXTR* gene. We first address the most prevalent SNPs in the *OXTR* gene associated with impairments in social behavior and secondly, we review studies on epigenetic regulatory mechanisms, in particular DNA methylation, of the *OXTR* gene and the involvement in social behavior. As this is a focused review on the genetic and epigenetic regulatory mechanisms of the *OXTR*, oxytocin administration studies and the large body of literature focusing on hormonal interactions of oxytocin with estrogen and vasopressin are beyond the scope of this review.

The studies included in this review were searched using *Web of Science* and *PubMed* with the keywords *OXTR*, *social**, *SNP*, *ASD*, and *methylation*. We also included relevant papers not retrieved with the above keywords, but that were included in meta-analyses on oxytocin, ASD and social behavior.

2. Effect of SNPs in the *OXTR* gene on brain activity and structure and the implications for social behavior

Genetic variants (SNPs) of the *OXTR* have been linked to morphometric alterations of key limbic structures. Although many SNPs have been identified within the *OXTR* gene, this review will focus on rs53576 and rs2254298 which are located in the third intron on positions Chr: 8,762,685 and Chr: 8,760,542 respectively (Chen et al., 2011a; UCSC Genome browser: Kent et al., 2002), as these SNPs are most frequently reported in relation to social behavior and autism. It should be noted that these genetic variants in the *OXTR* have not been shown to be functional, and might tag a yet to be identified functional SNP. Based on a cohort of 1445 adolescents of European origin, Loth et al. (2014) found a correlation coefficient of 0.38 between rs53576 and rs2254298 indicating they are in moderate linkage disequilibrium with each other. This review includes data of Caucasian (American and European), Chinese Han and Japanese populations. However, allele frequencies of rs53576 and rs2254298 differ among these populations. The A allele frequency of rs53576 and rs2254298 in the American population is 0.343 and 0.240 respectively. In the European population A allele frequency is 0.361 and 0.107, in the Japanese population 0.663 and 0.287 and in the Chinese Han population 0.716 and 0.320 (Butovskaya et al., 2016). We will start to set out the current state of literature regarding SNPs in the *OXTR* associated with morphological differences in brain structure and later report on the effects for social behavior. However, there is only a small body of literature that has investigated the link between SNPs in the *OXTR* gene and morphological differences in the brain (Table 1 for overview).

2.1. SNPs related to volumetric alterations in the human brain

Volumetric alterations associated with rs2254298A are shown to be consistent among different ethnicities. In both Asian and Caucasian populations A-allele carriers of rs2254298 have increased gray matter volume of bilateral amygdalae, decreased regional volume of the dorsal anterior cingulate cortex (dACC), decreased gray matter volume of the hypothalamus depending on the number of A-alleles and decreased right insular volume in males (Furman et al., 2011; Inoue et al., 2010; Marusak et al., 2015; Saito et al., 2014; Tost et al., 2011; Yamasue, 2013). The literature on rs53576 and volumetric alterations is even more parsimonious than that of rs2254298. Tost et al. (2010) are the first and only to tie rs53576 to volumetric alterations. Decreased hypothalamus and, in males increased right amygdala volume were associated to the A allele of rs53576, a previously suggested risk allele for autism (Wu et al., 2005).

The association between rs2254298 and autism differs between ethnicities. In a large Asian sample, the prevalence of rs2254298A was associated with autism, whereas the G-allele was associated with autism in a Caucasian sample (Wu et al., 2005; Liu et al., 2010; Jacob et al., 2007). The effects on volume and autism do not seem to be independent since several studies have shown a link between amygdalar volume and

autism. Volumetric MRI studies investigating young children with ASD have shown larger amygdala volume, whereas studies investigating older children and adolescents did not find differences in amygdala volume between individuals with ASD and typically developing individuals (Corbett et al., 2009; Schumann et al., 2004). In adults with ASD, amygdala volume has been reported to be smaller than in typically developing adults (Nacewicz et al., 2006; Rojas et al., 2004). Based on these results, abnormal course of amygdala development has been suggested as an intermediate phenotype of the genetic factor of ASD. However, all these studies included only Caucasian populations and the link between autism and amygdala volume in an Asian population remains to be further investigated.

A possible explanation for the differential link of rs2254298 to ASD between Caucasians and Asians comes from a remarkable direction. In a recent meta-analysis, Luo and Han (2014) showed that collectivistic cultural values are associated with higher prevalence of rs53576A. This SNP has been previously associated with deficits in empathy (Rodrigues et al., 2009), lower prosocial temperament (Tost et al., 2010) and an increased risk for autism in a Chinese population (Wu et al., 2005; Saphire-Bernstein et al., 2011). Luo and Han (2014) showed that higher prevalence of the rs53576A allele is significantly positively correlated with collectivism. Differences in allele frequencies between ethnicities are due to differences in population structure which could be explained by cultural differences. Although the link between rs2254298A and collectivistic cultural values was not investigated, based on the similar association of rs53576A and rs2254298A with autism, one could hypothesize that rs2254298A, like rs53576A, is also more prevalent in Asian cultures. In both Caucasian and the Chinese Han populations the G allele of rs2254298 was more prevalent than the A allele, however, the A allele frequency in the Chinese Han population was four times higher than in the Caucasian sample (Jacob et al., 2007; Wu et al., 2005).

2.2. SNPs and social behavior

There is an ongoing debate in the current literature about the relation between SNPs in the *OXTR* gene and social behavior. Many studies have performed analyses in which they genotyped multiple SNPs and/or haplotypes, the findings, however, are quite divergent. In this next part we set out the current state of literature and put the different findings into perspective with regard to social behavior (Table 2 for overview).

There is quite some divergence in the results of studies investigating the association between SNPs in the *OXTR* and social behavior. Rs53576 and rs2254298 are both shown to affect social behavior, although no consensus has been reached on which alleles are associated with prosocial and which with anti-social behavior. To start with rs53576, most studies report the G allele as the prosocial variant. The studies reporting rs53576A as the prosocial variant include a sample diagnosed with ADHD (Park et al., 2010). Also, rs53576G was found to be associated with poorer performance on neurocognitive tests assessing social cognition, but only in combination with rs2254298A (Slane et al., 2014). Impairments in social behavior and interaction are often reported as one of the main deficits in ASD. SNPs in the *OXTR* that are associated with ASD are often seen as characteristics for ASD. Parker et al. (2014) investigated both an ASD cohort and healthy controls and found that rs53576G and rs2254298A are linked to impaired affect recognition and global social impairments in both groups. Thus, these findings show that SNPs in the *OXTR* gene are not solely associated with ASD, but are instead heritable influences on social functioning in general.

However, a larger body of literature describes results contradicting the above mentioned findings whereby the G allele of rs53576 is associated with prosocial behavior. Differences in prosociality associated with rs53576 should manifest themselves behaviorally in displays of affiliative cues. In the study by Kogan et al. (2011) independent observers judged target individuals on their prosocial behavior, rated as trustworthiness, compassion and kindness. Target individuals homozygous for the G allele of rs53576 were judged to be more prosocial than A carriers of this SNP, and thus allelic differences in rs53576 are associated with behavioral displays of prosociality (Kogan et al., 2011). A meta-analysis of twenty-four independent samples by Li et al. (2015) showed that rs53576GG homozygotes had higher general sociality compared to A allele carriers. Phenotypes contributing to general sociality tested in this meta-analysis included among others extraversion, empathy and social loneliness. Chinese homozygous rs53576GG children (3–5 years) exhibited more prosocial behaviors like helping and comforting than A allele carrying peers and also performed better in a Theory of Mind task (Wu and Su, 2015). Another study, investigating the link between rs53576 and trust has shown that GG homozygous males were more trusting than AA males. This pattern was not found in women (Nishina et al., 2015). In addition to subjective ratings of prosociality as found by Kogan et al. (2011), rs53576AA homozygotes have also been found to show lower positive affect (Lucht et al., 2009) and A allele carriers revealed a decreased level of prosocial temperament (Tost et al., 2010). Although G carriers display beneficial social characteristics, evidence of lower self-esteem after social rejection in the Cyberball game might reflect elevated sensitivity in response to a social stressor (McQuaid et al., 2015). This perspective is in line with the social salience hypothesis stating that oxytocin increases the sensitivity to social cues regardless of whether they are positive or negative (Shamay-Tsoory and Abu-Akel, 2016). Individuals with one or two copies of the G allele of rs53576 were found to benefit more from social support when being subjected to stress than people with the AA genotype. G carriers showed lower cortisol responses to stress after social support (Chen et al., 2011b). In addition, heart rate variability was increased in rs53576GG homozygotes during direct social interaction in anticipation of a social stressor (Kanthak et al., 2016). Accordingly, A allele carriers exhibited enhanced stress reactivity and lower dispositional empathy (Rodrigues et al., 2009), and perceived threat predicted less charitable activities (Poulin et al., 2012).

The debate does not end with rs53576, but continues with rs2254298. Since differences in the association with social behavior were found across and within multiple ethnicities, they cannot be explained by a different pattern of linkage disequilibrium between ethnicities and hence require further investigation. Concerning autism, a disorder with impairments in social communication as a core deficit, Jacob et al. (2007) found overtransmission of the G allele in the intronic SNP rs2254298 for Caucasian autistic subjects. In an Israeli sample of autistic subjects, both single SNPs and haplotypes were tested for their association with autism. In accordance with Jacob et al. (2007), although the rs2254298 SNP did not reach significance as a single SNP, the G allele was overtransmitted in the autistic sample and a core SNP in the haplotypes associated with ASD. The G allele was hence linked to less sociable behavior, and thus the A allele is suggested to be associated with prosocial behavior (Lerer et al., 2008). A study investigating attachment in human infants, which was assessed using the Strange Situation developed by Ainsworth et al. (1978), found an association of rs2254298A with increased attachment in non-Caucasian infants (including Hispanic/Latino, American Indian, Asian, African American and Hawaiian) but not in Caucasians. In accordance with the above-mentioned, these findings suggest a role for rs2254298A in prosocial behavior (Chen et al., 2011a). Although investigating different ethnicities, these three studies all showed consistent results concerning the association of rs2254298A with social behavior.

Despite the congruent results of the studies described above, there are other studies showing opposite findings where rs2254298G is associated with more prosocial behavior and the A allele with ASD and less sociable behavior. A family-based association test revealed an association between the A alleles for both rs53576 and rs2254298 and autism in the Chinese Han population (Wu et al., 2005). In a Japanese population, the A allele of rs2254298 was also linked to ASD, which is

Table 2
SNPs affecting social behavior structured by domain.

Study	SNP	Sample size	Ethnicity	Sex	Domain	Findings
Bakermans-Kranenburg and van Ijzendoorn (2014)[a]	Rs53576 Rs2254298	17559 13547	Mixed	Not reported	Biology, personality, social behavior, psychopathy and autism	No effects were found regarding the two SNPs.
Campbell et al. (2011)[a]	Rs53576 Rs2254298	5432	Caucasian	Not reported	Autism	No association between rs53576, rs2254298 and autism.
LoParo and Waldman (2015)[a]	Rs2254298	3941	Mixed	Not reported	Autism	Rs2254298A is associated to ASD.
Park et al. (2010)	Rs53576G	450	Caucasian children	405m, 45f	ADHD	Rs53576AA genotype is associated with better social ability compared to AG in ADHD participants.
Jacob et al. (2007)	Rs2254298G	57	Caucasian children and adolescents	45m, 12f	Autism	Overtransmission of rs2254298G in autistic participants
Lerer et al. (2008)	Rs2254298G	152	Israeli	128m, 24f	Autism	Rs2254298G is overtransmitted in autistic sample, and a core SNP in the haplotypes significantly associated with ASD
Liu et al. (2010)	Rs2254298A	728	Japanese	518m, 210f	Autism	Rs2254298A is associated with autism
Parker et al. (2014)	Rs53576 Rs2254298	193	Not reported	131m, 62f	Autism	In both ASD and control groups, Rs53576G carriers showed impaired affect recognition performance and Rs2254298A carriers had greater global social impairments.
Wermter et al. (2010)	Rs53576 Rs2254298	100	Caucasian	95m, 5f	Autism	No association of both SNPs to autism.
Wu et al. (2005)	Rs53576A Rs2254298A	195	Chinese	174m, 21f	Autism	Rs53576A and rs2254298A are associated with autism.
Apicella et al. (2010)	Rs53576A Rs2254298A	684	Caucasian	Predom. female	Social behavior	No associations between both SNPs and social preferences as elicited from two standard economic games.
Chen et al. (2011a)	Rs53576A Rs2254298A	176	Caucasian vs. non-Caucasian infants	98m, 78f	Social behavior	Rs2254298A is associated with attachment security in non-Caucasians. No associations were found with the rs53576 SNP in any ethnic group.
Chen et al. (2011b)	Rs53576G	194 males	Caucasian	194m	Social behavior	Rs53576G carriers benefit more from social support after social stress exposure.
Chen and Johnson (2012)	Rs53576 Rs2254298	178	Mixed	70m, 108f	Social behavior	Female rs2254298A carriers reported greater attachment anxiety, male rs2254298A carriers reported more autism-associated traits.
Feng et al. (2015)	Rs53576G	204	Unknown	104m, 100f	Social behavior	Oxytocin administration increased left ventral caudate nucleus activation during cooperation in rs53576GG homozygous males, but decreased activity in GG homozygous females.
Kanthak et al. (2016)	Rs53576G	40	Unknown	40m	Social stress	Rs53576G carriers have increased heart rate variability during social support
Kogan et al. (2011)	Rs53576G	116	Mixed	56m, 60f	Social behavior	Rs53576GG homozygotes are more prosocial than A allele carriers.
Kryski et al. (2014)	Rs53576G	409	Caucasian children	201m, 208f	Social behavior	Rs53576AA homozygotes displayed more negative emotionality and avoidance and greater compliance.
Lucht et al. (2009)	Rs53576G Rs2254298A	406	European	161m, 245f	Social behavior	Male Rs53576AA homozygotes show lower positive affect on the PANAS.
McQuaid et al. (2015)	Rs53576G	128	Caucasian	128f	Social exclusion	Rs53576G carriers are more emotionally sensitive (lower self-esteem) in response to social ostracism.
Nishina et al. (2015)	RS53576G	427	Japanese	242f	Social behavior	Rs53576GG male homozygotes showed more behavioral trust in a monetary trust game.
Poulin et al. (2012)	Rs53576A	348	European American	Not reported	Social behavior	Greater perceived threat predicted fewer charitable activities for rs53576A carriers.
Rodrigues et al. (2009)	Rs53576A	192	Mixed ethnicity	79m, 113f	Social behavior	Rs53576A carriers have lower empathy and higher stress reactivity.
Slane et al. (2014)	Rs53576G Rs2254298A	48	Caucasian children	25m, 23f	Social behavior	Participants with the combination rs2254298A and rs53576G performed worse on social cognition measures like CBCL Social Problems, RMET, SRS.
Tost et al. (2010)	Rs53576A	212	Caucasian	103m, 109f	Social behavior	Rs53576A carriers have a decreased level of prosocial temperament.
Waller et al. (2016)	Rs53576 Rs2254298	406	Caucasian	193m 213f	Antisocial behavior	No association between rs53576 and rs2254298 and angry facial expressions.
Wu and Su (2015)	Rs53576G	87	Chinese children	44m, 43f	Social behavior	Rs53576GG homozygotes exhibit more prosocial behavior and better Theory of Mind than A carriers.

[a] Meta-analysis. CBCL: child behavior checklist, RMET: reading the mind in the eyes test, SRS: social responsiveness scale. SRABS: Self-Reported Antisocial Behavior Scale. Predom.: predominantly.

consistent with the findings from the Chinese Han population. This suggests that the rs2254298A increases the risk of ASD in Asians, whereas it might be protective in Caucasians (Jacob et al., 2007; Lerer et al., 2008). Furthermore, in a sample with mixed ethnicities (Caucasian, Asian and other), females with at least one copy of the A allele of rs2254298 had greater attachment anxiety than females homozygous for the G allele, whereas males with the A allele reported more autism-associated traits (Chen and Johnson, 2012). These findings indicate sex-specific effects between *OXTR* polymorphisms and social behavior. It is possible that estrogen plays a role in the different effects of rs2254298A in males and females, reinforcing the link between attachment anxiety and oxytocin in females and autism-spectrum traits in males (Chen and Johnson, 2012).

Adding to the debate whether rs53576 and rs2254298 are involved in the regulation of social behavior, a number of studies including a large meta-analysis did not find any relation between these SNPs and social behavior (Apicella et al., 2010, Bakermans-Kranenburg and van Ijzendoorn, 2014, Campbell et al., 2011, Wermter et al., 2010). However, Bakermans-Kranenburg and van Ijzendoorn (2014) included a large number of studies unrelated to ASD or social behavior, which could explain why they did not detect an association between these SNPs and social behavior. In an emotional face-matching task, no associations were found between amygdala reactivity to angry versus neutral faces (Waller et al., 2016). Despite the few studies that failed to detect a link, a much larger body of research indicates there is indeed a connection between these SNPs and social behavior.

The lack of consensus forces one to keep a critical eye when interpreting these results. There are a few possible confounding factors that have to be discussed. First, the different prevalence of alleles in different populations is caused by a yet undetermined factor. Despite some hypotheses mentioned earlier, there is no consensus on what causes this effect. Second, in this analysis we included a lot of studies investigating autism. Autism is known for its higher prevalence in boys than in girls and hence males are overrepresented in the studies in this review. Third, studies investigating autism often include young children and/or adolescents. There is evidence that amygdala volume in ASD depends on the stage of development (Corbett et al., 2009), and results based on young children should therefore be interpreted with caution. Finally, the two SNPs discussed here are both located in an intron. As introns are the parts of the genetic code that are removed by RNA splicing during maturation of pre-mRNA (containing introns) to the final mRNA, their code does not contribute to the configuration of the protein. However, the large body of literature linking intronic SNPs in the *OXTR* to changes in social behavior suggests there has to be some mechanism that affects the chemical properties of the oxytocin receptor. Intronic SNPs could be non-coding markers that are in linkage disequilibrium with other, undetermined functional variants in the genetic code (Chen et al., 2011a). Another, speculative hypothesis is that the biochemical process of splicing out introns of pre-mRNA could be a potential target for intronic SNPs to affect the final mRNA and hereby change the properties of the protein. SNPs in the final mRNA could lead to another amino acid being included in the protein. If this amino acid is on an active site of the protein, it could change the binding properties or the signal transmission of the oxytocin receptor and influence the effectiveness of oxytocin. Another possibility is that these SNPs impede the binding of the spliceosome to the pre-mRNA, which is a large protein that binds to pre-mRNA sequences to remove introns and connect the exons together (Papasaikas and Valcarcel, 2016). As these hypotheses are speculative, further research is necessary to unravel the exact mechanism by which intronic SNPs affect the functionality of the *OXTR*.

The two SNPs, rs225498 and rs53576 discussed above are among 150 common SNPs with ≥1% minor allele frequency (UCSC Genome Browser: Kent et al., 2002). Although discussing all of them would not be feasible within the boundaries of this work, a short note is in place. The majority of SNPs other than rs2254298 and rs53576 is mostly investigated in haplotype studies. These studies seek combinations of SNPs that together are associated with a certain trait. Instead of a priori hypotheses which SNPs contribute to the haplotype associated with the trait, a large number of randomized combinations is used to detect associative haplotypes. By using this approach, the limited number of haplotype studies yielded inconclusive results. For example, Lerer et al. (2008) found a five-locus haplotype associated with ASD consisting of rs237897-rs13316193-rs237889-rs2254298-rs2268494. Wermter et al. (2010) also performed haplotype analysis, but only found a nominally significant haplotype with the SNPs rs237851-rs6791619-rs53576-rs237884. Other studies investigating haplotypes found associations with ASD (Wu et al., 2005; Liu et al., 2010) and depressive temperament (Kawamura et al., 2010). In all studies different SNPs contributed to the significant haplotypes, hence no two studies have yielded the same results. As cultural differences affect which allele is associated with a trait, they are likely to also influence haplotypes. Thus, albeit haplotypes might contain valuable insights; we are only at the beginning of unraveling the genetic variation underlying social behavior.

3. Epigenetic regulation of the *OXTR*

Epigenetic regulatory mechanisms affect the transcriptional activity of a cell without changing the DNA sequence. DNA methylation, chromatin modification, and regulation of mRNA expression by microRNAs have been previously described as epigenetic mechanisms that control gene expression (Jaenisch and Bird, 2003). Most studies investigating epigenetics focus on DNA methylation, which chemically modifies the DNA by adding methyl groups to single nucleotides in the DNA helix. In most cases, methyl is added to the cytosines in cytosine-guanine dinucleotides at so-called CpG sites. These are regions in the DNA where a cytosine nucleotide precedes a guanine nucleotide in the 5′ → 3′ direction of a single-stranded sequence (Gardiner-Garden and Frommer, 1987). Regions in the DNA that contain a lot of CpG sites (G + C content > 50%) are so called CpG islands (Gardiner-Garden and Frommer, 1987). These islands are often located close to the promoter region of genes and are associated with active gene expression (Saxonov et al., 2006). The exact position of the CpG island is chr3:8,767,276–8,769,594 and spans 2318 base pairs (bp) (UCSC Genome Browser: Kent et al., 2002). It may seem like the CpG island is located towards the end of the gene as the *OXTR* spans from chr3:8,750,408 – 8,769,617. However, because the *OXTR* is located on the reverse DNA strand, the 5′ → 3′ direction of the gene is in the opposite direction (Fig. 1). Kusui et al. (2001) investigated how DNA methylation of this CpG island in the promoter region of the *OXTR* gene affects the transcriptional activity. Using an *OXTR* promoter-luciferase reporter gene assay, they showed that the CpG island had significant promoter activity. Three constructs of the promoter region of the *OXTR* gene were created. Although they did not report which definition of the CpG island they used, the constructs were defined relative to the transcription start site (TSS). The first one ranging from −2860 (downstream) to +1342 (upstream) bp relative to the TSS, including the CpG island. The second construct ranged from −2860 to +144 bp including the promoter but lacking most of the CpG island. The last construct had the same range as the first but with a deletion where the level of methylation was previously found to be most different (MT2 region) (Kusui et al., 2001). After methylation, the transcriptional activity of the first construct was reduced to 30.6%, whereas the second construct, without the CpG island, still had 81.4% of transcriptional activity. Deletion of the MT2 region in the third construct restored the transcription rate after methylation to 68%. This shows that MT2 is an important region of the CpG island to regulate gene suppression of the *OXTR*. Their findings are among the first that show methylation of a CpG island can effectively suppress transcription. Despite the shown importance of the MT2 region in the transcriptional activity of the *OXTR* gene, it is not yet clear how increased methylation of the CpG island in the MT2 region leads to transcriptional down regulation of the *OXTR* gene (Kumsta et al., 2013).

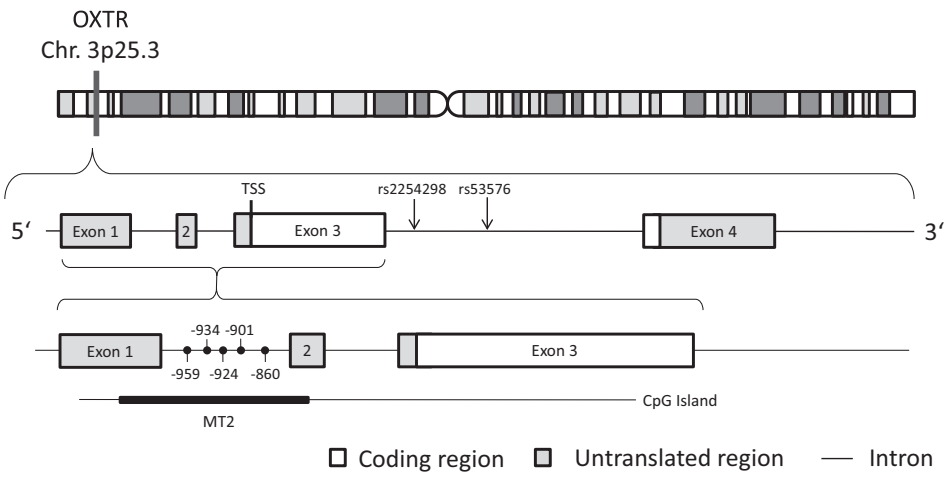

Fig. 1. Schematic overview of the OXTR gene. The OXTR gene is located on Chr. 3p25.3 and consists of three introns and four exons. The single nucleotide polymorphisms (SNPs) rs53576 and rs2254298 (indicated with arrows) in the third intron have frequently been reported as target locations associated with sociobehavioral phenotypes. The two coding exons are indicated as the light boxes, and the untranslated regions are depicted as the grey boxes. The filled circles in the bottom part represent hypermethylation sites in the MT2 (shown as thick black line) region of the CpG island that spans exon 1 through exon 3. TSS is the transcription start site.

The first evidence of an association between methylation of the *OXTR* and autism came from the study by Gregory et al. (2009) who described a case of two autistic brothers, one of which inherited a 0.7 Mb deletion from the mother within Chr. 3p25.3 containing the *OXTR* gene. The other, however, did not inherit the deletion, but instead showed increased methylation in CpG sites −924 and −934 (relative to TSS) of the MT2 region compared to his father (Fig. 1). Unclear was if the autistic brothers were diagnosed with the same autistic disorder, as the sibling with increased methylation was only referred to as the 'affected sibling'. In a larger sample, consisting of 20 individuals with autism and 20 healthy controls, increased methylation in peripheral blood mononuclear cells (PBMCs) was found for the loci −860, −934 and −959 in individuals with autism. In another sample of 8 autistic individuals and 8 matched controls, a similar pattern of methylation at CpG −860, −901, −924 and −934 was observed in the temporal cortex, an important brain area in the etiology of autism. In males (6 of 8 autistic individuals), increased methylation at these sites corresponded to 20% decrease in expression level of *OXTR* mRNA (Gregory et al., 2009). Because methylation at CpG −934 was significantly different between autism cases and controls in both PBMCs and the temporal cortex, measuring the methylation status of *OXTR* in PBMCs could potentially serve as a marker for methylation status in the temporal cortex and assist in the diagnosis of autism (Gregory et al., 2009). These findings also indicate that methylation of a single CpG nucleotide is sufficient to influence transcription and that whole-cluster methylation is not required for epigenetic regulation.

Contrary to hypermethylation in the MT2 region, hypomethylation in the MT1 and MT3 region of the *OXTR* gene in peripheral blood cells was found to be associated with ASD in children (21–94 months) (Yuksel et al., 2016). The different samples used in the study by Gregory et al. (2009) and Yuksel et al. (2016) could account for the inconsistent findings as the hypomethylation in MT1 and MT3 was found in a sample of young Turkish children whereas the other sample included Americans. These studies together point towards genetic dysregulation as a potential mechanism for the development of autism.

Recent imaging studies investigated neural responses in relation to DNA methylation and social stimuli. Jack et al. (2012) reported a strong positive correlation between methylation of *OXTR* site −934 and BOLD activity in the STG and dACC during perception of animacy. At first sight, these findings seem to contradict previous literature where methylation of *OXTR* was shown to be associated with decreased transcription of *OXTR* in the brain; hence processes mediated by oxytocin are expected to be compromised by increased methylation (Kusui et al., 2001; Gregory et al., 2009). However, increased activity could indicate more resource-intensive processing and act as a coping mechanism to deal with the impaired functioning of the oxytocin system due to methylation. For example, Pelphrey et al. (2004) found increased activity in the posterior superior temporal sulcus (pSTS) in situations where more elaborate processing of social stimuli was required, in this case moving social stimuli. The range of methylation detected in the sample of Jack et al. (2012) (29–61%) does not cover the entire theoretical range (0–100%) and the positive association might therefore only apply to typically functioning individuals. Extremely high levels of methylation may predict lower activity in the areas associated with social perception (Jack et al., 2012).

Additional evidence came from a study investigating the impact of *OXTR* methylation on variability in neural responses during emotional face processing (Puglia et al., 2015). A positive association was found between methylation of *OXTR* site −934 and activation in areas associated with emotion processing including the amygdala, insular cortex, dACC and pSTS. However, functional coupling between areas involved in social perception such as the insular cortex, cingulate cortex and orbitofrontal cortex was negatively correlated with *OXTR* methylation, i.e. increased coupling for lower methylation (Puglia et al., 2015). Given the attenuation of amygdala responses to angry faces after oxytocin administration (Gamer et al., 2010), Puglia et al. (2015) hypothesized that an attenuated amygdala response might indicate an enhanced regulation of affective responses to negative stimuli among individuals with lower *OXTR* methylation. Although their findings showed that lower *OXTR* methylation was associated with lower activity across multiple areas crucial for processing social stimuli (dACC, insular cortex), these areas showed increased coupling with the amygdala.

Epigenetic regulation through DNA methylation has previously been associated to trait effects in autism (Gregory et al., 2009). However, Unternaehrer et al. (2012) found first evidence for dynamic changes in *OXTR* methylation after a psychosocial stressor. Participants were subjected to the Trier Social Stress Test (TSST), a laboratory stressor consisting of extemporaneous public speaking and mental arithmetic tasks. Methylation levels of two target sequences located in the third exon were assessed immediately before (pre-stress), 10 min after (post-stress) and 90 min after (follow-up) the TSST. Methylation increased between pre and post-stress, but decreased from post-stress to follow-up in the first target sequence, which is located in a protein-coding region of exon 3. In the second target sequence methylation was decreased between post-stress and follow-up. The oxytocin system has been found to antagonize the short-term stress response (Heinrichs et al., 2003) and increased methylation of the *OXTR* is associated with decreased oxytocin receptor expression (Kusui et al., 2001). The changes in methylation between pre- and post-stress and post- and follow-up could be part of the immediate stress response that activates and mobilizes resources to increase responses. Increased *OXTR* methylation could temporarily dampen the attenuating effect of oxytocin on the stress response. After the stressor, decreased *OXTR* methylation

allowing for an upregulation of the oxytocin system, could be a potential mechanism for physiological recovery after acute stress. These results should, however, be interpreted with care. Due to a measurement error, the amount of methylation can vary between measurements of the same sample. The authors do not report multiple measurements per sample, so the found methylation changes could be due to the error rather than to actual changes in methylation. When replicated, these results are first evidence for a dynamic regulation of DNA methylation in the *OXTR* gene after psychosocial stress. Although this study could be first evidence that DNA methylation is involved in the regulation of the stress response, a number of other confounding factors have to be taken into account. Not only were the differences in methylation quite small (0.38% increase and 1.04% decrease), it was assessed using peripheral blood of which the leucocyte composition can rapidly change in response to stress (Richlin et al., 2004). There was no physiological validation of the stress response via cortisol-level assessments, heart rate measurements or subjective measures. Despite the TSST being a well-established social stressor (Kirschbaum et al., 1993; Rimmele et al., 2009), this study based their conclusions without demonstrating the elicitation of the stress response. The study population, aged between 61 − 67 years, had a high likelihood of early life (war-related) adversities and hence might have been sensitized to stress. Stressful early life events such as maternal separation, violence, psychological abuse or growing up during a war can affect a person's long-term wellbeing and increase the risk to develop psychiatric disorders (Schiavone et al., 2015). For example, low maternal care has been found to result in increased methylation of the *OXTR* (Unternaehrer et al., 2015). Consequently, the subjects tested in the study by Unternaehrer et al. (2012) could have been more susceptible to changes in *OXTR* methylation after acute psychosocial stress. Epigenetics mechanisms might be the catalyst that turns the effects of early life events into long-lasting changes. Therefore future studies should include other populations without increased likelihood of early life adversities to test the generalizability of the results by Unternaehrer et al. (2012).

4. Sex differences in *OXTR* mediated social behavior

Sex differences can be observed on several levels of oxytocin research, starting from the oxytocin receptor density, to SNPs, to administration studies. *OXTR* binding density has been shown to be sexually dimorphic within areas of the “social behavior network” (Goodson, 2005). In a social investigation test, female rats did not only spend less time investigating an unfamiliar juvenile rat compared to males, they also had lower oxytocin receptor binding density in most forebrain regions including the medial amygdala (for detailed description see Dumais et al., 2013). These findings indicate that *OXTR* density might play a role in a neural circuitry regulating social interest, with higher density *OXTR* associated with higher social interest and lower density with lower social interest.

As research on *OXTR* binding density requires harvesting brain tissue, it is usually carried out on rodents. Human research regarding the *OXTR* mostly focuses on SNPs, epigenetic regulation and the effects of direct application of oxytocin. Besides *OXTR* binding density, genetic variations in the *OXTR* gene might account for a part of the sex-specific variations in social behavior. Increased amygdala and decreased hypothalamus gray matter volume was found for male but not female rs53576A carriers, a SNP associated with deficits in social behavior (Tost et al., 2010). Although not sex-specific, the same study also showed reduced amygdala activation during processing of emotionally salient social cues for carriers of the risk allele (rs53576A) for social dysfunction. Tost et al. (2010) provided evidence that a genetic risk for social dysfunction, which is related to the *OXTR*, is reflected in morphometric alterations of the amygdala and hypothalamus. Some studies also found sex-specific associations between SNPs in the *OXTR* gene and empathy, whereby two SNPs (including rs2254298) are associated with higher trait empathy in females compared to males (Wu et al., 2012). However, other studies did not investigate or find sex-specific differences related to SNPs in the *OXTR* gene (Feldman et al., 2012; Rodrigues et al., 2009). Regardless of finding sex differences, studies often do not report the genotype distribution between males and females or do not have sufficient statistical power for performing such analyses. With regard to reliable inferences of sex differences, we would like to stress the importance of reporting this information and if possible, including a sufficient number of participants of each sex. Investigating sex differences is especially relevant in the field of social behavior, as sex-dependent hormones interact differently with the oxytocinergic system. For example, estrogen stimulates oxytocin production in the PVN and *OXTR* density in the amygdala (Choleris et al., 2003, 2006), and hence provides a beneficial effect for social behavior in women. The *OXTR* also has high affinity for arginine vasopressin (AVP), and may also affect social behavior through the *OXTR* (Gimpl and Fahrenholz, 2001). Contrary to oxytocin, AVP is more essential for social behavior in males than females. This is likely due to the greater AVP expression in males and that AVP is often associated to male behaviors such as aggression and territoriality (Donaldson and Young, 2008).

Sexually dimorphic effects have been mirrored in oxytocin administration studies. Intranasally applied oxytocin led to reduced amygdala activation in men when watching fearful, angry and happy faces, but increased amygdala activation in women when viewing fearful faces (Domes et al., 2007a; Domes et al., 2010). Although these studies used the same paradigm, the sample sizes were rather small (13 men, 16 women respectively). These sex-dependent changes in amygdala activation are in opposite directions to stimuli of the same valence. With a larger sample size (n = 74) Gao et al. (2016) recently found that oxytocin administration enhances the salience of positive social cues in women, but of negative cues in men. Using a first-impression task, left amygdala activation was increased for both men and women, however, for differently valenced stimuli. Women responded with greater amygdala activity to individuals exhibiting praise, whereas amygdala activation increased in men for individuals exhibiting criticism. Taken together, these findings suggest that oxytocin's functional role in modulating social interactions via the amygdala serves different purposes in men and women.

5. Conclusion and summary

The role of oxytocin in social behavior has been intensively studied. It attenuates the stress response and increases pair-bond formation and empathy among others (Donaldson and Young, 2008). Not only has oxytocin a widespread function, there are numerous factors and mechanisms affecting the oxytocin system, mainly at the level of the *OXTR*, and indirectly the processes regulated by oxytocin. This review has dealt with genetic and epigenetic mechanisms influencing social behavior through manipulation of oxytocin and the *OXTR* gene. Social behavior is a collective term we previously described as all behaviors including social interaction between individuals. These behaviors range from attachment and prosocial temperament to more anti-social behaviors like avoidance and social ostracism. However, proceedings that together make up social behavior are affected by multiple factors that function on different levels, rendering the underlying mechanisms highly complex. Research cannot take into account all facets of social behavior in one study design and therefore often focuses on a specific aspect. Despite a large body of literature regarding oxytocin and social behavior, to the best of our knowledge, there are no studies integrating the effects of multiple factors like SNPs and epigenetic regulation on social behavior. Another interesting line of research would be to combine genetics with oxytocin administration to investigate whether people with a predisposition for antisocial or autistic-like traits respond differently to oxytocin administration. Moreover, studies often use a single task or test to assess social behavior. One of the major limitations is that different assessments of social behavior make it difficult to directly compare the outcomes of these studies. Attachment security (Chen et al., 2011a), social ostracism (McQuaid et al., 2015), social

cognition questionnaires including reading the mind in the eyes test (RMET) and the social responsiveness scale (SRS) (Slane et al., 2014) and prosocial temperament (Tost et al., 2010) are a few examples of the diversity among the paradigms used to investigate social behavior. The current state of literature is constrained by the lack of integration studies that incorporate multiple assessments of social behavior and influencing factors. For example, recent evidence suggested a role for oxytocin in antisocial behavior by enhancing the salience of social stimuli (Shamay-Tsoory et al., 2009). The previous belief that oxytocin is specifically involved in promoting prosocial behaviors appears to be too simplistic. Investigating both pro-and antisocial valenced behaviors in one sample could contribute to unraveling the bigger picture of oxytocin mediated behaviors. Not only should future studies incorporate multiple domains, like SNPs and epigenetics, also different levels of social behavior such as social perception, automatic reactions like mimicry and more complex behavior such as trust, should be taken into account. This also holds for investigating the effects of impaired regulatory mechanisms on ASD. Complementing the main impairments of ASD given in the introduction, other behaviors characteristic for ASD include deficits in eye contact, facial recognition, and lack of social and emotional reciprocity (Jacob et al., 2007; Parker et al., 2014). Most studies, however, focus on the interaction of the SNP with the disorder, but desist from elucidating on the specific behaviors that are impaired.

Also, most studies do not mention the signaling cascade of *OXTR*. SNPs and epigenetic regulatory mechanisms affect the genetic structure and transcription of the *OXTR* gene respectively; however, the effects on the molecular pathway initiated after oxytocin binds to the *OXTR* and the expression on the *OXTR* in the cell membrane are highly underrepresented.

This review is an attempt to bring together research on molecular and epigenetic mechanisms regulating social behavior via modulation of the *OXTR* and bridges the gap between underlying biological mechanisms and social behavior. Because the wide range of topics covered here, a systematic approach was not possible and hence this review serves as an overview of recent developments in the field of social behavior. We have taken a multidimensional approach to the topic of social behavior highlighting genetic and epigenetic influences and sex differences, pointed out gaps in the current literature and proposed avenues for new lines of research. As evident from this review, a large body of literature investigated mechanisms that contribute to social behavior. Social behavior is the product of complex interactions of these mechanisms, including interplay with environmental effects. To avoid adding complexity, environmental effects were left out, as they are beyond the scope of this review.

The first part of this review has set out the genetic regulatory mechanisms that affect social behavior the most evident remark here is the lively debate which variants of the SNPs are in favor of social behavior and which are associated with the darker side of avoidance, lower empathy and decreased prosocial temperament. From here we segued into the epigenetic regulatory mechanisms. DNA methylation of the *OXTR* has been described as a heritable as well as a dynamic epigenetic regulatory mechanism that affects social behavior by blocking transcription of the *OXTR*. The effects of both SNPs and DNA methylation have been substantially linked to social impairments characterizing ASD. As the oxytocinergic system appears to be a key factor in this disorder, future research using a multimodal approach has to further elucidate the regulatory mechanisms to unravel the complex nature of the disorder, which may lead to potential targets for treatment.

Acknowledgements

This research project is supported by the START-program of the Faculty of Medicine, RWTH Aachen (691505) and by the International Research Training Group (IRTG2150) of the German Research Foundation (DFG).

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