Article

Oxytocin pathway genes (*CD38*, *OXTR*) and psychosocial characteristics defined according to Strengths and Difficulties Questionnaire in urban Siberian adolescents: a school-based study

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Abstract: Oxytocin (OT) is regarded as an extremely important prosocial neuropeptide that dramatically affects the establishment of social connections from infancy to adulthood. OT effects on the psychoemotional state are pretty individual and may be dependent on age, gender, ethnocultural factors, social environment, the presence of stress factors, and features of personality. The Strengths and Difficulties Questionnaire (SDQ) is a brief psychopathological screening tool and is recommended for the detection and classification of psychosocial problems in adolescents. The current field school-based study, conducted among urban Siberian adolescents (n = 298 aged 12–18) explored the relation of SDQ scales in relation to genotypes of *CD38* gene that controls oxytocin release, rs3796863, and oxytocin receptor gene (*OXTR*), rs53576. The results of our study show that during the adolescence period, OT pathway high activity can cause some negative effects, such as emotional instability in young (aged 12–14) adolescent girls in the case of carriage of the rs3796863 A allele and emotional disturbances in older (aged 15–18) adolescent boys who are carriers of a GG variant of rs53576. Our results support the hypothesis of OT-mediated excessive social sensitivity which can lead to some age-sex depending psychosocial problems during adolescence.

Keywords: oxytocin; CD38; OXTR; rs3796863; rs53576; polymorphism; adolescents; psychosocial characteristics; Strengths and Difficulties Questionnaire

1. Introduction

Oxytocin (OT) is a nonapeptide neurohormone that is mainly produced in the supraoptic and paraventricular nuclei of the hypothalamus. Large-cell oxytocin-producing neurons of the hypothalamus have axonal connections with the posterior lobe of the pituitary gland, where OT is deposited and subsequently released into the bloodstream with implementation of its peripheral action occurring via the activation of specific receptors. Additionally, OT has a direct central effect on various parts of the brain, mediated through its dendritic release followed by diffusion into adjacent areas. A significantly small part of the OT pool is also produced in peripheral tissues, such as the uterus, testes, thymus, gastrointestinal tract, heart muscle, and bones, where it exerts mainly autocrine and paracrine effects as well as vagus-mediated effects.

The main hormonal role of OT is to regulate the processes of gestation, labor, and lactation as well as the establishment of social bonds from infancy through to adolescence and adult life. Its central action constitutes an important part of cognitive, emotional, and behavioral processes [1].

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Moreover, OT takes part in the regulation of eating and sexual behavior [2,3] and in mechanisms of visceral hypersensitivity [4] and pain perception [5].

Oxytocin production is accomplished through hydrolyzation of the inactive precursor (encoded by the OXT gene) to small peptides via a series of enzymes, including oxytocin and neurophysin I, known as the "oxytocin transporter". Cluster of differentiation 38 (CD38), a transmembrane glycoprotein that catalyzes the formation of calcium signaling molecules, also plays an important role in the secretion of oxytocin: it has been shown that the plasma OT concentration in CD38-deficient mice is sharply reduced, and there are significant disorders in social behavior [6]. The metabolization of OT is mediated by enzymatic degradation under the influence of several enzymes, particularly oxytocinase and leucyl/cysteinyl aminopeptidases. The main hormonal functions of OT are carried out through a specific OT receptor, which belongs to the family of paired G-protein transmembrane receptors that receive and transmit an extracellular hormonal signal ("second messenger" system). Oxytocin receptors are expressed in the brain (especially the amygdala), uterus (expression increases during pregnancy), mammary glands, gastrointestinal tract, myocardium, and vascular endothelium.

The results of a large number of studies on the oxytocinergic system in infancy allow us to draw three important conclusions: (1) the oxytocinergic system starts to function actively during the first months of life; (2) the concentration of oxytocin in the body fluids of infants is sufficient for measurement and research purposes; and (3) OT levels are closely and predictably associated with the degree and quality of a child's social contacts [1]. For example, it has been shown that the children's oxytocinergic system actively responds to episodes of interaction with their parents and can be used to predict the degree of infant–parent synchronization [7], which has been confirmed by neuroimaging techniques [8,9]. Infants with higher OT levels at the age of 6 months show more interest in social interactions [10], calm down faster in the mother's attendance [11], and are not prone to crying when they are separated from their parents [10]. It has been shown that the level of plasma OT can increase after mild stimulation of skin receptors [12,13], which further emphasizes the importance of tactile contact between the infant and parents. The infant's OT level may positively correlate with the parent's OT level, which allowed some authors to hypothesize the "psychobiological transmission of oxytocin" through active parent–child interaction [14].

In pre-pubertal individuals, positive correlations have been found between the OT level and a close, emotionally colored relationship with parents, an attachment to them [15], generous and magnanimous character traits [16], and greater visual fixation on the interlocutor's facial expression [17]. Apter-Levy et al., in their study, showed that maternal depression was associated with lower OT production in 6-year-old children [18]. It was shown that such a calming post-stress factor as the creation of psychophysical comfort by the child's mother had a positive effect on the OT content in the urine of adolescents [19]. Another study showed that creating psychological comfort by parents increased OT levels in adolescents during conditions of stress [20]; interestingly, the support of best friends did not have such an impact (especially for boys). These findings confirm the important role of oxytocin in establishing close and trusting relationships in the social environment, particularly those between parents and children.

In recent years, the genetic aspects of regulation of the production and reception of OT in various psychopathological conditions have attracted the close attention of researchers. Studies of the genetic basis for the oxytocinergic system have mainly focused on single nucleotide variants of the *OXTR* gene (rs53576, rs2254298), *OXT* gene (rs2740210, rs4813627, rs4813625), and *CD38* gene (rs3796863, rs6449197) [21]. Many studies have shown the association between these variants and aggressiveness, poor tolerance to psychological stress [22], as well as suicidal tendencies [23], problems with behavior, the parent–child relationship [24], and attention deficit hyperactivity disorder [25]. A large number of studies have demonstrated the existence of a link between different polymorphic regions of the *OXTR* as well as *CD38* genes and various psychiatric diseases, including autism spectrum disorders (analyzed in detail in the review by Feldman et al. [21]).

CD38 is a transmembrane glycoprotein with adenosine diphosphateribosyl-ribosyl cyclase activity, which plays an important role in the regulation of hormonal production as well as cell

differentiation and migration [26]. CD38 is expressed in hematopoietic cells (B- and T-lymphocytes) and hypothalamic neurons. The first reports on the ability of CD38 to regulate OT production through Ca2+-signaling and influence social interactions were published by Jin et al. in 2007 [6]. Subsequent studies have shown that *CD38* knockout mice have an outstanding reduction in OT production [27]. The single nucleotide polymorphism rs3796863 (A>C) is located in intron 7 of the *CD38* gene, which is has been mapped in the 4p15 chromosomal region [28]. It is assumed that the A allele of rs3796863 variant is associated with high expression of CD38, increased plasma oxytocin concentration, and a pronounced level of social sensitivity [29].

The oxytocin receptor (OXTR) belongs to class I of the G-protein family, has seven transmembrane domains, and is encoded by the *OXTR* gene located in the 3p25–3p26.2 chromosomal region. The *OXTR* gene contains three introns and four exons; the role of the rs53576 (G>A) polymorphic variant, localized in the third exon, has been studied intensively regarding its association with human social functions [21]. It is not entirely clear how the *OXTR* rs53576 variant is translated into phenotypic variations. It has been assumed that the rs53576 variant influences the methylation of the *OXTR* gene: the carriage of the G allele may be associated with a low level of methylation and subsequent high transcription of the gene, enhanced expression of the OT receptor, and an increased level of social sensitivity [30–33].

The Strengths and Difficulties Questionnaire (SDQ) was developed by Goodman et al. [34] as a brief psychopathological screening tool and is recommended for the detection and classification of psychosocial problems in adolescents. The SDQ is now very widely used both in clinical practice and scientific research because of its brevity, reliability, and ability to assess various aspects of the psychosocial state in adolescents. An undoubted advantage of the SDQ is also its wide availability: currently, it has been translated into more than 80 languages. It also is freely available on the developers' website (https://sdqinfo.org/), which has made cross-cultural comparisons possible. The Russian version of the SDQ has been thoroughly validated by Ruchkin et al. [35] and Slobodskaya et al. [36] on a sample group of Siberian schoolchildren (Novosibirsk, Russia).

To the best of our knowledge, there are no field studies on the effect of OT gene polymorphism on the psychosocial characteristics of adolescents in an unbiased school sample using the SDQ questionnaire.

2. Results

Descriptive statistics for the major study variables, SDQ scales, *CD38* rs3796863, and *OXTR* rs53576 are presented in Table 1. Girls in our sample group showed higher scores in the SDQ scales of emotional symptoms and prosocial behavior compared to boys. Similar gender differences have been described for other populations [35,37]. The frequencies of the *CD38* rs3796863 and *OXTR* rs53576 genotype distribution in the sample group are comparable to their frequencies in Caucasian populations (according to data on www.ensembl.org) and do not depend on the gender of participants.

Table 1. Descriptive statistics for major study variables, SDQ scales, *CD38* rs3796863, and *OXTR* rs53576.

Variables	All participants	Boys	Girls	p (boys vs girls)
Age 12–14	139	51	88	—
Age 15–18	159	62	97	—
Total	298	113	185	—
		SDQ scales		
Total difficulties score	12 (8–16)	10 (6–13)	13 (8–13)	<0.001
Conduct problems	2 (1–3)	2 (1–3)	2 (1–3)	0.286

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score				
Emotional symptoms score	3 (1–5)	2 (0–4)	4 (2–6)	<0.001
Hyperactivity score	3 (2–5)	3 (2–5)	3 (2–5)	0.099
Peer problem score	3 (1–4)	2 (1–4)	3 (1–4)	0.429
Prosocial behavior score	7 (6–9)	7 (5–8)	8 (6–9)	<0.001
***CD38* rs3796863 genotypes**				
AA	33 (11%)	16 (14%)	17 (9%)	0.179
AC	113 (38%)	39 (35%)	74 (40%)	0.389
CC	152 (51%)	74 (51%)	94 (51%)	1.000
***OXTR* rs53576 genotypes**				
AA	48 (16%)	20 (18%)	28 (15%)	0.500
AG	142 (48%)	51 (45%)	91 (49%)	0.502
GG	108 (36%)	42 (37%)	66 (36%)	0.862

Note: Data for the SDQ are presented as medians (25%–75% quartiles) of SDQ scale points. The Mann–Whitney U test was used for SDQ points and two-tailed Fisher's exact test for genotypes.

It is known that oxytocin production decreases in adolescents in comparison with pre-pubertal individuals, and there are sex differences in OT concentration in biological fluids (levels are higher in girls [20]). Moreover, median values of individual SDQ scales for boys significantly differs from that of the girls in our sample group (Table 2). To take into consideration such age and gender differences, we carried out discrete analysis of the *CD38* rs3796863 and *OXTR* rs53576 genotype influences on the indicators of the SDQ questionnaire scales in two age groups (12–14 and 15–18 years old) separately for boys and girls.

As is the case for a large number of similar studies that evaluated genotypic differences for the rs3796863 variant [38–42], we used the dominant inheritance model to ensure a sufficient number of participants in each group to be analyzed, where the minor homozygotes and heterozygotes for *CD38* rs3796863 (AA and AC) were combined and compared with the homozygotes for the major allele (CC). The same analysis strategy was used to assess the *OXTR* rs53576 genotypes: minor homozygotes and heterozygotes (AA and AG) were combined and compared with homozygotes for the major allele (GG), which was also used in several studies of Caucasoid populations, in which the G allele predominates (in contrast to Asian populations, in which the A allele is more common) [43-46].

The median values of SDQ scales according to the different *CD38* rs3796863 and *OXTR* rs53576 genotypes are respectively presented in Table 2 and 3.

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Table 2. Values of SDQ questionnaire scales for different *CD38* (rs3796863) genotypes in different sex and age groups of adolescents.

SDQ scales	*CD38* rs3796863 genotypes											
	Age 12-14						Age 15-18					
	Boys (n = 51)			Girls (n = 88)			Boys (n = 62)			Girls (n = 97)		
	AA+AC (n = 21)	CC (n = 30)	p	AA+AC (n = 40)	CC (n = 48)	p	AA+AC (n = 34)	CC (n = 28)	p	AA+AC (n = 46)	CC (n = 51)	p
Total difficulties score	11 (8–13)	10 (9–16)	0.840	16 (13–19.5)	14 (9–17)	0.053	9 (5–12)	9 (4.5–14)	0.843	11 (7–13)	11.5 (8–17)	0.585
Conduct problems score	3 (2–3)	2 (1–3)	0.066	3 (2–4)	3 (1–5)	0.996	2 (2–3)	2 (1–2)	0.078	2 (1–3)	2 (1–3)	0.973
Emotional symptoms score	2 (0–3)	2 (0–4)	0.401	6 (4–7)	3 (2–7)	0.022	2 (0–3)	1.5 (0–3)	0.628	3 (2–5)	4 (1–6)	0.847
Hyperactivity score	3 (2–5)	3.5 (2–5)	0.816	4.5 (3–6)	3.5 (2–6)	0.102	3 (1–4)	3 (1–6)	0.453	3 (1–5)	3 (1–5)	0.895
Peer problem score	3 (2–4)	3 (2–4)	0.976	3.5 (2–5)	3 (1.5–4)	0.266	2 (1–3)	2 (1–4)	0.908	2 (1–4)	3 (2–4)	0.101
Prosocial behavior score	6 (5–8)	7 (5–8)	0.353	8 (6.5–9)	7 (6–8)	0.075	6.5 (4–8)	7 (5.5–8)	0.493	8 (7–9)	8 (7–9)	0.716

Note: Data are presented as medians (25%–75% quartiles) of SDQ scale points; values shaded in gray indicate scales that have a tendency towards statistical significance (Mann–Whitney U test $p \leq 0.1$) and are described in the full text of the article.

Table 3. Values of SDQ questionnaire scales for different *OXTR* rs53576 genotypes in different sex and age groups of adolescents.

SDQ scales	*OXTR rs53576* genotypes											
	Age 12-14						Age 15-18					
	Boys (n = 51)			Girls (n = 88)			Boys (n = 62)			Girls (n = 97)		
	AA+AG (n = 30)	GG (n = 21)	p	AA+AG (n = 51)	GG (n = 37)	p	AA+AG (n = 41)	GG (n = 21)	p	AA+AG (n = 68)	GG (n = 29)	p
Total difficulties score	11 (8–16)	10 (9–12)	0.323	15 (12–19)	15 (9–18)	0.573	8 (4–12)	11 (8–13)	0.050	11 (7.5–14)	11 (7–16)	0.850
Conduct problems score	2 (1–3)	2 (2–3)	0.944	3 (2–4)	3 (2–4)	0.403	2 (1–3)	2 (1–2)	0.286	2 (1–3)	2 (1–3)	0.661
Emotional symptoms score	1,5 (0–4)	2 (2–4)	0.822	5 (2–7)	5 (2–7)	0.752	1 (0–2)	3 (2–4)	0.004	3.5 (2–5)	3 (1–6)	0.680
Hyperactivity score	4 (2–5)	3 (2–5)	0.283	4 (2–5)	4 (3–6)	0.310	1 (0–2)	3 (2–4)	0.103	3 (1–5)	3 (1–5)	0.824
Peer problem score	3 (2–5)	3 (2–3)	0.325	3 (2–5)	3 (1–4)	0.156	2 (1–3)	3 (1–4)	0.586	3 (1–4)	3 (2–4)	0.677
Prosocial behavior score	7 (5–8)	6 (6–8)	0.810	7 (6–8)	7 (6–9)	0.983	7 (4–8)	7 (5–8)	0.314	8 (7–9)	8 (7–9)	0.310

Note: Data are presented as medians (25%–75% quartiles) of SDQ scale points; values shaded in gray indicate scales that have a tendency towards statistical significance (Mann–Whitney U-test $p \leq 0.1$) and are described in the full text of the article.

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The greatest correlation between *CD38* rs3796863 genotypes and SDQ scores was found in girls aged 12–14 years (Table 2). In this group of adolescents, carriage of the high-OT-producing genotypes (AA + AC) was associated with high values of the Emotional symptoms score ($p = 0.022$) and a tendency towards high values of the hyperactivity score ($p = 0.102$) and total difficulties score ($p = 0.053$). At the same time, girls with the rs3796863 (AA + AC) genotype showed a tendency towards high values of the prosocial behavior score ($p = 0.075$), reflecting the adolescent's desire toward providing help, sacrifice, generosity, and cooperation. Apparently, young adolescent girls with a genetically determined ability to produce more OT are more susceptible to negative social stimuli with a greater emotional response (in some cases, exceeding the normal level and leading to problems in the emotional sphere). However, the process of growing up changes those tendencies, and such connections are no longer revealed in older adolescent girls (15–18 years old). The carriage of high-OT-producing genotypes (AA + AC) is manifested only by a tendency towards better social relations with peers according to the peer problem score ($p = 0.102$).

In boys of both age groups carrying high-OT-producing genotypes (AA + AC), we revealed a tendency towards high conduct problems scores. When the age groups of boys are combined, the differences in the conduct problems score for different *CD38* rs3796863 genotypes become statistically significant (carriers of the A allele (AA + AC) — 2.0 (2–3), CC homozygotes — 2 (1–3), $p = 0.020$). Detailed analysis shows that differences in high- and low-producing genotypes of *CD38* rs3796863 were evident in only one out of five similar questions that characterize behavioral problems. In our sample group, carriers of the high-OT-producing A allele (AA + AC) were found in 72% of cases when boys answered "not true" ($n = 25$) to question № 7 ("I usually do as I am told") and only in 36%, $p = 0.022$, when the answer was "certainly true" ($n = 25$). This answer, in our opinion, can hardly be regarded as a direct sign of an adolescent's bad behavior in the absence of other typical symptoms of the dissocial disorder. It rather indicates greater independence of the adolescent, the expression of his point of view, and a desire to conduct a social dialogue with adults. Thus, we can confidently assume that the genetically determined ability to produce high levels of OT in adolescent boys is not associated with behavioral problems; on the other hand, it shows the natural desire of adolescents to have their own social position, which is undoubtedly an important factor in the formation of personality.

SDQ score analysis based on *OXTR* rs53576 genotypes showed a statistically significant correlation only in the subgroup of older (15–18 years old) adolescent boys (Table 3). Homozygosity for the G allele, which is presumably associated with high activity of the oxytocin receptor, was associated with the presence of emotional problems ($p = 0.004$) and a tendency towards high values of the hyperactivity score ($p = 0.103$) and total difficulties score ($p = 0.050$) in these adolescents. It is typical for young adolescent girls to have the genetically determined ability to produce high levels of OT, but still, it results in emotional problems with a tendency towards hyperactivity (Table 2). A similar trend manifested itself in the general group of girls in our sample group (Table 1). It is likely that high activity of the oxytocinergic system is manifested by a special pattern combination of high emotionality with social activity which, in this case, is not a sign of hyperactivity in the generally accepted clinical sense.

3. Discussion

We were able to find only two studies focused on the role of the oxytocinergic system in assessing the behavior of children that were conducted using the SDQ questionnaire. In their study, Levy et al. showed that the concentration of oxytocin in saliva was negatively correlated with the severity of behavioral problems identified by the SDQ questionnaire in 16-year-old adolescent boys admitted to psychiatric counseling because of antisocial behavior [47]. It was also found that OT production was reduced in adolescents with insufficient emotional response and an unemotional type of character. These data correlate with the results of our study, which show relatively greater emotionality — in some cases, reaching problematic degree — in adolescents with genotypes corresponding to high production and reception of OT. Choi et al. [48] showed that the carriage of

the A allele of *OXTR* rs53576 in a homozygous state, in combination with the occurrence of postpartum depression in the mother, was associated with a high risk of conduct problems and hyperactivity in 6-year-old children. In our study, no association was found between the carriage of the *OXTR* rs53576 A allele and conduct problems in adolescents.

The results of our study clearly show the presence of age–sex features of the influence of OT production (*CD38*) and OT reception (*OXTR*) genes on the psychosocial characteristics of adolescents. This is not surprising, as there are two parallel processes in adolescence: the age-dependent decrease in OT production and the emergence of sex differences in its production [20]. In addition to these, such differentiation can be influenced by a complex and insufficiently studied interaction between OT and the entire spectrum of sex hormones, which exhibits extremely dynamic changes in adolescence [49]. Our data show that in terms of age-related oxytocinergic system development, adolescent girls aged 12–14 years and boys aged 15–18 years are the most vulnerable. Moreover, there are genetically programmed mechanisms of OT production in younger adolescent girls, such as *CD38* variants, which can have a greater influence on psychosocial characteristics, whereas in older boys, OT reception (OXTR) plays a greater role.

We presume that a relatively large production of OT, mediated by carriage of the A allele of the rs3796863 variant region of the *CD38* gene, is associated with disturbances in the emotional sphere in young adolescent girls due to a higher level of social sensitivity, which corresponds with the results of other studies.

The hypothesis of CD38-mediated social sensitivity as a general mechanism of oxytocin moderation of an increased psychoemotional response to positive and negative social stimuli was originally put forward by Bartz and McInnes [50,51]. This hypothesis was later confirmed. For example, in the examination of 400 adolescents, Tabak et al. showed that carriers of the A allele rs3796863 of the *CD38* gene were more sensitive to chronic interpersonal stress than CC homozygotes [39]. Mediated by genetic variations in CD38, high levels of social sensitivity as a factor of emotional problems were demonstrated in a study by McQuaid et al. [52]. The authors conducted genetic testing of 19-year-old students and found that AA homozygotes of rs3796863 experienced heightened feelings of alienation from parents and peers, symptoms of depression, and an increased level of suicidal ideation. Later, the same authors showed that carriers of the A allele of rs3796863 were more sensitive to unsupportive social interactions with their peers (relationships that bring pain, suffering, sadness, isolation, rejection, and troubles) [40]. Lebowitz et al. found that the influence of negative relationships with peers more often led to suicidal ideations in adolescents with high levels of OT in saliva, which also supports the hypothesis of OT-mediated excessive social sensitivity [53].

According to our data, the mechanisms of OT reception, mediated by carriage of the G allele of the *OXTR* rs53576 gene, are more vital for older adolescent boys in the regulation of emotions and behavior, as this age–sex group experiences the conditions of relatively low OT production in comparison with girls and younger boys. The provocative role of G-allele carriage in the formation of psychoemotional problems in adolescents has been described in several studies. Smearman et al. revealed a greater level of behavioral problems under the influence of stress factors in adolescents with the G allele of rs53576 [54]. McQuaid et al. described the association of G allele of rs53576 carriage with depressive symptoms in students who underwent a traumatic situation in childhood [55]. The authors considered these results to be paradoxical, since a large number of studies have simultaneously shown the association of the G allele of rs53576 with extremely socially useful qualities, such as empathy, optimism, and trust [30,31,43,56,57]. As a possible explanation for their findings, the authors proposed the hypothesis of excessive social sensitivity in individuals with high production and reception of OT, which is described above. Similar results were later obtained by Hostinar et al.: in adolescents who experienced childhood maltreatment, a high level of anxiety and depression symptoms were more often found in those with homozygosity for GG of rs53576 [58]. Unfortunately, these studies did not stratify adolescents by gender.

Sex differences in the effects of the oxytocinergic system on human mental functions have been discussed in numerous publications. Data on the direct influence of gonads on the processes of

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production, reception, and modulation of OT effects are currently limited [49,59]. Nevertheless, there are data obtained in experiments with animals that indicate that estrogens have a stimulating effect on the production of OT in the hypothalamus and its reception in the middle part of the amygdala (medial amygdala), whereas testosterone regulates social functions predominantly through vasopressin pathway [60]. The data of Taylor et al. are particularly interesting in this regard, as they show that young women respond to distress in relationships with a partner with an increase in plasma OT, and the same applies to men but with an increase in vasopressin [61]. Some authors believe that gender differences in OT production and reception largely determine general strategies for responding to stress in individuals of different genders: from seeking support in girls and women ("tend-and-befriend" behavior) to the strategy of "fight or flight" in boys and men [1,62].

Some studies confirm the existence of sex differences in the regulation of OT reception in adolescent populations. Thus, Andreou et al. conducted genetic testing of 1591 Swedish adolescents and revealed an association between the G allele of the rs53576 region of the *OXTR* gene and antisocial behavior in cases of maltreatment, but this was still only applicable to girls, not boys [24]. The authors concluded that it is mandatory to take into account the gender factor in studies on the role of the oxytocinergic system in adolescents. In a prospective study of 593 15-year-old Estonian adolescents, it was shown that in boys (but not girls), homozygosity for the allelic variant A of rs53576 was associated with more frequent alcohol consumption and the development of addiction to alcohol by the age of 25 [63]. It was found that in a Chinese population of adolescents homozygous for the major allele in Asian populations, which is the A rs53576 *OXTR* allele, there is a greater level of hostility and aggressiveness when the individual is exposed to stress factors [22]. The effect was much more typical for boys than for girls, which is fairly consistent with our data.

It is known that oxytocin receptors are concentrated mainly in the amygdala, and the size of the amygdala in men is larger than that in women, on average, but still, it is negatively correlated with prosocial behavior. In this regard, the data of Tost et al., who found that the right amygdala was smaller in homozygous carriers of the G allele of the *OXTR* rs53576 gene (typical only for men, not women), are extremely interesting [64]. It is also intriguing that intranasal administration of OT led to the suppression of right amygdala activity, which is responsible for the formation of aggressiveness and negative emotions in response to stress and is more active in men [65]. There are well-known data on sex differences in psychological reactions to the administration of exogenous OT, which were obtained both in experiments with animals and in controlled studies in humans [49,59]. Lucas-Thompson et al. investigated the psychological response to the September 11 terrorist attack and found that the stress response was moderated by the *OXTR* rs53576 polymorphism only in men, but not in women, and homozygosity for GG of rs53576 was associated with poorer stress tolerance [45]. In men, but not in women, GG homozygosity of rs53576 was associated with an increased sympathetic response of the cardiorespiratory system to stress in comparison with carriers of the A allele [66]. Finally, Nishina et al. found a higher level of confidence in carriers of the GG genotype of rs53576 variant in Japanese men but not women [46]. The results of the studies mentioned above correspond well enough with our data on the greater effect of the *OXTR* rs53576 gene variant on the psychosocial characteristics of boys, but not girls, and this phenomenon manifested only in older adolescents in the process of growing up. It can be assumed that the differences in the structure and function of the amygdala are fully formed only after reaching older adolescence.

The lack of influence of OT reception on the psychosocial characteristics of young girls and boys may be explained by higher levels of OT production when its reception does not have a decisive psychophysiological significance, as well as by the presence of some age-related features of the amygdala. Additionally, the well-known fact of a certain delay in the onset of puberty in boys can be a subject of study in the context of the age-related interaction of sex hormones and the oxytocinergic system on the development of behavior in gender groups. Such assumptions require additional research.

We believe that the increased capacity for OT reception mediated by the carriage of the G allele of rs53576 may act as a "cruel joke" in older adolescent boys. Rivalry and aggressiveness are more

welcomed than the ability to display empathy or gullibility in this age–sex group. OT-mediated oversensitivity towards negative social stimuli, described above, is not encouraged at this age. These adolescent boys will be rated as "weak" and "not aggressive/courageous enough" by their peers. The discrepancy between their psychological feelings and those that are socially approved may lead to adolescent boys with a high level of OT reception experiencing intrapersonal conflict and problems in the emotional sphere. However, addressing problems in communication with peers with increased social empathy and an altruistic personality can be a successful way of overcoming these contradictions. The general orientation of the pedagogical process towards the approval of prosocial behavior as well as the influence of socially significant personalities, which adolescents can choose as a moral example to follow, can help here. The ability of socioeducational and ethnocultural factors to moderate the genetic regulation of the oxytocinergic system has been demonstrated in some studies [20,21,67–70]. The accumulated evidence of the individual psychosocial consequences of high activity of the oxytocinergic system, which may differ from person to person depending on the context of the social environment (e.g., competitive vs. cooperative environment), has allowed researchers to formulate the "social salience hypothesis of oxytocin" [51,71]. In the context of this hypothesis, Van Anders et al. warned against being overly optimistic about the exceptional helpfulness of oxytocin for the psychosocial functions of an individual [72]. We are in agreement with this assessment, as the results of oxytocinergic system function may depend on age, gender, ethnicity, social environment, and other factors.

The present study is characterized by a number of limitations. Our study has low statistical power as it was conducted on small age–sex comparison groups. This led to a situation in which the majority of the gene–phenotype correlations were described only as a statistical trend, and confidence in the findings may be improved by increasing the size of comparison groups in future. The study was not anonymous; the SDQ was not completed individually and children filled in the forms in class. The study design was based on voluntary consent to fill out a questionnaire and collect saliva. It can be assumed that some adolescents with psychological problems could not answer questions truthfully enough and/or explicitly or implicitly avoided these procedures, especially those that are associated with an unesthetic saliva collection technique in the presence of researchers. These circumstances could distort the overall picture of the identified correlations. The nationality of the adolescent was determined only based on the mother's nationality, which is why the ethnic composition of the sample group could have been described inaccurately. However, the distribution of *OXTR* rs53576 genotypes in our sample corresponded to those characteristics of Caucasoid populations with a predominant G allele (as opposed to Asian populations, where the A allele is dominant).

4. Materials and Methods

4.1. Participants

In the present study, psychological and genetic testing was carried out on 298 adolescents aged 12–18 from unbiased school samples in three large cities of Central Siberia (Krasnoyarsk, n = 190; Abakan, n = 75; Kyzyl, n = 33). The nationality of all adolescents included in the study is Russian Caucasian (verified by the mother's nationality).

4.2. Procedure

The research was carried out in 13 general education schools after the end of the lessons. Each school was randomly assigned for testing. After receiving informed consent from parents, schoolchildren were notified of the voluntariness and confidentiality of the study, and that it is not an anonymous study. Participants were asked to complete a questionnaire that included demographic data (gender, age, the mother's nationality) and one-sided self-rated SDQ for children aged 11–17 years. Adolescents were asked to provide saliva samples in special containers after filling out the form.

The SDQ consists of 25 statements regarding problematic and socially approved behavior for assessment in the adolescents over the prior 6 months. Answers are assessed on a 3-point scale (0 =

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not true, 1 = somewhat true, and 2 = certainly true; points were assigned in forward or reverse order for each question following the instructions of the authors of the questionnaire [34]) and are grouped according to five scales: emotional symptoms, conduct problems, hyperactivity/inattention, peer problems, and prosocial behavior.

Following the instructions of the authors of the questionnaire [34], the scores for the statements were summed and grouped to calculate the indicator for each scale: emotional symptoms are characterized by statements № 3, 8, 13, 16, and 24; conduct problems are summed from the points of № 5, 7, 12, 18, and 22; hyperactivity/inattention are reflected by statements № 2, 10, 15, 21, and 25, while peer problems are determined from questions № 6, 11, 14, 19, and 23. The total number of points reflects the severity of problems in a particular area for a particular teenager. Additionally, the scores of the first four scales form another scale named "total difficulties score". The prosocial behavior score is calculated separately based on the sum of points for statements № 1, 4, 9, 17, and 20. For our study, we used the Russian version of the questionnaire, which can be freely downloaded from the developers' site (https://sdqinfo.org/).

The study was approved by the Ethics Committee of the Federal Research Center "Krasnoyarsk Science Center of the Siberian Branch of the Russian Academy of Sciences" (# 18.12.2018).

4.3. Genotyping

Saliva samples for genotyping were collected using "Saliva DNA Collection and Preservation Devices" (Norgen Biotek Corp., Thorold, ON Canada). Genomic DNA was extracted from the sample using "DIAtom DNA Prep kits" (IzoGen, Russia). Variants were determined by real-time polymerase chain reaction (RT-PCR) using "Rotor-Gene 6000" (Corbett Life Science, Australia). Genotyping was carried out using TaqMan allele discrimination technology and commercially available TaqMan probes (DNA-Synthesis, Russia). The PCR reaction system, with a total volume of 25 μL, contained 1 μL of DNA template (about 10 ng), 10 μL of 2.5× reaction mix for RT-PCR, 2 μL of 25 mM MgCl2, 8.5 μL of ddH2O (M-428, Syntol, Russia), 2.5 μL of 10 μM primer mix, and 1 μL of each fluorescent probe (DNA-Synthesis, Russia). RT-PCR conditions were as follows: 95 °C for 3 min; 95 °C for 20 s, 55 °C for 30 s, and 72 °C for 20 s (50 cycles). More details related to genotyping are shown in Table 4.

Table 4. Primer and fluorescent probe sequences and genotype distribution in the study.

Variant	RT-PCR primers	RT-PCR probes	Amplicon length (bp)	HWE *p*-value
***CD38* rs3796863**	Fwd: 5'-CATGTCGGGAGGGGAGCTA-3' Rev: 5'-GCCTTGGTTGCTGCTCCTG-3'	FAM-TGACCA**G**CAGGTG-BHQ1 VIC-TTGACCA**T**CAGGTG-BHQ1	67	0.092
***OXTR* rs53576**	Fwd: 5'-GCATTCATGGAAAGGAAAGGT-3' Rev: 5'-CCCATCTGTAGAATGAGCTTCC-3'	FAM-CCCGAGG**A**TCCTCAG -BHQ1 VIC-CCCGAGG**G**TCCTCA-BHQ1	94	0.908

4.4. Statistical Analysis

Statistical analysis was performed using Statistica v.12.0 software (StatSoft Inc., USA). SDQ score data are shown as medians (25%–75% quartiles). The Mann–Whitney U test was used to determine whether there are differences in SDQ scores between groups according to genotypes. Differences in categorical data were assessed using the two-tailed Fisher's exact test. Differences were considered statistically significant at $p < 0.05$. Statistical tendencies were assumed at $0.05 < p \leq 0.10$.

5. Conclusions

Consequently, even though OT is regarded as an extremely important prosocial neuropeptide that dramatically affects the establishment of social connections from infancy to adulthood and leads to the formation of enhanced empathy and socially positive character traits, its effects on the psychoemotional state are pretty individual and may be dependent on age, gender, ethnocultural factors, social environment, the presence of stress factors, and features of personality. Moreover, the genetically determined increase in the production and reception of OT as a "prosocial neuropeptide" does not always play an exclusively positive role. The results of our study show that during the difficult period of growing up, OT can also cause some negative effects, such as emotional instability in young adolescent girls in the case of carriage of the A allele in the polymorphic region of the rs3796863 *CD38* gene, associated with a higher ability to produce OT and emotional disturbances in older adolescent boys who are carriers of a homozygous variant of the G polymorphic region rs53576 of the *OXTR* gene, associated with increased activity of the oxytocin receptor. Our findings are consistent with the ideas expressed by Bartz et al. [51], Van Anders et al. [72], Feldman et al. [21], and Shamay-Tsoory and Abu-Akel [71]: the psychophysiological role of OT should always be assessed in the context of a specific social situation, age, and gender characteristics (e.g. stratification by age and sex should be mandatory in this type of study in adolescents). It is also important that the characteristics of adolescence not be automatically translated to the entire population: the OT-mediated high level of social sensitivity, which can lead to some problems during adolescence, can develop into extremely useful social skills in adulthood.

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Abbreviations

OT	Oxytocin
CD38	Cluster of differentiation 38
OXTR	Oxytocin receptor
SDQ	The Strengths and Difficulties Questionnaire
DNA	Deoxyribonucleic acid
RT-PCR	Reverse transcription polymerase chain reaction
HWE	Hardy–Weinberg equilibrium

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