

Emotion recognition associated with polymorphism in oxytocinergic pathway gene ARNT2

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Abstract

The ability to correctly understand the emotional expression of another person is essential for social relationships and appears to be a partly inherited trait. The neuropeptides oxytocin and vasopressin have been shown to influence this ability as well as face processing in humans. Here, recognition of the emotional content of faces and voices, separately and combined, was investigated in 492 subjects, genotyped for 25 single nucleotide polymorphisms (SNPs) in eight genes encoding proteins important for oxytocin and vasopressin neurotransmission. The SNP rs4778599 in the gene encoding aryl hydrocarbon receptor nuclear translocator 2 (ARNT2), a transcription factor that participates in the development of hypothalamic oxytocin and vasopressin neurons, showed an association that survived correction for multiple testing with emotion recognition of audio-visual stimuli in women ($n = 309$). This study demonstrates evidence for an association that further expands previous findings of oxytocin and vasopressin involvement in emotion recognition.

Key words: oxytocin; vasopressin; ARNT2; emotion recognition; social cognition

Introduction

The ability to correctly understand the emotional expression of other individuals, and thus to interpret their internal states and intentions, is essential for social interactions and relationships. This ability, present in humans as well as non-human primates, is displayed very early in infancy (Tate *et al.*, 2006; Grossmann and Johnson, 2007). The heritability of emotion recognition and of cortical processing of facial emotion is moderate (Anokhin

et al., 2010; Knafo-Noam and Uzevovsky, 2013). Other observations that support a genetic component are that first-degree relatives appear to share impairments in emotion recognition (Neves *et al.*, 2011; Oerlemans *et al.*, 2013; Allott *et al.*, 2015), and recent positive genetic association findings in large samples (Warrier *et al.*, 2017).

The neuropeptides oxytocin (OXT) and arginine vasopressin (AVP) have been implicated in social behaviors in animals as

Received: 28 June 2017; Revised: 31 October 2017; Accepted: 19 November 2017

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well as humans (Lee et al., 2009; Baribeau and Anagnostou, 2015). Intranasal OXT administration has been shown to enhance the recognition of emotion—positive and negative—in faces (Domes et al., 2007; Shahrestani et al., 2013) and in body language (Bernaerts et al., 2016), whereas AVP administration to men has been shown to reduce recognition of negative emotion in male faces (Uzefovsky et al., 2012) and the perception of friendliness in happy male faces (Thompson et al., 2006). Administration of either neuropeptide has also been reported to influence the processing and memory of emotional faces (Guastella et al., 2008, 2010; Rimmele et al., 2009; Meyer-Lindenberg et al., 2011).

OXT and AVP are nonapeptides with peripheral and central functions, synthesized in the paraventricular and supraoptic nuclei of the hypothalamus and released through the pituitary to the periphery as well as into the brain by local dendrites and synapses in regions including the amygdala, the hippocampus, the striatum and the brainstem (Ross and Young, 2009; Baribeau and Anagnostou, 2015). Aryl hydrocarbon receptor nuclear translocator 2 (ARNT2) and single-minded 1 (SIM1) are two dimerizing transcription factors that participate in the development of OXT and AVP neurons in the paraventricular and supraoptic nuclei in mice (Michaud et al., 2000; Kublaoui et al., 2008; Duplan et al., 2009). A few studies suggest that variation in the genes encoding ARNT2 and SIM1 may be associated with human phenotypes related to social cognition (Chakrabarti et al., 2009; Ramachandrapa et al., 2013; Di Napoli et al., 2014; Hovey et al., 2014). The transmembrane glycoprotein cluster of differentiation 38 (CD38) has been shown to be important for social behavior in mice via an influence on hypothalamic OXT release (Jin et al., 2007). Human gene association studies have reported associations between variation in CD38 and face processing and phenotypes characterized by social impairment (Munesue et al., 2010; Sauer et al., 2012), and expression of the gene has been coupled to social skills (Riebold et al., 2011).

The effects of OXT and AVP are mediated by the G-protein-coupled OXT receptor (OXTR) and vasopressin receptors (AVPR1A and AVPR1B). These receptors are expressed in different regions in different species in a manner that suggests that its involvement in social attention is conserved through evolution (Young et al., 1999; Yoshida et al., 2009; Roper et al., 2011; Boccia et al., 2013; Freeman et al., 2014). Human genetic studies have shown associations between phenotypes related to social cognition and face processing, and polymorphisms in OXTR (Tost et al., 2010; Ebstein et al., 2012; Westberg and Walum, 2013; Skuse et al., 2014; LoParo and Waldman, 2015), AVPR1A (Yirmiya et al., 2006; Walum et al., 2008; Meyer-Lindenberg et al., 2009; Tansey et al., 2011; Ebstein et al., 2012; Kantojärvi et al., 2015; Uzefovsky et al., 2015) and AVPR1B (Wu et al., 2015; Francis et al., 2016), respectively. Variation in the OXTR has also been associated with emotion recognition (Rodrigues et al., 2009; Melchers et al., 2013; Chen et al., 2015).

Here, we studied the recognition of 12 different emotional expressions in three modalities, i.e. visual, auditory and audio-visual, using ecologically valid video and sound recordings, and genotyped 25 single nucleotide polymorphisms (SNPs) in eight genes (Table 1) linked to OXT and AVP signaling. These included OXT, AVP, OXTR, AVPR1A and AVPR1B, the two transcription factors genes ARNT2 and SIM1, as well as CD38. To the best of our knowledge, previous studies have only investigated the OXTR gene in relation to emotion recognition. We hypothesized that variation in these genes, by virtue of their role in social behavior and cognition, would be associated with ability to discern human emotional expression. Since emotion recognition has been linked to autism traits, alexithymia, emotional expressivity and

perspective taking (Oberman et al., 2007; Ponari et al., 2012; Bird and Cook, 2013; Cook et al., 2013; Brewer et al., 2015; Berggren et al., 2016; Fridenson-Hayo et al., 2016; Trubanova et al., 2016) and thus may be involved in a potential relationship between emotion recognition and genetic variation, *post hoc* tests included assessment of correlations with these self-reported traits, as well as potential associations for SNPs significantly associated with emotion recognition.

Materials and methods

Participants

The study included 492 participants, recruited from the normal population, for whom both behavioral and genetic data were available, 182 men (age range: 18–36 years, mean \pm s.d.: 23.7 \pm 3.1) and 310 women (age range: 18–34 years, mean \pm s.d.: 23.0 \pm 3.2). All included participants were Caucasian, right-handed, fluent in Swedish, healthy and reported no past or present psychiatric diseases or substance abuse. All participants provided written informed consent in accordance with the Declaration of Helsinki. The study was approved by the Stockholm regional ethical review board (2012/1511-31/2). Ethnicity was assessed by asking which country parents and grand-parents were born in. Due to previously reported differences in allele frequencies and associations between different ethnic groups, e.g. (Barzan et al., 2013), subjects of non-Caucasian or unknown ethnicity ($n = 91$) were excluded from the original sample ($n = 583$). Allele frequencies differed significantly between the Caucasians and non-Caucasians also in the current sample.

Multimodal emotion recognition task

Emotion recognition accuracy was assessed using the emotion recognition assessment in multiple modalities (ERAM) test, which is based on video clips of emotion expressions portrayed by professional actors from the Geneva Multimodal Emotion Portrayal corpus (Bänziger et al., 2012). Actors were instructed to improvise interactions wherein they expressed emotions while pronouncing pseudolinguistic sentences with standard content (e.g. 'ne kali bam sud molen!'). Each video shows close-up frontal views of the actor's face and upper torso and contains facial, vocal and bodily cues to emotion.

The ERAM test contains 72 items conveying 12 different emotional expressions: the positive emotions happiness, interest, pleasure, pride and relief, and the negative emotions hot anger, anxiety, despair, disgust, panic fear, irritation and sadness. The items were presented in three conditions—video only (24 video clips presented without sound), audio only (24 sounds presented alone) and audio–video (24 video clips presented with sound)—which allowed for separate assessment of visual, auditory and audio–visual emotion recognition ability. The duration of the video clips ranged between 1 and 5 s and sound levels were normalized within each of the 10 actors.

Participants on average required 15 min to complete the ERAM test. Experiments were conducted individually using *Authorware* (Adobe Systems Inc, San Jose, CA) running on computers to present stimuli and record responses. Video content was presented on 24" LED monitors and audio content was presented through headphones (AKG K619, AKG Acoustics GmbH, Vienna, Austria) with volume kept constant across participants. Participants first took part in a brief training session and were then presented with the video only stimuli, followed by the audio only and lastly audio–video stimuli, in a fixed order. For

Table 1. SNP information

Gene	SNP	Chromosome	Position	References
OXT	rs2740210	20p13	downstream	Yrigollen et al. (2008)
	rs2770378		downstream	Chakrabarti et al. (2009); Hovey et al. (2014)
	rs4813627		downstream	Mileva-Seitz et al. (2013)
AVP	rs2740204	20p13	downstream	Yrigollen et al. (2008)
OXTR	rs7632287	3p25	3'	Hovey et al. (2015); LoParo and Waldman (2015); Walum et al. (2012)
	rs1042778		3' UTR	Israel et al. (2009); Lerer et al. (2008)
	rs237887		intron 3	LoParo and Waldman (2015); Skuse et al. (2014); Wu et al. (2012)
	rs2254298		intron 3	Inoue et al. (2010); Israel et al. (2009); LoParo and Waldman (2015); Wu et al. (2012)
	rs53576		intron 3	Bakermans-Kranenburg and van IJzendoorn (2008); Rodrigues et al. (2009); Tost et al. (2010)
	rs4686302		exon 3	Wu et al. (2012)
	rs4564970		5' UTR	Hovey et al. (2015); Johansson et al. (2012a, b)
	rs2268498		5'	Christ et al. (2016); Laursen et al. (2014); Melchers et al. (2013)
	rs75775		5'	Wang et al. (2009)
	AVPR1A	rs11832266	12q14-15	5'
rs10877969		5'		Yang et al. (2010)
rs1042615			exon 1	Bernhard et al. (2016)
rs11174811			3' UTR	Maher et al. (2011)
rs1587097			3'	Levrant et al. (2009)
AVPR1B	rs35369693	1q32	exon 1	Francis et al. (2016)
ARNT2	rs3901896	15q25.1	intron 1	Chakrabarti et al. (2009); Hovey et al. (2014); Di Napoli et al. (2014)
	rs4778599		intron 5	Chakrabarti et al. (2009)
	rs4072568		exon 18	Swarbrick et al. (2011)
SIM1	rs3734354	6q16.3	exon 3	Hovey et al. (2014); Swarbrick et al. (2011)
CD38	rs6449182	4p15.32	intron 1	Hovey et al. (2014); Jamrozik et al. (2009); Riebold et al. (2011)
	rs3796863		intron 7	Munesue et al. (2010); Sauer et al. (2012)

UTR, untranslated region.

each stimulus, participants were instructed to choose the label that best represented the expression conveyed by that portrayal from a list of 12 alternatives (which were the same as the 12 intended expressions). A match between the chosen label and the intended expression was scored as a correct response.

The multimodal emotion recognition task was followed by other tests on social perception and memory as well as self-report questionnaires, resulting in a test battery with a duration of approximately one and a half hours. The additional data will be presented in future scientific reports.

Genotyping

DNA was extracted from saliva samples using OraGene DNA self-collection kit (DNA Genotek, Inc, Ottawa, ON, Canada). In total, 25 SNPs in eight different genes (Table 1) were genotyped with KASPar, a competitive allele-specific polymerase chain reaction SNP genotyping system using FRET quencher cassette oligos (<http://www.lgcgenomics.com>). The genotyping success rate was >95%. The SNPs were chosen either because they have been shown to influence protein function or because they have been associated with behavioral phenotypes (Table 1). All SNPs had a minor allele frequency > 5%.

Questionnaires

Autism traits were measured by means of the autism quotient scale (AQ; Baron-Cohen et al., 2001), alexithymia was measured by the Toronto Alexithymia Scale (TAS-20; Bagby et al., 1994; Simonsson-Sarnecki et al., 2000), including subscales measuring reduced ability to identify and describe one's own feelings as well as the preference and habit to focus on external factors

rather than feelings. Expressivity was measured by the Berkeley expressivity questionnaire (BEQ; Gross and John, 1997). The subscale perspective taking of the interpersonal reactivity index (IRI; Davis, 1983) was used to measure the habit or motivation of taking another person's perspective as this subscale was deemed relevant for the phenotype of emotion recognition. The other subscales were not included.

Statistical analysis

We studied three different emotion recognition phenotypes as primary outcome variables, namely recognition of the emotional expression of faces (visual), of the emotional expression of voices (audio) and their combination (audio-visual). Linear regression analyses in SPSS (version 23, Armonk, NY: IBM Corp) were used. The 25 SNPs were analyzed for men and women separately, since previous studies have demonstrated that the underlying mechanisms of facial emotion processing vary between the sexes (Stevens and Hamann, 2012; Thompson and Voyer, 2014). The statistical threshold for the associations was therefore corrected for 25 SNPs, three phenotypes and two sexes, resulting in a threshold of $\alpha = 0.00033$. The accuracy was conceptualized as the percentage of correct answers. To control for the large number of options and therefore types of potential errors (false alarms) or potential response biases (e.g. the tendency to choose the anger response button every time the subject is uncertain of what emotion is displayed), the accuracy measure was also determined as the joint probability of (i) the emotion being correctly labeled (e.g. the number of times the emotion anger is labeled as anger divided by the number of times the emotion anger is shown) and (ii) the response option being correctly used (e.g. the number of times the emotion

anger was labeled as anger divided by the number of times the anger response button was chosen) (Wagner, 1993). Since the results for this measure were almost identical to those of the main analyses, we only mention the results for Wagner's response bias control measure for the main finding in the Results section. Differences in performance between outcome variables were assessed by paired samples t-tests and differences between men and women with independent sample t-tests. Descriptives (mean \pm s.d.) and uncorrected P-values are shown in the Results section.

Results

Allele frequencies are displayed in Table 2. All SNPs were in Hardy Weinberg equilibrium. For the emotion recognition task, performance was higher for the audio-visual condition (M: 0.65 ± 0.13 ; F: 0.68 ± 0.12) than for the visual (M: 0.53 ± 0.11 ; F: 0.55 ± 0.13 ; P-values < 0.001) or the audio conditions (M: 0.50 ± 0.13 ; F: 0.49 ± 0.12 , P-values < 0.001). There was a nominally significant sex difference for the audio-visual condition only ($P = 0.02$).

In women, the ARNT2 SNP rs4778599 showed a significant association, surviving correction for multiple testing, with emotion recognition of audio-visual stimuli ($P = 0.00001$, $\beta = -0.24$, Table 2) that was also significant after controlling for response biases using Wagner's (1993) unbiased hit rate ($P = 0.00006$). Post hoc tests of specific emotional expressions, pooling the visual, audio and audio-visual items, showed strongest associations for despair ($P = 0.00004$, $\beta = -0.23$).

Nominally significant associations were also observed for hot anger ($P = 0.005$), anxiety ($P = 0.02$) and relief ($P = 0.01$) such that the phenotypic value was highest for the common GG genotype. There were no significant effects or trends for auditory or visual emotion recognition ($P > 0.05$). No significant associations for ARNT2 rs4778599 were observed in men ($P > 0.7$), who also did not show the same pattern of mean differences between genotypes (GG: 0.64 ± 0.14 GA: 0.66 ± 0.11 AA: 0.64 ± 0.13 ; see Table 2 for mean \pm s.d. for the different genotypes in women), indicating that the lack of association in men was not due to the smaller sample size ($n = 182$ men and 309 women). The SNP by sex interaction was nominally significant ($P = 0.006$) in a full factorial general linear model, thus showing that the association was larger in women than in men.

Due to the absence of replication sample, as an alternative to replication we split the sample into two random halves using the random numbers RV. Bernoulli function in SPSS, resulting in two subsamples ($n = 157$ and 167 women, respectively). There were nominally significant associations with the rs4778599 SNP in both subsamples of women (P-values = 0.003 and 0.002; β s = -0.23 and -0.25). No associations surviving correction for multiple testing were found for other SNPs in any of the genes with either audio, visual or audio-visual stimuli. Trend associations are displayed in Table 2.

Previously reported relationships between emotion recognition and autism traits, alexithymia, emotional expressivity and perspective taking, motivated the post hoc correlations and association tests with the rs4778599 SNP. Scores for these tests as

Table 2. Association analyses between OXT- and vasopressin-relevant SNPs and recognition of emotional expressions presented in three modalities: audio, visual and audiovisual

Gene	SNP	MAF	Measure	P-value		n**	Mean emotion recognition accuracy \pm s.d.		
				Males	Females				
OXT	rs2740210	0.32		ns	ns				
	rs2770378	0.49		ns	ns				
	rs4813627	0.39	A	ns	0.03	74/163/73	GG: 0.47 ± 0.11	GA: 0.49 ± 0.13	AA: 0.51 ± 0.10
AVP	rs2740204	0.40		ns	ns				
OXTR	rs7632287	0.23		ns	ns				
	rs1042778	0.37		ns	ns				
	rs237887	0.40	AV	0.05	ns	66/88/27	AA: 0.67 ± 0.12	AG: 0.65 ± 0.13	GG: 0.61 ± 0.15
	rs2254298	0.12		ns	ns				
	rs53576	0.37		ns	ns				
	rs4686302	0.14	AV	ns	0.04	226/76/6	CC: 0.69 ± 0.12	CT: 0.66 ± 0.13	TT: 0.60 ± 0.11
			A	0.02	ns	138/40/3	CC: 0.51 ± 0.13	CT: 0.46 ± 0.13	TT: 0.46 ± 0.04
	rs4564970	0.08		ns	ns				
	rs2268498	0.45	V	0.02	ns	50/97/34	TT: 0.56 ± 0.12	TC: 0.53 ± 0.11	CC: 0.50 ± 0.11
	rs75775	0.15	V	ns	0.007	231/68/10	GG: 0.54 ± 0.12	GT: 0.58 ± 0.14	TT: 0.62 ± 0.13
AVPR1A	rs11832266	0.052		ns	ns				
	rs10877969	0.14	A	ns	0.04	232/73/3	TT: 0.50 ± 0.11	TC: 0.46 ± 0.12	CC: 0.47 ± 0.21
	rs1042615	0.43	AV	ns	0.004	101/155/53	GG: 0.65 ± 0.14	GA: 0.69 ± 0.11	AA: 0.71 ± 0.13
	rs11174811	0.13	A	ns	0.02	238/67/5	CC: 0.50 ± 0.11	CA: 0.46 ± 0.12	AA: 0.43 ± 0.14
	rs1587097	0.09	A	ns	0.01	255/52/2	CC: 0.50 ± 0.11	CT: 0.45 ± 0.11	TT: 0.46 ± 0.18
AVPR1B	rs35369693	0.06		ns	ns				
ARNT2	rs3901896	0.38	AV	ns	0.02	128/133/47	CC: 0.70 ± 0.12	CT: 0.67 ± 0.12	TT: 0.65 ± 0.13
	rs4778599	0.34	AV	ns	0.00001*	147/124/38	GG: 0.71 ± 0.10	GA: 0.67 ± 0.13	AA: 0.62 ± 0.12
	rs4072568	0.20	V	0.03	ns	117/55/9	GG: 0.54 ± 0.11	GA: 0.54 ± 0.11	AA: 0.42 ± 0.08
SIM1	rs3734354	0.15		ns	ns				
CD38	rs6449182	0.20	AV	ns	0.004	207/91/11	CC: 0.67 ± 0.12	CG: 0.70 ± 0.12	GG: 0.74 ± 0.11
	rs3796863	0.32	A	0.01	ns	81/81/20	CC: 0.52 ± 0.11	CA: 0.48 ± 0.14	AA: 0.45 ± 0.14

MAF, minor allele frequency; ns, non-significant as in uncorrected P-value > 0.05 ; A, audio; V, visual; AV, audio-visual.

*Survives correction for multiple testing ($P < 0.0003$), uncorrected P-values displayed.

**n, number of subjects in the group for which the association was significant ($P < 0.05$) of emotional expressions presented in three modalities: audio, visual and audio-visual.

Table 3. Descriptives (mean \pm s.d.) and correlations with questionnaire scores

Scales	Score		Sex difference	Correlation P-value with audio–visual emotion recognition (Pearson r)	
	F	M	P-value	F	M
Autism quotient AQ	16 \pm 5	17 \pm 5	0.002	0.12 (–0.09)	0.52 (–0.05)
Alexithymia TAS	46 \pm 12	46 \pm 10	0.55	0.01 (–0.14)	0.16 (–0.11)
Expressivity BEQ	4.9 \pm 0.8	4.1 \pm 0.8	<0.0001	0.14 (0.09)	0.56 (–0.04)
Perspective taking (IRI)	18 \pm 4	18 \pm 5	0.45	0.33 (0.06)	0.21 (0.09)

F, females; M, males.

well as nominally significant correlations with audio–visual emotion recognition are indicated in Table 3 for the 307 women and 181 men with data for questionnaires, genes and emotion recognition performance. Controlling for the questionnaire scores by adding them to the regression model did not affect the association between the ARNT2 SNP and recognition of audio–visual emotion ($P_{ARNT2} < 0.0001$ for all models and non-significant interaction terms). The ARNT2 SNP also did not display significant associations with any of the questionnaire scores (P -values > 0.15).

Discussion

We have demonstrated an association in women between audio–visual emotion recognition and the rs4778599 SNP in intron five of ARNT2, a gene that encodes a transcription factor involved in the development of OXT and vasopressin neurons in the hypothalamus. There were no significant or trend associations for accuracy on auditory or visual emotion recognition. The fact that we only observed an association in the multimodal, i.e. audio–visual, condition suggests that the association of the ARNT2 SNP with recognition of emotion may reflect an influence of OXT, or vasopressin, on multimodal integration. OXT has indeed been shown to influence different sensory modalities and promote cross-modal cortical development (Zheng et al., 2014). The audio–visual condition displayed higher accuracy than the auditory and the visual conditions, indicating it was the easier condition of the three. Since performance was not within reach of perfect for any of the three condition, one could imagine that an easier condition would imply larger variation and a higher power of finding an association. However, the standard deviations were similar for the three conditions, and, in particular, the variation for the audio–visual condition was not the higher one.

Although none of the associations between OXTR SNPs survived correction for multiple testing, we did find a nominally significant association between the rs2268498 T allele and superior visual emotion recognition (Table 2), which is in line with previous studies of this SNP and emotion recognition abilities (Rodrigues et al., 2009; Melchers et al., 2013, 2015; Chen et al., 2015). There is also evidence that the rs2268498 polymorphism is functional since it has been related to expression levels of the OXTR in the human hippocampus (Reuter et al., 2016).

There is some evidence that genetic variation in ARNT2 may be associated with autism spectrum conditions (Chakrabarti et al., 2009; Vaags et al., 2012; Di Napoli et al., 2014; Hovey et al., 2014), which have been linked to impairments in emotion recognition in some (Berggren et al., 2016; Fridenson-Hayo et al., 2016) but not all (Castelli, 2005; Tracy et al., 2011) studies. Functional SNPs upstream of rs4778599—in a block ranging from intron one to three, including also the intron one

rs3901896 that showed a nominal association (Table 2) in our study—have been associated with Asperger syndrome (Di Napoli et al., 2014). The intron one and five SNPs have been reported to be in high linkage disequilibrium in a Swedish population (Hovey et al., 2014). Although there is as of yet no independent evidence of rs4778599 being functional, there is some previous evidence that this SNP and the intronic rs3901896 may be linked to autism spectrum diagnosis and autism traits (Chakrabarti et al., 2009; Hovey et al., 2014).

In our sample, scores on the AQ scale were not associated with ARNT2 SNPs. AQ scores also did not modify the association between the ARNT2 SNP and audio–visual emotion recognition. The rs4778599 G allele, proposed to be associated with elevated autism risk or autism scores in a previous study, was in our sample associated with superior emotion recognition. Even though previous evidence of an association with autism did not survive correction for multiple testing (Chakrabarti et al., 2009), this direction of association was unexpected. However, if no relationship is to be expected between emotion recognition deficits and AQ scores, it may not be as contradictory as it appears. The discrepancy between studies regarding a relationship between autism spectrum conditions and emotion recognition may be due to the occurrence of emotion recognition deficits only in specific subgroups with autism spectrum conditions (Nuske et al., 2013; Berggren et al., 2016). A recent study attempting to identify subgroups of autism patients based on performance on a complex emotion recognition task did indeed show that that only one smaller subgroup of autism patients displayed accuracies that were lower than the range for the controls (Lombardo et al., 2016). A related theory posits that emotion recognition deficits in autism are present only in subgroups with comorbid alexithymia (Bird and Cook, 2013; Cook et al., 2013; Brewer et al., 2015; Oakley et al., 2016). In this study, there was a nominally significant correlation between alexithymia scores and audio–visual emotion recognition (Table 3) in the expected direction. Alexithymia scores were however not associated with the ARNT2 SNP and did not modify the association with emotion recognition, and the correlation thus does not give any insights into the mechanism by which ARNT2 variation may have an influence on emotion recognition.

Although we included the four questionnaires to further analyze and understand the association as well as the relationship between emotion recognition and the OXT and/or vasopressin systems in general, none of them appeared to influence the association between the ARNT2 polymorphism and emotion recognition, and thus we could not pursue this line of investigation. As mentioned, the lack of correlation in this study between emotion recognition and AQ may reflect that the subgroups for which such a correlation has been reported are absent in the present sample. This may also be the case for the less investigated measures of expressivity and perspective taking. The lack of

association between questionnaire scores and the ARNT2 polymorphism should be viewed in the light of the absence of correlation between the questionnaires and emotion recognition. Needless to say, the associations and correlations should be interpreted with caution until replicated in independent samples.

The association between emotion recognition and the ARNT2 SNP was only observed in women. Sex differences have been suggested for facial affect recognition (McBain et al., 2009; Vassallo et al., 2009), the neural mechanisms of face processing (Fischer et al., 2007; Ino et al., 2010) and emotion processing (Kret and De Gelder, 2012). In this study, women were slightly superior to men with respect to recognition of emotional audio-visual stimuli. Interestingly, animal studies have shown sexual dimorphism in the cerebral expression pattern of ARNT2 before gonadal formation (Dewing et al., 2003) and sexual dimorphism is an established fact when it comes to the OXT and vasopressin systems (Westberg and Walum, 2013; Dumais and Veenema, 2016), both of which are modulated by ARNT2 (Michaud et al., 2000). Furthermore, emotion processing is influenced by sex hormones (Toffoletto et al., 2014), which are naturally sex-specific, and also modulate the effects of OXT (Gabor et al., 2012). It therefore stands to reason that the effect of an SNP in this system may have sex-specific effects. In addition, sex-specific effects of genetic variation on emotion recognition have recently been reported (Warrier et al., 2017), further supporting a sex-specific genetic architecture underlying variation in this phenotype. Furthermore, null mutations in ARNT2 cause a variety of phenotypes in humans, including but not limited to neurological abnormalities, congenital hypopituitarism and abnormalities of the kidneys (Webb et al., 2013) suggesting that ARNT2 is involved in several different pathways.

In summary, we report a novel association between the ARNT2 SNP rs4778599 and emotion recognition in women, that further emphasizes and expands previous findings of OXT and vasopressin involvement in emotion recognition.

Funding

This work was supported by the Swedish Research Council (P.L., H.F. and L.W.). The funding bodies had neither role in the design and conduct of the study, preparation, review or approval of the manuscript, nor in the decision to submit the article for publication.

Conflict of interest. None declared.

Acknowledgements

The authors thank Christina Lindahl for data collection.

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