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RESEARCH ARTICLE

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Interaction between polymorphisms of the oxytocinergic system genes and emotion perception in inpatients with anorexia nervosa

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Abstract

Objective: The empirical literature describes the role of the oxytocinergic system in emotion perception (EP). Variants in the oxytocin (OXT) and oxytocin receptor genes have been associated with mental disorders, including anorexia nervosa (AN), that are characterized by difficulties in socioemotional functioning. Our study aimed to examine whether variability within the genes related to OXT pathways may play a role in facial EP in inpatients with AN.

Method: Single nucleotide polymorphisms (SNPs) of the following genes: oxytocin receptor (rs2254298, rs53576), OXT (rs6133010), OXT-arginine-vasopressin (rs2740204), CD38 (rs6449197, rs3796863), and human leucyl/cystinylaminopeptidase (rs4869317) were genotyped in 60 AN female inpatients and 60 healthy control females (HCs). Associations between genetic polymorphisms and EP as well as clinical symptoms were examined.

Results: The AN group showed decreased EP abilities compared with HCs. SNPs of rs2740204, rs6133010, and rs53576 were associated with differences in EP in women with AN and in HCs. The SNP of rs4869317 was associated with the level of eating disorders symptoms in HCs.

Conclusions: The OXT system may be involved in EP difficulties in AN. SNPs within genes related to OXT pathways may influence EP abilities. The leucyl/cystinylaminopeptidase rs4869317 SNP may be involved in the development of eating disorders psychopathology.

KEYWORDS
anorexia nervosa, eating disorders, emotion perception, gene polymorphisms of oxytocinergic system, oxytocin (OXT)

1 | INTRODUCTION

Social isolation and withdrawal are present in the majority of patients with anorexia nervosa (AN; Fairburn, Shafran, & Cooper, 1999; Karwautz, Troop, Rabe-Hesketh, Collier, & Treasure, 2003; Kaye et al., 2004). Findings from recent studies suggest that aberrant interpersonal abilities may result in social interaction deficits, observed in AN (see Krug et al., 2013). Abnormal processing of social signals has been described in the acute phase of AN (see Harrison, Sullivan, Tchanturia, & Treasure, 2009; Lang et al., 2015; Morris, Bramham, Smith, & Tchanturia, 2014; Zonnevylle-Bender et al., 2004). Abnormal processing of social signals has also been observed in people recovered from AN, which suggests that such impairment may be considered an endophenotype of this disorder (Harrison, Tchanturia, & Treasure, 2010). One of the factors that seems to be involved in social cognition is emotion perception (EP), which refers to detecting affective cues, for example, on the faces of other people. Impairment in this ability in AN is strongly supported by the empirical literature (see Harrison et al., 2009; Jänsch, Harmer, & Cooper, 2009; Kucharska-Pietura, Nikolaou, Masiak, & Treasure, 2004; Zonnevylle-Bender et al., 2004).

1.1 | Oxytocin and eating disorders

Oxytocin (OXT) is a nonapeptide produced mainly in the hypothalamus, released within the posterior part of the pituitary gland, and acting in the brain and the periphery. Although the role of this hormone peptide and neuropeptide in parturition and sexual functions is well established, its effect on socioemotional aspects of functioning is a topic of more recent studies (see Bachner-Melman & Ebstein, 2014; Jones, Barrera, Brothers, Ring, & Wahlestedt, 2017; Kim, Eom, Yang, Kang, & Treasure, 2015; Leppanen et al., 2017). Exogenous OXT administered intranasally may enhance social functioning in both healthy control participants (HCs) and patients with eating disorders (Kim, Eom, et al., 2015). Intranasal administration of OXT may lead to normalization of emotional processing of social as well as food- and shape-related stimuli (Kim et al., 2014; Leppanen et al., 2017). Most recently, Kim, Kim, Kim, and Treasure (2014) observed increased methylation of CpG dinucleotides in the oxytocin receptor (OXTR) gene in a small sample of patients with AN. This modification has been associated with reduced expression of the OXTR in the brain (Acevedo, Valencia, Lutter, & McAdams, 2015; Gregory et al., 2009). Demitrack et al. (1990) reported a low concentration of OXT in cerebro-spinal fluid of restrictive AN patients. However, that group included only five participants. Therefore, this result should not be interpreted as entirely conclusive. Other authors observed decreased serum levels of OXT in AN individuals (Lawson et al., 2011; Monteleone, Scognamiglio, Volpe, Di Maso, & Monteleone, 2016). Lawson et al. (2012) identified higher postprandial OXT concentration in acute AN and lower in weight-recovered AN in comparison with HCs. Abnormal postprandial OXT secretion in AN was associated with increased symptoms of anxiety and depression. These findings may suggest the role of OXT in socioemotional functioning in AN.

Highlights

- Both in individuals with anorexia nervosa (AN) and in healthy controls (HCs), A carriers of a common single nucleotide polymorphism (SNP) of the oxytocin receptor gene rs53576 showed higher emotion perception (EP) indicators as compared with non-A carriers.
- SNPs of rs2740204, rs6133010, and rs53576 were associated with differences in EP in patients with AN and in HCs.
- SNPs within genes related to oxytocin pathways may influence an individual's EP abilities.

1.2 | Genetic studies and socioemotional functioning in AN

Family and twin studies imply significant heritability of AN (Bulik et al., 2010; Kortegaard, Hoerder, Joergensen, Gillberg, & Kyvik, 2001; Steinhausen, Jakobsen, Helenius, Munk-Jørgensen, & Strober, 2015). However, attempts to find genetic variants associated with the disorder brought unsatisfactory results. Recent findings from genome-wide association studies were inconclusive, suggesting the necessity of conducting future studies with larger samples (Boraska et al., 2014; Duncan et al., 2017). One of the methods of finding genes predisposing to psychiatric disorders consists of analysing traits because they have simpler genetic underpinnings than clinical diagnoses. The endophenotype strategy assumes that finding a heritable trait related to a disorder and associated genes would lead to the explanation of the link between genetic liability and a clinical phenotype. One may hypothesize that genetic liability to AN, at least partly caused by polymorphisms in the OXT system, is

mediated via socioemotional deficits. Recent reports show that genetic variation within genes encoding various proteins related to OXT signalling may affect different aspects of emotional functioning (Parker et al., 2014; Skuse et al., 2014). Moreover, the attentional bias toward negative facial emotions (i.e., disgust and anger) is reported to be modified by OXT in AN (see Kim, Kim, Park, Pyo, & Treasure, 2014). These findings suggest that the OXT system may be involved in fear-related stimuli and social cue processing in AN patients (Kim, Eom, et al., 2015).

1.3 | SNPs of the oxytocinergic system genes in psychiatric populations with socioemotional functioning deficits

Single nucleotide polymorphisms (SNPs) in the OXT and CD38 (protein responsible for OXT secretion) genes have been associated with emotion recognition, several aspects of theory of mind abilities, and activity in brain areas associated with social processes (Zhang, Zhang, Han, & Han, 2017). The OXT and CD38 genes are mapped respectively to chromosome 20p13 (Rao, Löffler, Battey, & Hansmann, 1992) and to chromosome 4p15 (Nakagawara et al., 1995). On the basis of literature review, we selected four SNPs in our study (two in the OXT gene and two in the CD38 gene) to assess their associations with EP in patients with AN and in HCs. We hypothesized that the selected OXT and CD38 SNPs would be associated with EP in patients with AN. The SNP rs2740204 in 3'region of the shared promoter of OXT and arginine vasopressin (AVP) was repeatedly reported as important for multiple psychiatric phenotypes: schizophrenia (see Teltsh et al., 2012), negative symptoms of schizophrenia (see Souza, De Luca, Meltzer, Lieberman, & Kennedy, 2010), behavioural symptoms in autism (see Yrigollen et al., 2008), and childhood-onset mood disorders (see Dempster et al., 2009). Conversely, rs6133010 OXT SNP has been reported as linked to the functioning of the gastrointestinal tract via peripheral action of OXT (see Truedsson, Carlson, Simrén, & Ohlsson, 2009). This SNP has also been related to autism spectrum disorder (Ebstein et al., 2009). Two polymorphisms of CD38 (i.e., rs6449197 and rs3796863) showed associations with high functioning autism (Munesue et al., 2010) and with lab-based indices of socioemotional functioning (Algoe & Way, 2014). Ebstein, Knafo, Mankuta, Chew, and San Lai (2012) suggest a potential role of polymorphisms of rs4869317 leucyl-cystinyl aminopeptidase (LNPEP) in social cognition. LNPEP is a protein disintegrating OXT and AVP and thus regulates their function. Therefore, we hypothesized that rs4869317 SNP might be related to EP in patients with AN as well.

Research results suggest that two SNPs within the OXTR gene—rs2254298 and rs53576—may be associated with socioemotional functioning. The A allele of rs2254298 has been related to the volume of the amygdala, known as a structure associated with anxiety and fear processing (Inoue et al., 2010). This polymorphism has also been linked with a sexual dimorphism related to the expressed psychological phenotype, with male carriers expressing autistic traits and female carriers expressing anxiety traits (Chen & Johnson, 2012). Parker et al. (2014) found that carriers of the A allele of rs2254298 exhibited greater global social impairment, and carriers of G allele of rs53576 showed impaired affect recognition performance among children with and without autism spectrum disorder. We hypothesized that the minor alleles of the OXTR would be more common in patients with AN, because high anxiety, low self-esteem, and difficulty managing social stress are also common among these patients (Acevedo et al., 2015; Grilo et al., 2012; Gual et al., 2002; Herpertz-Dahlmann et al., 2001). AN Q5 differs greatly from schizophrenia, autism, and anxiety disorders, but one similarity between them is that social impairment is their significant feature. In addition, OXT clinical trials in AN have produced mixed results so far (see Kim, Kim, Cardi, et al., 2014; Leppanen et al., 2017; Russell et al., 2018).

1.4 | Study purpose

We aimed to investigate whether the genetic variability in the OXT system may play a role in EP in patients with AN. We analysed whether there are differences in EP and clinical symptoms between carriers and noncarriers of a specific allele within each of the selected OXT system SNPs in AN patients and in HCs.

We selected SNPs using information from the National Center for Biotechnology Information (NCBI dbSNP: http://www.ncbi.nlm.nih.gov/SNP). The SNPs with minor allele frequencies >0.10 were selected. Variants (SNPs) with proven or potential functional significance were chosen, that is, polymorphisms with consequences for gene function (i.e., gene expression, protein structure/function, and gene splicing). Most common polymorphisms are potential regulatory polymorphisms located in noncoding regions, including promoter/upstream, downstream, and intron regions (Albert, 2011). For each investigated SNP (with the exception of rs2740204) as specific allele, minor (variant) allele was chosen. In statistical analyses, we compared specific allele carriers with noncarriers.

We compared G carriers and non-G carriers within the OXT rs6133010 (A > G). It is currently unclear whether

this intronic SNP performs a functional role by exerting a direct effect on the OXT gene expression and OXT serum level. SNP rs6133010 AA genotype has been associated with physical aggression in alcohol-dependent subjects (Yang et al., 2017). For AVP-OXT SNP rs2740204 (C > A), we compared C carriers and non-C carriers. Previously, it was shown that rs2740204 CC genotype is significantly associated with lower expression levels of the *OXT* gene in bipolar disorder patients as compared with A allele carriers (Teltsh et al., 2012).

We also decided to investigate the two SNPs of CD38—rs6449197 (C > T) and rs3796863 (C > A). The C allele of rs6449197 of CD38 gene showed significant associations with high-functioning autism (Munesue et al., 2010). Carrying the C allele within rs3796863 has been associated with lower CD38 expression compared with the A allele in immortalized lymphocytes derived from subjects with autism (Lerer et al., 2010). Also, CC genotype within rs3796863 was associated with lower plasma OXT level (Feldman et al., 2012). In our study, we compared T carriers with non-T carriers of rs6449197 and A carriers with non-A carriers of rs3796863.

We compared A carriers with non-A carriers within OXTR rs2254298 (G > A) and rs53576 (G > A). The rs2254298 GG genotype was associated with lower plasma OXT level (Feldman et al., 2012). Also, G carriers of rs53576 performed better on recognizing the emotional state of others than those carrying the A allele for rs53576 (Rodrigues, Saslow, Garcia, John, & Keltner, 2009). In our study, we also investigated the LNPEP SNP rs4869317 (T > A). TT genotype is associated with increased plasma vasopressin clearance (Nakada et al., 2011). Although there has been no direct evidence for the involvement of LNPEP in altered human behavioural phenotypes, this aminopeptidase may play a regulatory role in human social behaviours via influencing the central OXT and/or AVP levels (Zhang et al., 2017). We compared A carriers and non-A carriers of rs4869317.

We also aimed to compare mean values of EP and mean values of clinical symptomatology scales in AN and in HCs. The clinical assessment included measurement of eating disorders symptoms, alexithymia, and depression. Patients with AN are reported to show high levels of alexithymia (Westwood, Kerr-Gaffney, Stahl, & Tchanturia, 2017), and an association between high levels of alexithymia and depression has been found with reference to this disorder (see Speranza et al., 2005; S. Torres et al., 2015). Kessler, Schwarze, Filipic, Traue, and von Wietersheim (2006) reported that basic facial emotion recognition may be independent from the reported alexithymia in AN. However, other authors suggest that alexithymia contributes to EP in AN (Brewer, Cook, Cardi, Treasure, & Bird, 2015); thus, we decided to include a measure of this construct in our study.

2 | METHODS

2.1 | Participants

A total of 120 participants (60 AN patients and 60 HCs) were included in the study. Patients were recruited from inpatient wards: the Department of Child and Adolescent Psychiatry and the Department of Neuroses, Personality Disorders, and Eating Disorders at the Institute of Psychiatry and Neurology in Warsaw, Poland. HCs were recruited from a community setting. All participants were White Caucasians of Polish origin, and controls were matched for age and years of education. The study design was approved by the local IRB, and subjects signed the informed consent sheet. Participants from the clinical group were assessed with a structured clinical interview based on DSM-5 (American Psychiatric Association, 2013) diagnostic criteria for AN and asked about their medical and family history as well as previous neurological and psychiatric diagnoses. A routine blood analysis was also performed. The clinical diagnosis was confirmed by a consultant psychiatrist.

A vast majority of the AN group was diagnosed with the restrictive type ($n = 49$; 81.6%). The AN binge-eating/purging type was confirmed in 11 patients (18.32%). The mean age of onset was 17.70 years ($SD = 1.82$). Participants in the clinical group were aged between 18 and 28 years ($M = 22.38$; $SD = 2.76$). The mean BMI value in the clinical group equalled $M = 15.02$ kg/m^2 ($SD = 1.33$). Participants from the clinical group received on average $M = 13.80$ ($SD = 1.81$) years of education.

Respondents from the control group were aged between 18 and 31 years ($M = 22.85$; $SD = 3.35$). The mean BMI value in control group equalled $M = 21.34$ kg/m^2 ($SD = 1.58$). On average, HCs received 13.30 ($SD = 1.81$) years of education. Although the samples significantly differed in BMI ($t_{(118)} = -20.34$; 95% CI [−5.95, −4.89]; $d = -1.75$; $p < .001$), they did not differ in terms of education ($t_{(118)} = 1.63$; 95% CI [−0.11, 1.14]; $d = 0.30$; $p = .11$).

3 | MEASURES

3.1 | Emotion perception

Penn Emotion Recognition Test (Erwin et al., 1992; Gur et al., 2010) from the University of Pennsylvania's Computerized Neurocognitive Test Battery. (a) The Penn Emotion Recognition Test is a measure of emotion recognition. Participants are shown a series of 40 faces, one at a

time, and asked to determine what emotion the face is showing for each trial. There are five answer choices: *happy*, *sad*, *anger*, *fear*, or *no emotion*. (a) The Penn Emotion Discrimination Test is a measure of emotion discrimination. Participants are shown 40 pairs of faces, one pair at a time. Each pair of faces consists of two pictures of the same person with or without a subtle, computer-generated difference in emotion expression. For each pair, participants must decide which face expresses a given emotion more intensely or whether they are equally intense. (b) The Penn Emotional Acuity Test 40 is a measure of emotion recognition and discrimination. The task presents 40 faces. The presentation takes place in two blocks, the first of which contains sad and neutral faces (sad–neutral block), and the second includes happy and neutral faces (happy–neutral block). Participants are asked to rate the emotional valence of each facial expression on a 7-point scale: *very sad*, *moderately sad*, *somewhat sad*, *neutral*, *somewhat happy*, *moderately happy*, and *very happy*. This test battery has been previously used to investigate deficits in recognizing facial emotions, for example, in patients with psychotic disorders (see Rubin et al., 2016; Ruocco et al., 2014). Due to its satisfactory psychometric properties (Moore, Reise, Gur, Hakonarson, & Gur, 2015), the test has been widely applied in studies with populations manifesting difficulties in socioemotional functioning (see, e.g., Lahera et al., 2013; Meyer & Kurtz, 2009).

3.2 | Psychopathology

Eating Attitudes Test-26 (Garner, Olmsted, Bohr, & Garfinkel, 1982) is a self-report measure consisting of 26 items. It is used to assess the severity of eating disorders symptoms both in clinical and non-clinical populations and has good reliability and validity.

Beck Depression Inventory-II (Beck, Steer, & Brown, 1996) is a self-rated tool including 21 items assessing mood, cognitions, and somatic symptoms of depression. This scale was administered in our study to capture comorbid symptomatology.

Toronto Alexithymia Scale-20 (Bagby, Parker, & Taylor, 1994) is a 20-item self-report questionnaire and is the most widely employed measure of the alexithymia construct.

3.3 | Genotyping

Genomic DNA was extracted from 1 ml of peripheral blood using the Genomic Mini AX BLOOD SPIN kit (A&A Biotechnology), according to the manufacture's recommended protocol. Genotyping was performed by polymerase chain reaction-restriction fragment length polymorphism method using the designed primers and appropriately selected restriction enzymes (data are given in the Table 1). The fragments obtained after restriction enzyme digestion were separated in ethidium bromide-stained agarose gels. T1

3.4 | Procedure

All participants were assessed using a battery of self-rated psychopathology scales and computer-based EP tests. AN patients were assessed in the acute phase of illness in the first week of admission. The venous blood was collected in all participants, and DNA was isolated with standard procedures.

4 | STATISTICAL ANALYSES

The assessment of the frequency of different alleles' occurrence was performed using the χ^2 test. *T* tests for independent samples were used to assess the differences between the compared groups in all of the analysed variables.

5 | RESULTS

5.1 | Genotype frequency

Eight polymorphisms were marked during the study, and the frequency distribution of each of the compared samples is presented in Table 2. T2

The assessment of the frequency of different alleles' occurrence was performed using the χ^2 test. The results demonstrated that differences in the frequency distribution across the groups were insignificant for all alleles except for rs3796863, in case of which there were more C/A carriers in the clinical group and C/C carriers in the control group.

For the purpose of subsequent statistical analyses and due to unequal distribution of different alleles, we decided to create two groups for each comparison—a group of individuals with a specific allele (e.g., C carriers) and a group of individuals without that allele (e.g., non-C carriers). In Table 3, we presented the applied differentiation both for clinical and control groups. T3

The differences across the groups were calculated using the χ^2 test, which suggested no differences in haplotypes frequency distribution at all.

TABLE 1 Primers and restriction enzymes used in genotyping of tagged SNPs

Gene (SNP localization)	SNP	Minor allele	Primer F sequence	Primer R sequence	Annealing temperature	Restriction enzyme
AVP (downstream)	rs2740204	A	GACATCACTGTCTGTCCAGTGC	GTCTTCATGTCTGGGAGCTAATG	65°C	*TruI1*
CD38 (intron 1)	rs6449197	T	GTTAGCTGTGGGGTTTAATAGATG	ATCAATTTAATGTGCTGTATTTTGTAG	53°C	*TasI*
CD38 (intron 7)	rs3796863	A	CAAGAGACCGTAGGATACATC	CACCTGTTAGGTACTTATCTAAGG	56°C	*BccI*
OXT (promoter)	rs6133010	G	ATTACAGAAGGCCCTGGGGAC	GAGTGCCCTCTGCAGGTGG	55°C	*BsuRI*
OXTR (intron 3)	rs2254298	A	CACATTTATGCATGTCAGCAGCTG	ATCCTTTGAAGCCCAAGTCCATTG	67°C	*BsrI*
OXTR (intron 3)	rs53576	A	GTGTCTGAAGTTAACTGTCCATC	CTGAAACAGAACTGGCAAC	57°C	*BamHI*
LNPEP (intron 1)	rs4869317	A	CTTTTGCCCATTCCTTTACATTG	CTCTGGAGTTGGTGCGACTAC	55°C	*PacI*

Abbreviations: AVP, arginine vasopressin; LNEP, human leucyl/cystinylaminopeptidase; OXT, oxytocin; OXTR, oxytocin receptor; SNP, single nucleotide polymorphism.

TABLE 2 Genotype frequency

	Control group (%)	Clinical group (%)	χ^2	*p*
	rs2740204		4.17	.12
A/A	8 (13.3%)	11 (18.3%)		
C/A	30 (50%)	19 (31.7%)		
C/C	22 (36.7%)	30 (50%)		
	rs6449197		2.14	.34
T/T	0	2 (3.3%)		
C/T	15 (25%)	16 (26.7%)		
C/C	45 (75%)	42 (70%)		
	rs3796863		6.87	.03
A/A	10 (16.7%)	6 (10%)		
C/A	17 (28.3%)	31 (51.7%)		
C/C	33 (55%)	23 (38.3%)		
	rs6133010		1.29	.26
A/A	51 (85%)	55 (91.7%)		
A/G	9 (15%)	5 (8.3%)		
G/G	0	0		
	rs2254298		3.49	.18
G/G	54 (90%)	47 (78.3%)		
G/A	6 (10%)	12 (20%)		
A/A	0	1 (1.7%)		
	rs53576		2.72	.26
G/G	21 (35%)	29 (48.3%)		
G/A	35 (58.3%)	26 (43.3%)		
A/A	4 (6.7%)	5 (8.3%)		
	rs4869317		1.35	.51
T/T	37 (61.7%)	31 (51.7%)		
T/A	19 (31.7%)	25 (41.7%)		
A/A	4 (6.7%)	4 (6.7%)		

5.2 | Comparisons in psychopathology and EP between different haplotypes

The significant differences between different haplotypes in the clinical group and in the control group are presented in Table 4. T4

The analyses in the clinical group revealed no differences in psychopathology; however, a few haplotypes differentiated distinct aspects of EP as presented in Table 4. In the AN group, we found that there was a difference in EP between carriers and noncarriers of a specific allele for three investigated OXT system SNPs. Specifically, C carriers of AVP-OXT rs2740204 showed significantly longer response time for recognition of

TABLE 3 The differentiation of specific polymorphisms groups in the control group and in the clinical group

	Control group (%)	Clinical group (%)	F	*p*
	rs2740204		0.56	.45
C carriers	52 (86.7%)	49 (81.7%)		
Non-C carriers	8 (13.3%)	11 (18.3%)		
	rs6449197		0.38	.54
T carriers	15 (25%)	18 (30%)		
Non-T carriers	45 (75%)	42 (70%)		
	rs3796863		3.35	.07
A carriers	27 (45%)	37 (61.7%)		
Non-A carriers	33 (55%)	23 (38.3%)		
	rs6133010		1.31	.26
G carriers	5 (8.3%)	9 (15%)		
Non-G carriers	55 (91.7%)	51 (85%)		
	rs2254298		3.06	.08
A carriers	6 (10%)	13 (21.7%)		
Non-A carriers	54 (90%)	47 (78.3%)		
	rs53576		2.19	.14
A carriers	39 (65%)	31 (51.7%)		
Non-A carriers	21 (35%)	29 (48.3%)		
	rs4869317		1.22	.27
A carriers	23 (38.3%)	29 (48.3%)		
Non-A carriers	37 (61.7%)	31 (51.7%)		

sadness than non-C carriers and non-A carriers of OXTR rs53576 took more time to recognize happy faces than A carriers. Another difference in patients with AN was also observed for the ability to recognize anger. It appeared that non-G carriers of OXT rs6133010 identified correctly a lower number of angry faces than G carriers.

Similar to the clinical group, several significant differences were observed for EP variables in the control group. Non-G carriers of OXT rs6133010 showed less correct fear identifications than G carriers. C carriers of AVP-OXT rs2740204 showed longer response time for correct recognition of emotions and longer response time for recognition of fear specifically than non-C carriers. Also, non-A carriers of OXTR rs53576 identified correctly less facial emotions than A carriers.

In the control group, only one haplotype (i.e., rs4869317) significantly differentiated eating disorders psychopathology. The presence of the A allele at this locus was associated with increased Eating Attitudes Test-26 scores.

5.3 | Comparisons between clinical and control group

The significant differences between the clinical group and the control group are shown in Table 5. T5

Participants from the clinical group scored significantly higher on all psychopathology scores and obtained lower scores on measures of facial affect recognition than the control group. Moreover, it took patients with AN significantly longer to complete given tasks, and they made less correct responses. In other words, participants from the clinical group were slower and less accurate in facial emotion recognition than HCs, which may indicate impaired EP in AN.

6 | DISCUSSION

The aim of this study was to examine whether the genetic variability in the OXT system may play a role in EP in patients with AN. Our hypotheses were partially confirmed. EP skills are highly heritable in the general population (Scourfield, Martin, Lewis, & McGuffin, 1999; Skuse et al., 2014), which suggests that individual differences in EP may be strongly influenced by corresponding individual differences in gene expression. Our study provides evidence that polymorphisms of the OXT system genes are relevant to social EP in AN. G carriers within the rs6133010 OXT gene recognized angry faces significantly better compared with non-G carriers in the patient group, and G carriers of rs6133010 in HCs recognized fearful faces better compared to non-G carriers. It can therefore be interpreted that carrying the G allele may be associated with better recognition of negative emotions both in AN individuals and in HCs. Importantly, the combination of having AN and carrying either of the C alleles for SNP in the OXT-AVP gene rs2740204 was associated with longer reaction time for correct facial recognition of sadness compared with non-C carriers. Similar to the clinical group, HC C carriers of rs2740204 were slower at recognizing facial emotions, especially at recognizing fear, than non-C carriers. Hence, these findings suggest that C carriers of OXT-AVP rs2740204 show decreased abilities in EP in comparison with non-C carriers, regardless of eating disorders psychopatology. Referring to the hypothesis concerning the association between EP in AN and CD38 rs6449197 and rs3796863 SNPs, it was not confirmed by the results obtained in the current study.

We also found differences in EP in patients diagnosed with AN, who are non-A carriers of OXTR rs53576. These patients showed longer reaction time for correct

TABLE 4 Significant differences within the clinical sample and within the control sample

Group	Variable	*M* (*SD*)		*t*	95% CI	*d*	Power
Clinical group	rs2740204	C carriers	Non-C carriers				
	SADRTCR	3,916.55 (919.26)	3,301.46 (862.84)	2.03*	[7.49, 1,222.70]	0.66	.40
	rs6133010	G carriers	Non-G carriers				
	ER40ANG	6.00 (1.12)	4.96 (1.40)	2.11*	[0.52, 2.03]	0.74	.34
	rs53576	A carriers	Non-A carriers				
	HAPRTCR	3,840.03 (753.58)	4,304.85 (867.76)	−2.22*	[−884.06, −45.57]	−0.56	.53
Control group	rs2740204	C carriers	Non-C carriers				
	ER40_CRT	2,488.63 (439.86)	2,113.34 (395.59)	2.27*	[44.79, 705.80]	0.83	.69
	ER40FEARRT	2,627.65 (681.41)	1,947.56 (438.55)	2.73**	[180.72, 1,179.46]	0.98	.82
	rs6133010	G carriers	Non-G carriers				
	ER40FEAR	7.80 (0.45)	6.96 (0.82)	2.25*	[0.09, 1.58]	1.02	.79
	rs53576	A carriers	Non-A carriers				
	ER40_CR	34.79 (2.02)	33.43 (2.98)	2.11*	[0.71, 2.66]	0.55	.55
	rs4869317	A carriers	Non-A carriers				
	EAT-26	6.30 (3.57)	4.46 (2.89)	2.19*	[0.16, 3.52]	0.56	.57

Abbreviations: 95% CI, 95% confidence interval for the mean difference across compared groups; *d*, Effect size; EAT-26, Eating Attitudes Test; ER40_CRT, Penn Emotion Recognition Test correct responses median response time (ms); ER40ANG, Penn Emotion Recognition Test correct anger identifications; ER40CR, Penn Emotion Recognition Test correct responses; ER40FEAR, Penn Emotion Recognition Test correct fear identifications; ER40FEARRT, Penn Emotion Recognition Test median response time for correct fear identifications (ms); HAPRTCR, Penn Emotion Discrimination Test median response time for correct happy trials (ms); SADRTCR, Penn Emotion Discrimination Test response time for recognition of sad faces (correct responses).

*$p < .05$. **$p < .01$.

recognition of happy faces than A carriers. Similarly, non-A carriers of OXTR rs53576 in HCs revealed a significantly worse emotional recognition of faces compared with A carriers. It may be inferred that non-A carriers of rs53576 in both the AN group and in HCs show worse EP abilities. Our results are in line with the results of other authors, who found that carriers of the G allele (AG or GG) of rs53576 performed worse on the facial recognition task than those with two A alleles (Parker et al., 2014). However, in a study conducted by Acevedo et al. (2015), carrying either of the A alleles for rs53576 and rs2254298 by the remitted AN participants was associated with the increased severity of eating disorders symptoms related to cognitions and behaviours. In our study, no associations were found between EP and the OXTR gene rs2254298 in AN. Our results support a theory that the OXTR haplotype may be important for affect processing and related social behaviour (see Melchers, Montag, Markett, & Reuter, 2013). Referring to the initial hypothesis, we did not observe an increased representation of the OXTR minor alleles in the AN group. This is in line with large genome-wide association studies examining genome-wide sets of genetic variants in people with eating disorders that have not found significant differences in these allelic frequencies (Boraska et al., 2014; Pinheiro et al., 2010). The social implications of allelic variations in the OXTR gene rs53576 are exemplified by individual differences in maternal and empathic behaviour (Rodrigues et al., 2009; Skuse et al., 2014). The results of association studies on the potential role of the OXTR gene rs53576 remain inconclusive. In a study by Rodrigues et al. (2009), A allele carriers of rs53576 reported less dispositional empathy as well as less accurate judgement on facial affect. Aupperle et al. (2016), in their functional magnetic resonance imaging study analysis, described the relationship between the parental OXT AA/AG allele and reduced activation to criticism and greater activation to praise within the right amygdala in adolescent girls. Finally, Kim, Kim, Kim, Shin, and Treasure (2015) found an association between the OXTR rs53576 G allele and high scores on the avoidance motivational personality dimension known as behavioural inhibition system in patients with bulimia nervosa.

The hypothesis concerning the potential role of the LNPEP rs4869317 SNP in EP in patients with AN was not confirmed. No association between rs4869317 haplotype and EP was found neither in AN participants nor in HCs. However, we found an association between carrying the A allele of rs4869317 and the increased eating disorders psychopathology level in the HCs group. In the context of theory concerning the potential role of LNPEP in social cognition and behaviour (see Torres, Martins, Santos, Prata, & Veríssimo, 2018; Zhang et al., 2017) and in the context of findings that these difficulties may be a characteristic for individuals with AN (Ambwani et al., 2016), the obtained result may have implications for the design of future studies investigating the role of the oxytocinergic system genes in developing

TABLE 5 Differences in emotion perception and psychopathology between the clinical group and the control group

	M (*SD*)					
Variable	**Clinical group**	**Control group**	***t***	**95% CI**	***d***	**Power**
EAT-26	43.42 (10.83)	5.17 (3.27)	26.20*	[35.36, 41.14]	1.84	1.00
BDI-II	28.07 (9.46)	4.92 (3.79)	17.59*	[20.54, 25.76]	1.69	1.00
TAS-20	57.78 (8.85)	42.28 (6.23)	11.09*	[12.73, 18.27]	1.42	1.00
ER40_CR	27.53 (4.79)	34.32 (2.46)	−9.77*	[−8.16, −5.41]	−1.33	1.00
ER40_CRT	2,757.34 (497.57)	2,438.59 (449.84)	3.68*	[147.26, 490.23]	0.64	0.94
ER40_ANG	5.12 (1.40)	6.18 (0.93)	−4.91*	[−1.50, −0.64]	−0.82	0.99
ER40_FEAR	6.62 (1.21)	7.03 (0.82)	−2.21	[−0.79, −0.43]	−0.39	0.56
ER40_HAP	4.78 (1.65)	7.58 (0.62)	−12.32*	[−3.25, −2.35]	−1.50	1.00
ER40_NOE	4.38 (1.64)	6.63 (1.10)	−8.83*	[−2.76, −1.75]	−1.26	1.00
ER40_SAD	6.63 (1.21)	6.88 (1.04)	−1.21	[−0.66, 0.16]	−0.22	0.22
ER40_ANGRT	2,785.98 (1,044.06)	2,583.63 (726.96)	1.23	[−122.89, 527.59]	0.22	0.22
ER40_FEARRT	2,950.25 (711.88)	2,536.98 (691.76)	3.23	[159.50, 667.04]	0.57	0.87
ER40_HAPRT	2,537.71 (528.64)	1,982.19 (441.92)	6.25*	[379.37, 731.67]	0.99	1.00
ER40_NOERT	3,096.97 (776.49)	2,640.07 (775.02)	3.23	[176.43, 737.37]	0.57	0.87
ER40_SADRT	2,415.80 (884.43)	2,450.10 (718.04)	−0.23	[−325.54, 256.94]	−0.04	0.05
HAP_CR	11.08 (2.83)	13.75 (2.74)	−5.25*	[−3.67, −1.66]	−0.87	1.00
SAD_CR	12.50 (2.58)	13.55 (2.40)	−2.31	[−1.95, −0.15]	−0.41	0.61
HAPRTCR	4,064.69 (837.25)	3,186.30 (551.55)	6.79*	[622.08, 1,134.71]	1.06	1.00
SADRTCR	3,803.78 (933.42)	3,082.81 (592.20)	5.05*	[438.37, 1,003.58]	0.84	1.00
ED_A	23.67 (4.93)	27.30 (4.60)	−4.17*	[−5.36, −1.91]	−0.71	0.97

Abbreviations: 95% CI, 95% confidence interval for the mean difference across compared groups; BDI-II, *Beck* Depression Inventory-II; *d*, Effect size; EAT-26, Eating Attitudes Test; ED_A, Penn Emotion Discrimination Test total correct trials; ER40_ANG, Penn Emotion Recognition Test correct anger identifications; ER40_CRT, Penn Emotion Recognition Test correct responses median response time (ms); ER40_FEAR, Penn Emotion Recognition Test correct fear identifications; ER40_FEARRT, Penn Emotion Recognition Test median response time for correct fear identifications (ms); ER40_HAP, Penn Emotion Recognition Test correct happy identifications; ER40_HAPRT, Penn Emotion Recognition Test median response time for correct happy identifications (ms); ER40_NOE, Penn Emotion Recognition Test correct neutral identifications; ER40_NOERT, Penn Emotion Recognition Test median response time for correct neutral identifications (ms); ER40CR, Penn Emotion Recognition Test correct responses; HAP_CR, Penn Emotion Discrimination Test correct responses for happy trials; HAPRTCR, Penn Emotion Discrimination Test median response time for correct happy trials (ms); SAD_CR, Penn Emotion Discrimination Test correct responses for sad trials; SADRTCR, Penn Emotion Discrimination Test median response time for correct sad trials (ms); TAS-20, Toronto Alexithymia Scale.

*Bonferroni correction applied (.05/20), significant at $p < .0025$.

eating disorders. To our knowledge, this is the first study in which the association between the level of eating disorders symptoms and carrying a specific allele of the LNPEP rs4869317 was found in healthy participants. Interestingly, no such association was found in AN. The empirical literature indicates decreased basal or mean OXT levels in this disorder (Culbert, Racine, & Klump, 2016; Giel, Zipfel, & Hallschmid, 2018). One may speculate that the potential influence of LNPEP polymorphism and the level of oxytocinase itself on the OXT level in patients with AN (and hence on the level of eating disorders symptoms in this group) may not differ between A carriers and non-A carriers of rs4869317. However, in HCs—who theoretically have higher levels of serum OXT than individuals with AN—the influence of LNPEP on OXT level and eating disorders symptoms may be greater. Possibly, it could be the reason why we identified the association between the LNPEP polymorphism and the level of symptoms of eating disorders in HCs. The serum OXT levels were not measured in our study; however, such measurement could be applied in future studies to confirm or reject this theory.

Apart from the potential interaction between polymorphisms of the OXT system genes, overall facial affect recognition in our clinical sample appeared impaired such that significantly lower scores on measures of facial affect recognition were obtained in the AN group than in the control group, which is in line with other findings (see Kucharska-Pietura et al., 2004; Zonnevijlle-Bendek, Van Goozen, Cohen-Kettenis, Van Elburg, & Van Engeland, 2002). Furthermore, patients scored significantly higher

on all psychopathology measures compared with controls, thus showing a significantly higher level of eating disorder psychopathology, comorbid depression, and alexithymia. Again, these findings were largely supported by the recent empirical literature (see Beadle, Paradiso, Salerno, & McCormick, 2013; Lulé et al., 2014).

6.1 | Strengths and limitations

The role of polymorphisms within genes related to OXT pathways in human social and emotional functioning is a relatively new area of investigation. There are currently very few studies in the field, and the methods and findings are highly variable, precluding firm conclusions about the role of OXTR DNA.

There are a few strengths and limitations of this work. First, each group contained 60 participants, with each genetic subgroup (carriers and noncarriers) containing a minimum of eight participants. This resulted in underpowered comparisons regarding the genetic components; therefore, we suggest remaining cautions when interpreting our results. Larger sample sizes would be required to confirm these findings and identify any differences of smaller magnitude that may be missed due to Type II error. Finally, although such studies may identify SNPs of the OXT system genes associated with endophenotypes of EP in AN patients, functional consequences of these SNPs on the OXT pathway function in the brain remain unknown.

6.2 | Future directions

In the current study, we found a significant differences in EP between OXTR rs53576 A carriers and non-A carriers. It has recently been found that the methylation levels of the OXTR gene are increased in AN patients and affected by BMI, eating disorders psychopathology, and anxiety, which suggest that epigenetic mechanisms in the OXTR gene may be implicated in AN. Carrying minor alleles of OXTR may result in increased methylation of the OXTR gene in response to weight loss, potentially reducing social reward but increasing the importance of food (Kim, Kim, Kim, & Treasure, 2014). Another study, unlike ours, has found that carrying an A allele for rs53576 SNP was associated with increased severity of eating disorders symptoms in AN, including cognitions and behaviours (Acevedo et al., 2015). Thus, further studies should focus on examining the relationship between EP, cognitions and behaviours, and the OXT pathway genes polymorphisms.

Given the fact that AN is characterized by cognitive difficulties including both perception of other people's emotions and recognition of one's own emotions, we also believe that investigating these issues in relation to SNPs within the OXT system genes at the same time would be of high importance. It also seems that SNPs of genes related to the OXT system influence an individual's EP abilities. In addition, examination of these polymorphisms as moderators of the therapeutic process could shed light on the role of genetic polymorphisms in treatment efficacy for AN.

Additionally, our results suggest that the LNPEP rs4869317 SNP may be involved in etiopathogenesis of eating disorders; however, this issue requires further clarifying and conducting research on larger clinical samples.

7 | CONCLUSION

Females with AN show decreased EP abilities compared with healthy females. Findings of this study suggest a negative association of OXT and the OXTR haplotype with EP in AN. In other words, the oxytocinergic system may be involved in EP difficulties in this disorder. Similar associations between OXT and the OXTR haplotype and EP were also found in HCs. C carriers of OXT-AVP rs2740204, non-A carriers of OXTR rs53576, and non-G carriers of OXT rs6133010 showed decreased EP. SNPs within genes related to OXT pathways may influence an individual's EP abilities. The LNPEP rs4869317 SNP may be involved in the development of eating disorders psychopathology.

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CONFLICT OF INTEREST

None of the authors of this paper has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the paper.

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ETHICS SECTION

Study was conducted at the Department of Child and Adolescent Psychiatry in The Institute of Psychiatry and Neurology in Warsaw, Poland and the Department of Neuroses, Personality Disorders, and Eating Disorders in The Institute of Psychiatry and Neurology in Warsaw, Poland; Principal Investigator—Prof. K. Kucharska. Patients were assessed after giving informed consent. Informed consent of participation in the study were obtained from all participants. Approval for the study was obtained from the ethics committee of the Institute of Psychiatry and Neurology in Warsaw, Poland on February 26, 2015 (reference number 7/2015 KB IPiN).

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