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Oxytocin receptor and vasopressin receptor 1a genes are respectively associated with emotional and cognitive empathy

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ABSTRACT

Empathy is the ability to recognize and share in the emotions of others. It can be considered a multifaceted concept with cognitive and emotional aspects. Little is known regarding the underlying neurochemistry of empathy and in the current study we used a neurogenetic approach to explore possible brain neurotransmitter pathways contributing to cognitive and emotional empathy. Both the oxytocin receptor (*OXTR*) and the arginine vasopressin receptor 1a (*AVPR1a*) genes contribute to social cognition in both animals and humans and hence are prominent candidates for contributing to empathy. The following research examined the associations between polymorphisms in these two genes and individual differences in emotional and cognitive empathy in a sample of 367 young adults. Intriguingly, we found that emotional empathy was associated solely with *OXTR*, whereas cognitive empathy was associated solely with *AVPR1a*. Moreover, no interaction was observed between the two genes and measures of empathy. The current findings contribute to our understanding of the distinct neurogenetic pathways involved in cognitive and emotional empathy and underscore the pervasive role of both oxytocin and vasopressin in modulating human emotions.

The human ability to automatically connect and comprehend others, termed empathy, seems an intangible gift, yet it is deeply rooted in *Homo sapiens*' evolutionary history (Preston and de Waal, 2003). It is considered to be a primary building block in the creation and maintenance of social groups, and drives many aspects of social behavior, from child care (Preston and de Waal, 2003), to moral sense (Hoffman, 2001), to prosocial behavior towards kin and even strangers (Batson et al., 1988). Empathy can be conceptualized as the ability to understand and share in others' emotions, while maintaining a self-other distinction (Davis, 1980; Decety and Jackson, 2004). Considerable research points to a differentiation between the cognitive (i.e., cognitive empathy—CE) and emotional (i.e., emotional empathy—EE) facets of empathy. CE is the ability to recognize what the other is feeling (e.g., seeing someone cry and realizing they are upset), whereas EE is the sharing in others' emotions (e.g., seeing someone cry and feeling sad for them) (Davis, 1980; Zaki and Ochsner, 2012). The distinction between the cognitive and the emotional aspects of empathy is not only theoretical but is supported by a considerable body of empirical research. First, a meta-analysis showed that CE and EE have different etiologies, while both EE and CE are moderately heritable, shared environment was found to affect only cognitive and not emotional empathy (Knafo and Uzefovsky, 2013). Second, recently, it has been shown that a gene coding for the dopamine D4 receptor is specifically associated with CE but not EE (Uzefovsky et al., 2014). Third, neuroimaging and lesion studies point to two different, albeit interconnected, brain networks underlying CE and EE. CE is associated with the "mentalizing network," which is generally thought to include the ventromedial prefrontal cortex, the temporo-parietal junction and the temporal poles (Schnell et al., 2011; Shamay-Tsoory et al., 2009b; Zaki and Ochsner, 2012). On the other hand, the human mirror neuron system is arguably considered to be the basis for EE (Shamay-Tsoory, 2011a,2011b). This system is activated both when we experience an emotion and when the "other" experiences the same emotion and includes the inferior parietal lobule and the amygdala, among others (Cox et al., 2011; Shamay-Tsoory et al., 2004, 2009b). Notwithstanding the empirical distinction that can be made between CE and EE, it is important to note that during normal empathic processing both systems are activated (Schnell et al., 2011; Zaki and Ochsner, 2012).

While much is known regarding the activation of brain structures during empathy eliciting tasks, less research has focused on the neurochemical pathways and specific neurotransmitters involved in empathy.

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Two neuropeptides, oxytocin and vasopressin, are biologically plausible candidates to mediate the neural pathways underlying empathy. Oxytocin (OT) and arginine vasopressin (AVP) play a crucial role in vertebrate social signaling with a long evolutionary history from fish to primates (Donaldson and Young, 2008). Animal studies have established a role for these two social neuropeptides in a wide range of affiliative behaviors (Bosch and Neumann, 2012; Hammock and Young, 2004; Young and Wang, 2004). Human studies using intranasal administration of both neuropeptides have demonstrated their role in a variety of social behaviors including trust (Kosfeld et al., 2005), generous giving (Zak et al., 2007) and emotion recognition (Domes et al., 2006; Uzefovsky et al., 2011). Several studies reported on associations between plasma levels and a range of affiliative behaviors, including parenting and romantic bonds (Feldman, 2012; Feldman et al., 2011; Schneiderman et al., 2012). Additionally, genetic studies found associations with individual differences in prosocial behavior (Israel et al., 2009; Knafo et al., 2008) and with social deficits in autism (Lerer et al., 2008; Yirmiya et al., 2006).

Most of the phenotypes examined with respect to OT-AVP genetic pathways are reliant on empathy, yet little research has been dedicated to direct examination of empathy and its two facets. The few studies to examine the role of this system in empathy have focused on the *OXTR* gene and very little attention has been given to *AVPR1a* (Chakrabarti et al., 2009; Lucht et al., 2013; Montag et al., 2012; Rodrigues et al., 2009; Schneiderman et al., 2012; Wu et al., 2012) (See Supporting Material Table 1). No study to date has investigated the combined effects of these two important genes. In addition, previous genetic studies were characterized by small samples and the findings have been mixed prompting us in the current investigation to simultaneously examine both OXTR and AVPR1a common polymorphisms in a larger sample of 367 subjects.

To minimize issues of multiple testing, we selected for analysis a single polymorphic region within the *OXTR* and the *AVPR1a*. For *OXTR*, the rs53576 SNP was selected for analysis. This SNP is located within intron 3 of the *OXTR* gene and constitutes a G → A change. A considerable body of research shows associations between this rs53576-GG genotype and increases in social cognition, including empathy (Rodrigues et al., 2009), in both clinical and non-clinical subjects (Bakermans-Kranenburg and van IJzendoorn, 2008; Chen et al., 2011; Costa et al., 2009; Kogan et al., 2011; Park et al., 2010). Similarly, for the *AVPR1a* gene, we selected for analysis the well-studied RS3 polymorphic repeat region located in the promoter, and in particular, we targeted the second most common repeat allele (termed 327 or 334 bp allele, depending on genotyping method). The 327 repeat allele may be functionally significant since carriers of the 327-repeat risk allele showed higher amygdala activation (Meyer-Lindenberg et al., 2008). This repeat allele was also associated with lower partner bonding in men (Walum et al., 2008), lower altruistic giving (Avinun et al., 2011) and autism (Kim et al., 2002). In summary, we examined the OXTR rs53576 SNP and the AVPR1a-327 polymorphic repeat region for their roles in contributing to CE and EE in a non-clinical student population. Finally, based on these investigations, we hypothesized that the presence of the rs53576-A allele in the *OXTR* gene and the presence of the 327-repeat allele in the *AVPR1a* gene both independently would predict lower empathy scores.

Methods

Participants

A total of 367 young adults (52% female; mean age, 24.40 ± 2.80 years) were recruited by advertisements on campus bulletin boards for a study on personality and genetics. All subjects were aged 18–35 years, had no self-report history of psychiatric disorders, chronic illness or drug taking and were non-smokers. All participants were of Jewish descent (56.1% Ashkenazi Jews, 21.0% Sephardic Jews and 22.6% of mixed Jewish descent). This sample was analyzed previously as Study 1 in Uzefovsky et al.(2014), in relation to the dopamine D4 receptor gene. The project was approved by the S. Herzog Hospital IRB committee and the Israeli Ministry of Health.

Measures

To ensure a complete measurement of empathy, each participant filled out three widely used and highly validated self-report measures of empathy online: the Interpersonal Reactivity Index (IRI) (Davis, 1980), the Empathy Quotient (Baron-Cohen and Wheelwright, 2004) and the Questionnaire Measure of Emotional Empathy (QMEE) (Mehrabian and Epstein, 1972). Participants' scores on each of the measures were standardized and averaged out to create the total empathy score. All these measures tap into emotional and cognitive aspects of empathy; however, the IRI consists of four validated subscales, with two of the subscales measuring cognitive empathy (fantasy (F) and perspective taking (PT)) and two subscales measuring emotional empathy (empathic concern (EC) and personal distress (PD)). These subscales were used to create a CE and an EE scores in the same manner as the total empathy score (see also Uzefovsky et al., 2014).

DNA extraction and genotyping

DNA extraction was performed in the research lab of the S. Herzog Memorial Hospital. DNA was extracted using the MasterPure kit (Epicentre, Madison, Wisconsin, United States). Genotyping of *AVPR1a*.RS3 microsatellite repeats was performed jointly at S. Herzog Memorial Hospital and the Hadassah Medical Center, Jerusalem.

Amplification of the RS3 arginine vasopressin 1a microsatellites (*AVPR1a*) was achieved using the following primers (Bachner-Melman et al., 2005; Thibonnier et al., 2000; Wassink et al., 2004) forward (fluorescent) 5′-CCT GTA GAG ATG TAA GTG CT-3′ and reverse 5′-TCT GGA AGA GAC TTA GAT GG-3′. Each reaction mixture contained 0.5 μM primer and 20 ng of DNA. A ReddyMix master mix (Thermoprime plus DNA polymerase) was used (Abgene, Surrey, United Kingdom) at a magnesium concentration of 1.5–2.5 mM MgCl2. ReddyMix buffer consisted of 75 mM Tris–HCl (pH 8.8 at 25 °C), 20 mM (NH4)2SO4 and 0.01% (v/v) Tween 20. The sample was initially heated at 95 °C for 5 min, followed by 30 cycles of 95 °C (30 s), 55 °C (30 s) and 72 °C (40 s) and a final extension step of 72 °C for 10 min. The PCR product was analyzed on an ABI 310 DNA analyzer (Applied Biosystems, Foster City, California, United States).

Genotyping of the *OXTR* rs53576 SNP was performed at the National University of Singapore. SNP genotyping was performed in multiplex assays by MassARRAY using iPLEX Gold chemistry (Sequenom, San Diego, California), followed by MALDI-TOF mass spectrometry. PCR and extension primers were designed using MassARRAY Assay Design software v4.0.0.2 and online tools available at mysequenom.com (Sequenom) (forward: 5′-GCACAGCATTCATGGAAAGG-3′; reverse: 5′-CTGTAGAATGAGCTTCCCAG-3′, extended primer: TCTGTGGGACTGAG GA C(G) T(A)). Genotypes were called automatically using MassARRAY Typer software (Sequenom).

Ambiguous and undetermined genotype results were scanned by a researcher and determined when possible. The researcher had no knowledge of the self-report scores. When no confident interpretation could be made, the sample was assigned a missing value. Participants with missing genotype information were excluded from the analysis. In total, three people were excluded from the analysis due to missing genetic data. Results conform to the Hardy–Weinberg equilibrium for both *OXTR* (chi-square = .37, p value > .05) and *AVPR1a* (chi-square = .07, p value > .05). The distribution of genotypes in the sample is presented in Table 1.

Although all participants were of the same ethnic origin (Jewish) and therefore there is little possibility for population stratification, we tested to make sure that Jewish origin (Ahskenazi/Sephardic) was not associated with allele frequency. For both *OXTR* and *AVPR1a*, no

Table 1
Distribution of the *OXTR* rs53576 and *AVPR1a*.RS3 genotype in the current sample, coded for presence and absence of the risk allele in each gene.

OXTR rs53576		*AVPR1a*.RS3	
Allele	*N*	*Allele*	*N*
A present (AA/AG)	194	327 repeat present	137
A absent (GG)	173	327 repeat absent	230

association between Jewish origin and allele frequency was found (chi-square .89 and 1.71 $p > .05$, respectively).

Statistical analysis

Genotype of the *AVPR1a*.RS3 microsatellite was coded as the presence or absence of the 327-repeat allele and genotype of the *OXTR* rs53576 was coded as the presence or absence of the A-minor allele, both resulting in two-level predictor variables. Gender, *OXTR* genotype, *AVPR1a* genotype and the interaction term of *OXTR* and *AVPR1a* all served as predictors of questionnaire scores. All variables were dummy coded and centered. Variables were entered into the regression model in three steps; first—gender, second—OXTR and AVPR1a genotypes and third—the interaction of OXTR and AVPR1a. Three regression models were analyzed with the total empathy score, cognitive empathy score and emotional empathy score as the dependent measures. All results were confirmed using 1000 bootstrap samples. The bootstrap procedure repeatedly resamples the data to create 1000 samples. This allows to reduce uncertainty in the estimated parameters. The bootstrapping procedure was carried out using the bootstrapping option that is available as part of a linear regression analysis in SPSS v19. All statistical tests were carried out using SPSS v19 (Windows).

Results

The complete empathy score is based on scores of three self-report measures of empathy: the interpersonal Reactivity Index (IRI) (Davis, 1980), the Questionnaire Measure of Emotional Empathy (QMEE) (Mehrabian and Epstein, 1972) and the Empathy Quotient (EQ) (Baron-Cohen and Wheelwright, 2004). Mean scores (split by gender) and correlations between the measures are reported in Table 2. Theoretical considerations (all questionnaires aim to measure empathy) were supported by the correlations, allowing to construct a total empathy score.

We first turned to examine the association between the total empathy score and each of the genes, controlling for gender. We used a linear regression model with gender entered first. *OXTR* and *AVPR1a* genotypes were entered in the second step, and an interaction term (centered) between *OXTR* and *AVPR1a* genotype was entered in the third step. As expected, gender was a significant predictor of empathy ($p < .001$), with women scoring higher than men. Entering the *OXTR* and *AVPR1a* genotypes in the model revealed that both significantly predicted empathy, and gender and genes altogether explain a total of 13% of the variance in empathy scores. Results were confirmed with a bootstrap analysis. As we hypothesized, the presence of the rs53576-A allele in the *OXTR* gene, and the presence of the 327-repeat allele in the *AVPR1a* gene, both independently predicted lower empathy scores. The interaction between *OXTR* and *AVPR1a* genotypes was not a significant predictor of empathy (see Table 3).

We next turned to investigate the effect of genotype on the two empathy types. We carried out regression analyses similar to that described above, with cognitive empathy as the dependent variable in the first regression and emotional empathy the dependent variable in the second. In both analyses, gender significantly predicted both CE and EE, with women scoring higher than men (standardized β was .18 and .32, respectively, in the complete model). The *OXTR* rs53576-A allele predicted lower emotional empathy (standardized $\beta = -.11$, $p = .029$), but not cognitive empathy (standardized $\beta = -.08$, $p = .10$). On the other hand, the *AVPR1a* 327 allele predicted lower cognitive empathy (standardized $\beta = -.16$, $p = .002$), but not emotional empathy (standardized $\beta = -.08$, $p = .12$). The interaction between *OXTR* and *AVPR1a* genotypes was not associated with emotional or cognitive empathy. Results were confirmed with a bootstrap analysis (see Tables 4 and 5 for details). These results suggest that somewhat distinct molecular genetic and neurochemical architecture characterizes cognitive and emotional empathy.

Table 2
Mean scores of the individual empathy measures split by gender, and the correlations between the measures. All correlations are significant at the $p < .001$ level.
Note: IRI = Interpersonal Reactivity Index; QMEE = Questionnaire Measure of Emotional Empathy; EQ = Empathy Quotient.

	Mean score—females ($N = 190$)	Mean score—males ($N = 177$)	Correlations		
			IRI	QMEE	EQ
IRI	97.35	90.43	1		
QMEE	42.63	27.03	.70**	1	
EQ	44.25	40.43	.42**	.52**	1

Discussion

We have implemented a neurogenetic strategy to explore the neurochemical pathways underpinning human empathy in a relatively large sample of young adults. We tested the contribution of polymorphisms in the *AVPR1a* and *OXTR* genes to individual differences in empathy. Both of these genes are very plausible candidates for contributing to empathy, a core concept in social cognition. We further investigated the cognitive and emotional facets of empathy to gain a better understanding of the contribution of OT and AVP pathways to empathy. Both the *AVPR1a* 327 repeat and the *OXTR* rs53576 SNP variants were, as we predicted, associated with empathy and the allelic direction of association is consistent with other investigations of these two polymorphisms. Notably, *OXTR* rs53576-A allele solely predicted lower emotional empathy whereas the *AVPR1a* 327 repeat allele solely predicted lower scores on cognitive empathy. Interestingly, the interaction between the two genes was not associated with either empathy measure. Altogether, the neurogenetic approach taken in the current study allows a molecular distinction to be made between both facets of empathy and identifies at least two of the neurochemical pathways contributing to this most human of traits.

The current results give greater traction to an increasing body of research, suggesting that the neurochemical and neurogenetic underpinnings of emotional empathy are somewhat distinct from those of cognitive empathy. Neuroimaging, brain lesion studies, genetic studies and clinical research studies support the notion that empathy is multifaceted and relies on both partially distinct and yet apparently interconnected, brain circuits (Shamay-Tsoory et al., 2007, 2009a, 2009b; Shamay-Tsoory and Aharon-Peretz, 2007; Uzefovsky et al., 2014; Zaki and Ochsner, 2012). Hence, we suggest that empathy should not be studied simply as a monolithic concept but rather that its multifaceted nature needs to be taken into account. Moreover, our findings based on a neurogenetic strategy suggest the distinct involvement of oxytocinergic neural pathways in emotional empathy and vasopressin pathways in cognitive empathy. Although few studies have assessed the association between these genes and empathy, one study by Rodrigues et al. (2009) investigated the association between *OXTR* rs53576 SNP and empathy as measured by the Interpersonal Reactivity Index (IRI), finding that, as in the current study, the rs53576-A was associated with lower empathy scores (they did not distinguish between the cognitive and emotional subscales). However, Rodrigues et al. (2009) in the same investigation also finds an association between the *OXTR* rs53576 and the Reading the Mind in the Eyes Test (RMET) (Baron-Cohen et al., 2001), a measure of cognitive empathy, a result

Table 3
Linear regression analyses with gender, *OXTR* rs53576 genotype, *AVPR1a*.327 genotype and the interaction between *OXTR* and *AVPR1a* genotyped predicting empathy scores. Results show that (1) women have higher empathy scores than men; (2) the A allele of the *OXTR* rs53576 and the 327 repeat allele of the *AVPR1a* independently predict lower empathy scores; (3) the interaction between *OXTR* rs53576 and *AVPR1a*.327 is not predictive of empathy scores. Results were confirmed using a bootstrap procedure based on 1000 bootstrap samples.

Empathy	β (standardized)	Sig.	Block ΔR^2	*F*	Sig.	*B* (unstandardized)	Bootstrap 95% CI	
							Lower	Higher
Step 1			.11	44.08	$p < .001$			
Gender	.328	$p < .001$				.617	.425	.798
Step 2			.132	19.53	$p < .001$			
Gender	.333	$p < .001$				.625	.439	.807
OXTR rs53576	−.134	$p = .006$	.031		$p = .002$	−.217	−.399	−.051
AVPR1a.327	−.115	$p = .018$				−.261	−.443	−.064
Step 3			.130	14.62	$p < .001$			
Gender	.332	$p < .001$				.625	.435	.808
OXTR rs53576	−.115	$p = .019$				−.217	−.400	−.049
AVPR1a.327	−.134	$p = .006$				−.261	−.446	−.063
OXTR x *AVPR1a*	−.010	$p = .838$	.000		$p = .838$	−.039	−.390	.351

that is in conflict with our failure to find an association between this SNP and cognitive empathy using a self-report questionnaire. One possible explanation for the discrepancy in the results is that the Rodrigues et al. (2009) study included very mixed ethnicity including 35% Caucasians, 41% Asians and 24% mixed in their smaller sample of only 192 subjects. In addition, it is also possible that the type of the task (performance based vs. a questionnaire measure) affected this result. Similar findings have been reported by Lucht et al. (2013). They examined 3 OXTR SNPs, rs53576 among them, in a group of 76 adolescents and young adults, finding that the rs2228485 was associated with performance on the RMET (rs53576 and rs2254298 did not withstand multiple testing corrections) (Lucht et al., 2013). Similarly to the Rodrigues et al. (2009) study, several factors may explain the divergence in results; the sample size is very small in terms of genetic research, the task measures performance and the sample included adolescents. Notwithstanding, support for our current findings that the OXTR is associated with emotional but not cognitive empathy comes from a recent study that examined the effects of intranasal OT administration on EE and CE (Hurlemann et al., 2010). The study showed that the administration of OT brought on an increase in EE but not CE. Additional partial support comes from another study that examined the association between OXTR and empathy in individuals with Schizophrenia and controls (Montag et al., 2012). In their study, the rs2254298, but not the rs53576, was found to be associated with EE (specifically, the empathic concern subscale of the IRI) only in the schizophrenia group. Although this study does not constitute a full replication, it still supports the notion that OXTR is associated with emotional empathy. However, clearly, additional research with larger samples is needed to understand the specific role of the oxytocinergic and vasopressinergic systems in the two facets of empathy.

The current study joins an ever growing literature on the association between the oxytocin-vasopressin system and social cognition and behavior, although the biological mechanism of this association is yet largely unknown. Only a few studies examined the functionality of these polymorphisms (Knafo et al., 2008; Meyer-Lindenberg et al., 2008; Tansey et al., 2011; Tost et al., 2010; Wang et al., 2013). Several neuroimaging studies have begun to explore the functional effects of the *OXTR* rs53576 SNP and its association with brain areas associated with empathy. Tost et al. (2010) showed that the G-allele is associated with higher gray matter volume in the amygdala and hypothalamus. In addition, the connectivity between the amygdala and hypothalamus was associated with genotype (Tost et al., 2010). Similarly, Wang et al. (2013) showed that the G-allele is associated with higher volume of the amygdala. In addition, G carriers showed higher functional connectivity with the prefrontal cortex (Wang et al., 2013). A recent study revealed, using a SPECT analysis, an association between the G-allele and lower striatal availability of the dopamine transporter gene (DAT) (Chang et al., 2014). Taken together, these studies point to a role of the rs53576 in moderating the functionality of brain areas involved in social cognition. Again, studies of the functional significance of the RS3 polymorphism are scarce. The length of RS3 was previously associated with mRNA levels of AVPR1a in the hypothalamus (Knafo et al., 2008) and with promoter activity (Tansey et al., 2011). As mentioned, the 327 allele was associated with amygdala activation (Meyer-Lindenberg et al., 2008). Taken together, these studies suggest that the observed association between *OXTR* and *AVPR1a* genes and empathy is mediated by socio-emotional networks in the brain. However, future research in the field of social science can greatly benefit from studies on the basic biology of these (and other) polymorphisms in the *OXTR* and *AVPR1a* genes.

Table 4
Linear regression analyses with gender, *OXTR* rs53576 genotype, *AVPR1a*.327 genotype and the interaction between *OXTR* and *AVPR1a* genotyped predicting emotional empathy scores. Results show that emotional empathy is predicted by gender (women score higher than men) and by the *OXTR* rs53576 genotype (the A allele is associated with lower empathy). The *AVPR1a*.327 genotype and the interaction are not predictive of emotional empathy. Results were confirmed using a bootstrap procedure based on 1000 bootstrap samples.

Emotional empathy	β (standardized)	Sig.	Block ΔR^2	F	Sig.	B (unstandardized)	Bootstrap 95% CI	
							Lower	Higher
Step 1			.097	40.27	$p < .001$			
Gender	.315	$p < .001$				.627	.428	.821
Step 2			.11	16.01	$p < .001$			
Gender	.317	$p < .001$				.630	.433	.825
OXTR rs53576	−.108	$p = .029$	.018		$p = .028$	−.215	−.399	−.016
AVPR1a.327	−.077	$p = .122$				−.157	−.359	.051
Step 3			.11	11.98	$p < .001$			
Gender	.317	$p < .001$				.630	.432	.822
OXTR rs53576	−.108	$p = .029$				−.215	−.399	−.019
AVPR1a.327	−.077	$p = .122$				−.158	−.363	.047
OXTR x *AVPR1a*	.007	$p = .891$	.000		$p = .891$	.028	−.373	.392

Table 5
Linear regression analyses with gender, *OXTR* rs53576 genotype, *AVPR1a*.327 genotype and the interaction between *OXTR* and *AVPR1a* genotyped predicting cognitive empathy scores. Results show that cognitive empathy is predicted by gender (women score higher than men) and by the *AVPR1a*.327 genotype (the 327 allele is associated with lower empathy). The *OXTR* rs53576 genotype and the interaction are not predictive of cognitive empathy. Results were confirmed using a bootstrap procedure based on 1000 bootstrap samples.

Cognitive empathy	β (standardized)	Sig.	Block ΔR^2	F	Sig.	B (unstandardized)	Bootstrap 95% CI	
							Lower	Higher
Step 1			.026	10.90	$p = .001$			
Gender	.170	$p = .001$				.334	.141	.532
Step 2			.052	7.73	$p < .001$			
Gender	.176	$p = .001$				.346	.145	.543
OXTR rs53576	−.083	$p = .103$	.018		$p = .028$	−.164	−.354	.031
AVPR1a.327	−.156	$p = .002$				−.316	−.526	−.118
Step 3			.060	5.77	$p < .001$			
Gender	.176	$p = .001$				.346	.150	.544
OXTR rs53576	−.083	$p = .103$				−.164	−.352	.031
AVPR1a.327	−.156	$p = .002$				−.316	−.526	−.118
OXTR x *AVPR1a*	.007	$p = .895$	.000		$p = .895$	.027	−.365	.436

This is the first and the largest study to examine concurrently the role of *OXTR* and *AVPR1a* in contributing to individual differences in both facets of empathy, EE and CE. The current results show that EE and CE can be distinguished at the genetic level and by implication at the neurochemical level. *OXTR* was associated with emotional empathy, which we suggest is consistent with a large literature demonstrating a role of this gene in both animal and human affiliative behaviors. *AVPR1a* appears to contribute solely to cognitive empathy also consistent with previous findings, suggesting a role for this gene in various facets of social cognition and social memory (Dantzer et al., 1988; Ferguson et al., 2002; Walum et al., 2008).

As mentioned, the current study investigated the effects of *OXTR* and *AVPR1a* on empathy in the largest sample to date. However, a replication of the current findings is needed to establish the unique role of *OXTR* and *AVPR1a* in individual differences in cognitive and emotional empathy. Our findings help clarify the proximal mechanisms that are associated with cognitive and emotional empathy and, in doing so, may open new avenues for interventions in clinical conditions associated with difficulties in empathy such as autism and anti-social personality disorder.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.yhbeh.2014.11.007.

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