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REVIEW ARTICLE

The association between an oxytocin receptor gene polymorphism and cultural orientations

Siyang Luo · Shihui Han

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Abstract Recent research has revealed an association between collectivistic cultural values and allelic frequency of the serotonin transporter polymorphism (5-HTTLPR). The current study investigated whether collectivistic cultural values are also associated the allelic frequency of another gene, i.e., the oxytocin receptor gene polymorphism (OXTR rs53576), which has been linked to social cognition and behavior. In addition, we examined whether OXTR rs53576 can explain the relationships between pathogen prevalence, collectivistic cultural values and prevalence of major depression disorder. We found that, across 12 nations, A allelic frequency of OXTR rs53576 correlates with collectivistic cultural values. Moreover, A allelic frequency of OXTR rs53576 mediates the relationship between pathogen prevalence and collectivistic cultural values. Finally, A allele frequency of OXTR rs53576 is predictive of major depression disorder prevalence across nations and such associated is mediated by collectivistic cultural values. Taken together, our findings provide evidence for the mediating role of OXTR rs53576 in the association between pathogen prevalence and cultural values and support the functional role of OXTR rs53576 in human mental health.

Keywords Collectivistic cultural value · Oxytocin receptor gene polymorphism · Pathogen prevalence · Major depression disorder

S. Luo (✉) · S. Han
Department of Psychology, PKU-IDG/McGovern Institute for Brain Research, Peking University, Beijing 100871, China
e-mail: ljc520ida@163.com

S. Han
e-mail: shan@pku.edu.cn

Introduction

Human mental processes vary significantly across countries with different cultural backgrounds (Hofstede 2001). This notion has received widespread examinations by psychologists during the past decades who have identified two primary cultural orientations, namely, individualism and collectivism (Markus and Kitayama 1991; Triandis 1995; Nisbett et al. 2001). Individualism dominates Western societies where people tend to take responsible for themselves and be less group dependent in emotion and behavior. In contrast, collectivistic culture dominates East Asian societies where people care more for group interest than for individuals' and consider close people as integral parts of self, take responsible for ingroup members and prefer group harmony and group development to competition (Markus and Kitayama 1991; Triandis 1995; Nisbett et al. 2001). Cultural orientations of individualism and collectivism produce profound influences on human behaviors, cognition, emotion, motivation as well as self-regulation (Cross et al. 2011), and the underlying brain mechanisms (Han and Northoff 2008; Han et al. 2013).

The culture-gene coevolutionary theory proposes that cultural traits, such as individualism and collectivism, have evolved and are adaptive, during which process they are related to some biological factors (Boyd and Richerson 1985). Recent research has revealed geographical variability in historical and contemporary pathogen prevalence and shown that geographical variability can predict cultural variability in individualism-collectivism (Fincher et al. 2008). Nations with greater historical and contemporary prevalence of infectious diseases or disease-causing pathogens are more likely to endorse collectivistic cultural norms. A recent research further revealed that the association between pathogen prevalence and individualism-collectivism is mediated by short (S) allele distributions of the serotonin transporter polymorphism (5-HTTLPR) (Chiao and Blizinsky 2010). Moreover, S allele distributions of 5-HTTLPR can predict cultural variability via local prevalence of mood disorders. That is, nations with greater pathogen prevalence are more likely to have a greater population frequency of S allele of 5-HTTLPR, to endorse stronger collectivistic cultural norms, and to have lower prevalence of mood disorders. These observations suggest that cultural values of individualism and collectivism may serve as an adaptive, 'anti-pathogen' function, protecting vulnerable geographical regions from increased spread of disease-causing pathogens via the promotion of collectivistic social norms which is associated with genetic selection of S allele carriers (Fincher et al. 2008; Chiao and Blizinsky 2010).

While the previous research suggests a relationship between 5-HTTLPR allele frequency and cultural variability in individualism-collectivism, it remains unknown whether collectivistic cultural values are also associated the allelic frequency of other genes. The current work examined whether the oxytocin receptor gene polymorphism (OXTR rs53576) is associated with collectivistic cultural values across nations. In addition, we examined whether OXTR rs53576 can explain the relationships between pathogen prevalence, collectivistic cultural values and prevalence of major depression disorder. OXTR is located on chromosome 3p25, spans 17 kb, contains four exons and three introns, and encodes a 389-aa polypeptide with seven transmembrane domains belonging to the class I G protein-

coupled receptor family (Inoue et al. 1994). Recent research found rs53576, a single nucleotide polymorphisms with A and G variants in the third intron, can most likely explain the differences in oxytocinergic functioning (Meyer-Lindenberg et al. 2011). It has been shown that A allele of OXTR rs53576 promotes deficits in socioemotional domains such as empathy (Rodrigues et al. 2009), positive affect (Lucht et al. 2009), emotional support seeking (Kim et al. 2010), self-esteem (Saphire-Bernstein et al. 2011), maternal sensitivity (Bakermans-Kranenburg and Van IJzendoorn 2008; Walum et al. 2012), prosocial temperament (Tost et al. 2010), and trust behavior (Krueger et al. 2012). In addition, A compared to G allele has been associated with higher levels of physiological and dispositional stress reactivity and depressive symptomatology as well as increased risk for autism (Wu et al. 2005; Rodrigues et al. 2009; Saphire-Bernstein et al. 2011). Moreover, brain imaging research showed that A allele of OXTR rs53576 is associated with greater gray matter volume in amygdala and decreased amygdala activity during negative facial emotion processing (Tost et al. 2010).

Recent research samples of OXTR suggests a large variation of population frequency of OXTR rs53576 A allele carriers across geographical regions. For example, 85–90 % of individuals in a typical East Asian sample are A carriers, while in a typical European sample only 45–55 % are A carriers (Wu et al. 2005; Tost et al. 2010; Luo et al. under review). Given that the distribution of OXTR rs53576 A allele is similar to that of 5-HTTLPR and that increased frequency of A carriers with lower emotional sensitivity is in high collectivistic culture regions, OXTR rs53576 may play an essential role in the relationship among pathogen prevalence, individualism-collectivism culture norms and prevalence of mood disorders.

To test this hypothesis, we reviewed published data on allelic frequency of OXTR rs53576 across nations and examined the possible association between OXTR rs53576 distribution and local individualism-collectivism. Moreover, we explored the role of A allelic frequency of OXTR rs53576 in the relationships among pathogen prevalence and individualism-collectivism using a mediation analysis. In addition, given the prior evidence that both 5-HTTLPR and OXTR rs53576 are correlated with depression (Pezawas et al. 2005; Thompson et al. 2011; McQuaid et al. 2013) and that the association between 5-HTTLPR distribution and global prevalence of mood disorders was mediated by individualism-collectivism (Chiao and Blizinsky 2010), we further examined the association among A allelic frequency of OXTR rs53576, individualism-collectivism and prevalence of major depression disorders across nations.

Methods

Cross-national samples of the allelic frequency of OXTR rs53576

Data on the allelic frequency of OXTR rs53576 were compiled from 36 peer-reviewed publications that included 14,938 individuals from 12 countries (Australia, Finland, Germany, Italy, Japan, Korea, the Netherlands, People's Republic of

China, Sweden, Canada, UK and USA) (see Tables 1 and 2 for details of these publications). All published samples were identified based on a Google Scholar search conducted between October, 2012 and March, 2014 using one or more of the following keywords: oxytocin receptor gene, OXTR rs53576, genotype and country. All published studies that included allelic frequency information on the samples genotyped for the OXTR rs53576 were included in the data analysis. Sample size per country ranged from 110 (UK) to 3,186 (USA) individuals. Published studies that do not meet the requirements were excluded based on the following two exclusion criteria: either (1) no allelic frequency data was reported or allelic frequency could not be accurately inferred from reported distribution of genotype frequency (e.g., report combined frequency of homozygous and heterozygous carriers of the A allele of the OXTR rs53576) or (2) participants came from different countries and could not be differentiated.

Cross-national samples of the allelic frequency of 5-HTTLPR

Given the association between the allelic frequency of 5-HTTLPR and the cultural value of individualism-collectivism (Chiao and Blizinsky 2010), the data of the allelic frequency of 5-HTTLPR were compiled from 59 peer-reviewed publications (56 peer-reviewed publications used in Chiao and Blizinsky (2010) and three publications on Canadian subjects, see Table 2 for details). These publications included 27,281 individuals from 12 countries (Australia, Finland, Germany, Italy, Japan, Korea, the Netherlands, People's Republic of China, Sweden, Canada, UK and USA).

Cross-national sample of cultural values

Due to the strong correlations between independent measures of individualism and collectivism ($r = 0.80$) (Fincher et al. 2008), the difference between collectivism scores and individualism scores from the 12 nations (reversely calculated from Hofstede 2001) were used in the current study. In addition, a modified Suh et al.'s (1998) index that combines the differential collectivism-individualism scores and the ratings from a cross-cultural study (Triandis 1994) was also used in the current study (Table 2).

Cross-national samples of economic indices

Given that increased individualism may be a cultural consequence of economic development and urbanization (Hofstede 2001), we included data of two economic indices in the regression analyses, i.e., gross domestic product (GDP) and Gini index, from the 12 countries in our regression analyses (Table 2). All GDP and Gini index data were compiled from the Wikipedia (http://zh.wikipedia.org).

Table 1 The allele frequency of OXTR rs53576 in different studies

Study	Country	n	OXTR rs53576						Alleles				
			AA	%	AG	%	GG	%	n	A	%	G	%
Bryant et al. (2013)	Australia	185	25	13.51	72	38.92	88	47.57	370	122	32.97	248	67.03
Total		185	25	13.51	72	38.92	88	47.57	370	122	32.97	248	67.03
AVG				13.51		38.92		47.57			32.97		67.03
Malik et al. (2012)	Canada	152	15	9.87	49	32.24	88	57.89	304	79	25.99	225	74.01
Kryski et al. (2014)	Canada	270	55	20.37	170	62.96	183	67.78	816	280	34.31	536	65.69
Total		422	70	16.59	219	51.90	271	64.22	1120	359	32.05	761	67.95
AVG				15.12		47.60		62.83			30.15		69.85
Luo et al. under review	China	862	373	43.27	407	47.22	82	9.51	1,724	1,153	66.88	571	33.12
Wang et al. (2013a)	China	290	93	32.07	175	60.34	22	7.59	580	361	62.24	219	37.76
Wang et al. (2013b)	China	270	80	29.63	171	63.33	19	7.04	540	331	61.30	209	38.70
Wu et al. (2005)	China	195	80	41.03	98	50.26	17	8.72	390	258	66.15	132	33.85
Wu et al. (2012)	China	101	47	46.53	45	44.55	9	8.91	202	139	68.81	63	31.19
Total		1,718	673	39.17	896	52.15	149	8.67	3,436	2,242	65.25	1,194	34.75
AVG				38.51		53.14		8.35			65.08		34.92
Jern et al. (2012)	Finland	1,491	266	17.84	698	46.81	527	35.35	2,982	1,230	41.25	1,752	58.75
Johansson et al. (2012)	Finland	63	11	17.46	34	53.97	18	28.57	126	56	44.44	70	55.56
Total		1,554	277	17.82	732	47.10	545	35.07	3,108	1,286	41.38	1,822	58.62
AVG				17.65		50.39		31.96			42.85		57.16
Lucht et al. (2009)	Germany	289	37	12.8	114	39.45	138	47.75	578	188	32.53	390	67.47
Wermter et al. (2010)	Germany	100	11	11	49	49	40	40	200	71	35.5	129	64.5
Total		389	48	12.34	163	41.90	178	45.76	778	259	33.29	519	66.71
AVG				11.90		44.23		43.88			34.02		65.99
Costa et al. (2009)	Italy	192	18	9.37	94	48.96	80	41.67	384	130	33.85	254	66.15

Table 1 continued

Study	Country	n	OXTR rs53576						Alleles				
			AA	%	AG	%	GG	%	n	A	%	G	%
Total		192	18	9.37	94	48.96	80	41.67	384	130	33.85	254	66.15
AVG				9.37		48.96		41.67			33.85		66.15
Inoue et al. (2010)	Japan	203	73	35.96	98	48.28	32	15.76	406	244	60.1	162	39.9
Kawamura et al. (2010)	Japan	490	187	38.16	238	48.57	65	13.27	980	612	62.45	368	37.55
Liu et al. (2010)	Japan		–	–	–	–	–	–	880	543	61.7	337	38.3
Total		693	260	37.52	336	48.48	97	14.00	2,266	1399	61.74	867	38.26
AVG				37.06		48.425		14.515			61.42		38.58
Kim et al. (2010)	Korea	134	57	42.54	55	41.04	22	16.42	268	169	63.06	99	36.94
Kim et al. (2011)	Korea	99	50	50.51	40	40.4	9	9.09	198	140	70.71	58	29.29
Total		233	107	45.92	95	40.77	31	13.30	466	309	66.31	157	33.69
AVG				46.53		40.72		12.76			66.89		33.12
Bakermans-Kranenburg and Van IJzendoorn et al. (2008)	Netherlands	177	17	9.6	71	40.11	89	50.28	354	105	29.66	249	70.34
Luijk et al. (2011)	Netherlands	546	52	9.52	269	49.27	225	41.21	1,092	373	34.16	719	65.84
Riem et al. (2011)	Netherlands	80	10	12.5	38	47.5	32	40	160	58	36.25	102	63.75
Tops et al. (2011)	Netherlands	45	4	8.89	22	48.89	19	42.22	90	30	33.33	60	66.67
Verbeke et al. (2013)	Netherlands	141	17	12.06	53	37.59	71	50.35	282	87	30.85	195	69.15
Total		989	100	10.11	453	45.80	436	44.08	1,978	653	33.01	1,325	66.99
AVG				10.51		44.67		44.81			32.85		67.15
Walum et al. (2012)	Sweden	2,309	–	–	–	–	–	–	4,618	–	35	–	65
Total		2,309							4,618		35		65
AVG													
Park et al. (2010)	UK	110	8	7.27	41	37.27	61	55.45	220	57	25.91	163	74.09

Table 1 continued

Study	Country	n	OXTR rs53576						Alleles				
			AA	%	AG	%	GG	%	n	A	%	G	%
Total		110	8	7.27	41	37.27	61	55.45	220	57	25.91	163	74.09
AVG													
Chang et al. (2014)	USA	1,042	–	–	–	–	–	–	2,086	–	0.33	–	0.67
Cornelis et al. (2012)	USA	1,229	179	14.56	559	45.48	491	39.95	2,458	917	37.31	1,541	62.69
Jacob et al. (2007)	USA	114	9	7.89	44	38.6	61	53.51	228	62	27.19	166	72.81
Kim et al. (2010)	USA	108	13	12.04	41	37.96	54	50	216	67	31.02	149	68.98
Kim et al. (2011)	USA	152	33	21.71	68	44.74	51	33.55	304	134	44.08	170	55.92
Krueger et al. (2012)	USA	108	9	8.33	43	39.81	56	51.85	216	61	28.24	155	71.76
Luijk et al. (2011)	USA	522	62	11.88	234	44.83	226	43.3	1,044	358	34.29	686	65.71
Marsh et al. (2012)	USA	35	3	8.57	14	40	18	51.43	70	20	28.57	50	71.43
Poulin et al. (2012)	USA	447	32	7.16	185	41.39	230	51.45	894	249	27.85	645	72.15
Poulin et al. (2013)	USA	704	59	8.38	284	40.34	361	51.28	1,408	402	28.55	1,006	71.45
Sturge-Apple et al. (2012)	USA	193	11	5.70	64	33.16	118	61.14	386	86	22.28	300	77.72
Tabak et al. (2013)	USA	162	17	10.49	61	37.65	84	51.85	324	95	29.32	229	70.68
Tost et al. (2010)	USA	309	34	11	140	45.31	135	43.69	618	208	33.66	410	66.34
Total		5,125	461	11.29	1,737	42.54	1,885	46.17	10,252	2,659	32.56	5,507	67.44
AVG				10.64		40.77		48.58			28.67		63.72

Table 2 Aggregate data on OXTR rs53576, 5-HTTLPR, cultural values, economic indices, pathogen prevalence and major depression prevalence

	OXTR rs53576			5-HTTLPR			Hofstede's cultural value		Suh's cultural value		Economic indices		Pathogen prevalence		Major depression Prevalence(%)
	N	%A	%G	N	%S	%L	Indi-Coll	reverse	Indi-Coll	reverse	GDP	Gini	PathogenHist	PathogenCont	
Australia	185	33.0	67.0	1,758	45.9	54.1	90	10	9.00	1.00	67,723	30.5	−0.2	27	27.40
Canada	422	32.1	67.9	479	47.0	53.0	80	20	8.50	1.50	52,232	23	−1.29	26	10.80
China	1,718	65.3	34.7	1,896	75.2	24.8	20	80	2.00	8.00	6,076	47	1	37	3.60
Finland	1,491	41.4	58.6	4,269	42.5	57.5	63	37	7.15	2.85	46,098	26	−0.8	25	9.45
Germany	389	33.3	66.7	4,105	43.0	57.0	67	33	7.35	2.65	41,513	28	−0.93	24	9.90
Italy	192	33.9	66.1	876	48.5	51.5	76	24	6.80	3.20	33,115	33	0.22	26	9.90
Japan	693	61.8	38.2	1,176	80.3	19.7	46	54	4.30	5.70	46,736	38.1	0.51	28	7.60
Korea	233	66.3	33.7	931	79.5	20.5	18	82	2.40	7.60	23,113	35.1	0	32	3.60
Netherlands	989	33.0	66.0	989	42.7	57.3	80	20	8.50	1.50	46,142	30.9	−0.93	24	17.90
Sweden	2,309	34.7	65.3	752	43.6	56.4	71	29	7.55	2.45	55,158	23	−0.93	25	19.50
UK	110	25.9	74.1	5,888	44.0	56.0	89	11	8.95	1.05	38,589	34	−0.96	26	18.30
USA	5,125	32.7	67.3	4,162	44.5	55.5	91	9	9.55	0.45	49,922	45	−0.86	29	21.40

Cross-national samples of pathogen prevalence

Given the association between pathogen prevalence and the cultural value of individualism-collectivism (Fincher et al. 2008), the current study used data of both contemporary and historical pathogen prevalence for multiple regression analyses and mediation analyses (Table 2).

Cross-national samples of lifetime prevalence of major depression disorder

Data on global lifetime prevalence of major depression disorder were compiled from the world mental health surveys hosted by World Health Organization (Kessler and Üstün 2008; Chiao and Blizinsky 2010) and three peer-reviewed publications. The mediation analyses included the 12 nations (Australia, Finland, Germany, Italy, Japan, Korea, the Netherlands, People's Republic of China, Sweden, Canada, UK and USA) (Table 2).

Statistical analysis

Standard multiple regression and mediation analytic techniques were used to explore the relationship among cultural traits of collectivism-individualism, the allelic frequency of OXTR rs53576 and global prevalence of pathogens. First, multiple regression analyses were conducted to examine whether cultural values of individualism-collectivism predict gene frequency of the oxytocin receptor gene rs53576 across 12 nations. Second, multiple regression analyses were conducted to examine whether genetic (allelic frequencies of 5-HTTLPR and OXTR rs53576), economic and disease factors predict cultural values of individualism-collectivism across 12 nations. Third, mediation analyses were conducted to determine the extent to which the allele frequency of OXTR rs53576 mediates the associations between pathogen prevalence and cultural values of individualism-collectivism across the 12 nations. Fourth, multiple regression analyses were conducted to examine whether the allelic frequency of OXTR rs53576 predict lifetime prevalence of major depression disorder across the 12 nations. Finally, mediation regression analyses were conducted to determine the extent to which cultural values of individualism-collectivism mediate the association between OXTR rs53576 allelic frequency and major depression disorder prevalence across the 12 nations. The Sobel test (Sobel 1982) was conducted to confirm the significance of the mediator in the mediation analyses.

Geographical regions defined by nation served as the unit of analysis for all primary analyses given that numerous prior studies have shown that geopolitical regions are reliable proxies of societal cultures (Schwartz 2004; Fincher et al. 2008). In addition, each study also served as the unit of analyses in the following correlation analyses that explored the relationship between prevalence of the A allele and cultural values of individualism-collectivism.

Results

The associations between OXTR rs53576 and cultural values

We first assessed the global association between the allelic frequency of OXTR rs53576 and cultural values indexed by the differential collectivism-individualism scores. This revealed a significant correlation between A allelic frequency of OXTR re53576 and collectivistic cultural values ($r(38) = 0.93$, $p < 0.001$, Fig. 1a), suggesting that populations dominated by stronger collectivistic cultures comprise more A carriers of OXTR rs53576. The strong correlation between the prevalence of A allele and collectivistic cultural values was replicated when the modified Suh's index of collectivism cultures was used ($r(38) = 0.94$, $p < 0.001$, Table 3). The analysis based on nation units also revealed that increased collectivism was significantly positively correlated with increased prevalence of A alleles, irrespective of the difference within a nation group ($r(12) = 0.95$ and 0.95, ps < 0.001, Fig. 1b; Table 3).

We also conducted a multiple regression analysis to determine the specificity of the association between OXTR rs53576 and collectivistic values. The differential collectivism-individualism score was the criterion variable. Predictor variables include the frequency of A allele carriers and four other economic and health factors (i.e., GDP per capita, Gini index, historical and contemporary pathogen prevalence,

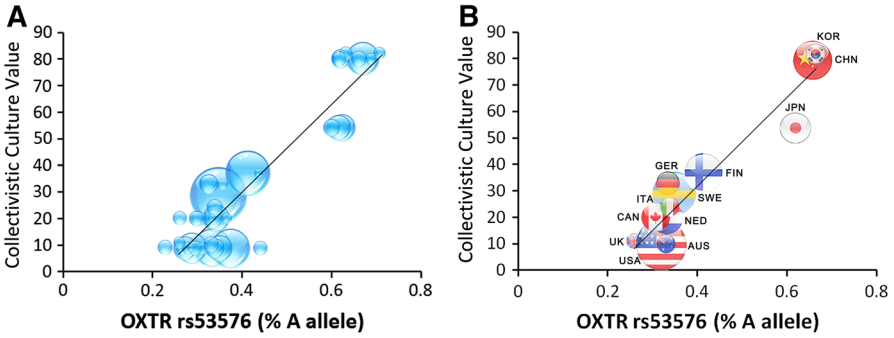


Fig. 1 Illustrations of the correlations between two levels of OXTR rs53576 allele frequency and collectivistic cultural values

Table 3 Correlations between two levels of OXTR rs53576 allele frequency and two measures of individualism/collectivism

	Criterion variable	Predictor variables	β	t	*p* value
By publication (n = 38)	IND-COL(Hofstede)	% A allele	0.93	15.20	$p < 0.001$***
	IND-COL(Suh)	% A allele	0.94	16.35	$p < 0.001$***
By nation (n = 12)	IND-COL(Hofstede)	% A allele	0.95	9.57	$p < 0.001$***
	IND-COL(Suh)	% A allele	0.95	10.01	$p < 0.001$***

*** $p < 0.001$

Table 4 Results from multiple regression analyses examining the association between cultural values of individualism–collectivism and the oxytocin receptor gene rs53576 across nations

Criterion variable	Predictor variables	β	t	*p* value
IND-COL (Hofstede)	% A allele	0.85	12.66***	$p < 0.001$***
	GDP	−0.34	−6.74**	$p = 0.001$**
	Gini index	−0.29	−4.79**	$p < 0.01$**
	pathogen historical	−0.13	−2.12	$p = 0.08$
	pathogen contemporary	0.15	1.68	$p = 0.14$
IND-COL (Suh)	% A allele	0.70	9.19***	$p < 0.001$***
	GDP	−0.35	−5.95**	$p = 0.001$**
	Gini index	−0.24	−3.46*	$p = 0.01$*
	pathogen historical	0.14	2.05	$p = 0.09$
	pathogen contemporary	0.05	0.51	$p = 0.63$

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Table 5 Results from the mediation regression analysis examining the relationship among oxytocin receptor gene rs53576, serotonin transporter gene and cultural values of individualism-collectivism across nations

Criterion variable	Predictor variables	β	t	*p* value
IND-COL(Hofstede)	% A allele	1.32	4.16	$p < 0.005$**
	% S allele	−0.39	−1.22	$p = 0.25$
IND-COL(Suh)	% A allele	0.97	2.95	$p < 0.02$*
	% S allele	−0.02	−0.06	$p = 0.96$

* $p < 0.05$

Fincher et al. 2008). Results indicated that the A allelic frequency was the most significant predictor of collectivistic values across the 12 nations ($\beta = 0.85$, $p < 0.001$, Table 4). This result was replicated using Suh's index of collectivistic values ($\beta = 0.70$, $p < 0.003$, Table 4).

We further conducted a multiple regression analysis to determine whether the frequency of A allele carriers of OXTR rs53576 can predict collectivistic cultural values when controlling the frequency of S allele carriers of 5-HTTLPR. The criterion variable was collectivistic cultural value. The predictor variables were the frequency of A allele carriers of OXTR rs53576 and frequency of S allele carriers of 5-HTTLPR. It was found that only A allele frequency of OXTR rs53576 was a significant predictor ($\beta = 1.32$, $p < 0.005$, Table 5) and this was replicated when Suh's index of collectivistic value was used ($\beta = 0.97$, $p < 0.05$, Table 5).

OXTR mediates associations between pathogen and cultural values

Given that S allelic frequency of 5-HTTLPR mediates the association between historical pathogen prevalence and collectivistic cultural values (Chiao and

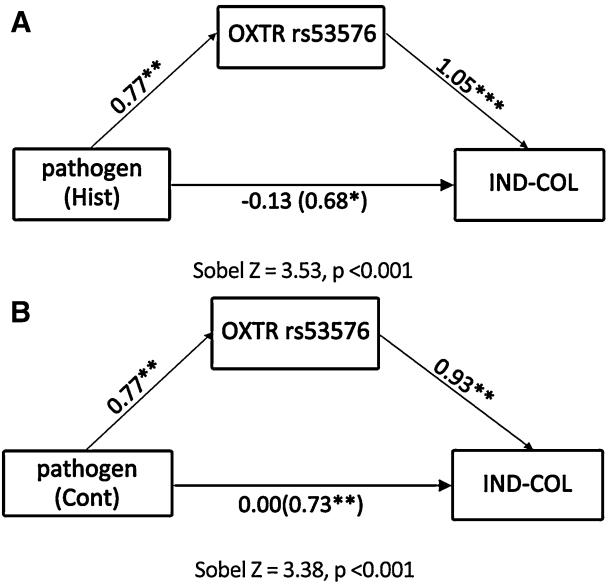
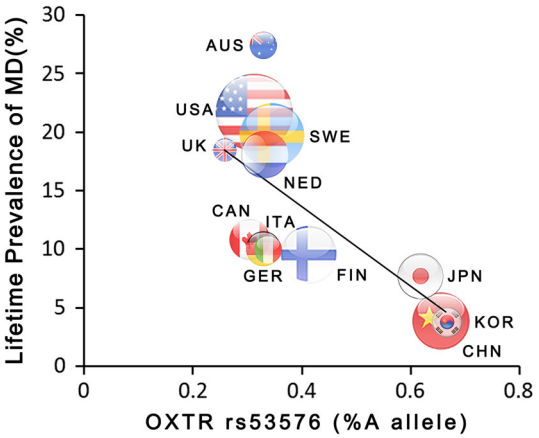


Fig. 2 **a** Illustration of mediation analyses among historical pathogen prevalence, A allele frequency of OXTR rs53576 and collectivistic cultural values across the 12 nations. **b** Illustration of mediation analyses among contemporary pathogen prevalence, A allele frequency of OXTR rs53576 and collectivistic cultural values across the 12 nations

Fig. 3 Illustration of the correlation between OXTR rs53576 allele frequency and lifetime prevalence of major depressive disorder



Blizinsky 2010), we also tested the specificity of the mediating role of the allelic frequency of OXTR rs53576 in the association between contemporary and historical pathogen prevalence and collectivistic cultural values. In the first step, we sought to determine whether contemporary and historical pathogen prevalence was associated with the allelic frequency of OXTR rs53576 as well as collectivistic cultural values across nations. The prevalence of both contemporary and historical pathogen was significantly positively correlated with the frequency of A allele carriers of OXTR

Table 6 Results from the mediation regression analysis examining the relationship among oxytocin receptor gene rs53576, cultural values of individualism-collectivism and major depressive disorder across nations

Criterion variable	Predictor variables	β	t	*p* value
Major depressive disorder	% A allele	0.63	1.11	$p = 0.30$
	IND-COL(Hofstede)	−1.42	−2.51	$p < 0.05$*
Major depressive disorder	% A allele	0.66	1.11	$p = 0.30$
	IND-COL(Suh)	−1.45	−2.43	$p < 0.05$*

* $p < 0.05$

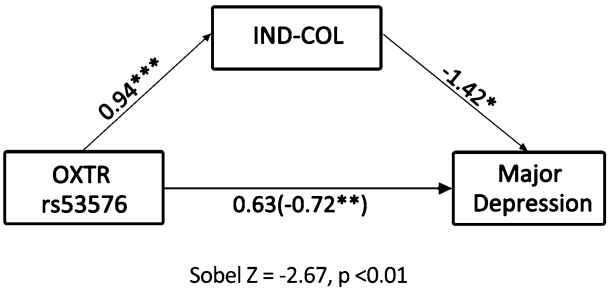


Fig. 4 Illustration of the mediation analyses among A allele frequency of OXTR rs53576, collectivistic cultural values and lifetime prevalence of major depression disorder across the 12 nations

rs53576 (historical: $\beta = 0.77$, $p < 0.005$; contemporary: $\beta = 0.77$, $p < 0.005$). In addition, across the 12 nations, the prevalence of both contemporary and historical pathogen positively predicted the collectivistic cultural values (historical: $\beta = 0.68$, $p < 0.02$; contemporary: $\beta = 0.73$, $p < 0.01$). In the second step, we examined whether the frequency of A allele carriers of OXTR rs53576 was associated with collectivistic cultures across the 12 nations. This revealed that the frequency of A allele was a significantly positive predictor of collectivistic cultural values ($\beta = 0.94$, $p < 0.001$, Fig. 1b), nations with a higher frequency of A allele carriers of OXTR rs53576 showed higher collectivistic cultural values.

In the mediation regression, when both contemporary pathogen prevalence and A allelic frequency of OXTR rs53576 were included as predictors of global collectivistic cultural values across 12 nations, the frequency of A allele carriers remained a reliable predictor ($\beta = 0.93$, $p = 0.001$, Fig. 2a), whereas the effect of contemporary pathogen prevalence decreased significantly (from $\beta = 0.73$ to $\beta = 0.00$; Sobel test $Z = 3.38$, $p < 0.001$, Fig. 2a). Similarly, when both historical pathogen prevalence and the frequency of A allele carriers were included as predictors in the mediation regression, the frequency of A allele carriers remained a reliable predictor ($\beta = 1.05$, $p < 0.001$, Fig. 2b), whereas the effect of historical pathogen prevalence decreased significantly ($\beta = 0.68$ to $\beta = -0.13$; Sobel test $Z = 3.53$, $p < 0.001$, Fig. 2b). These results indicate a significant mediating role of

A allelic frequency between contemporary and historical pathogen prevalence and collectivistic cultural values.

Cultural values mediates associations between OXTR and mood disorders

Finally, as collectivistic cultural values mediates the association between S allele frequency of 5-HTTLPR and global prevalence of anxiety and mood disorders (Chiao and Blizinsky 2010), we conducted a mediation regression to test whether the frequency of A allele carriers of OXTR rs53576 is associated with negative affect such as lifetime prevalence of major depression disorder across cultures and whether such associations are mediated by cultural values. We first showed that the frequency of A allele carriers of OXTR rs53576 was significantly positively correlated with collectivistic cultural values ($\beta = 0.94$, $p < 0.001$, Fig. 1b). Moreover, across the 12 nations, the frequency of A allele carriers of the OXTR rs53576 was significantly negatively correlated with lifetime prevalence of major depression disorder ($\beta = -0.72$, $p < 0.01$, Fig. 3). Nations with more A allele carriers of OXTR rs53576 showed lower prevalence of major depression disorder. We then examined whether collectivistic cultural values were associated with major depression disorder across cultures. It was found that collectivistic cultural values were significantly negatively correlated with lifetime prevalence of major depression disorder ($\beta = -0.82$, $p = 0.001$). Nations with stronger collectivistic cultural values showed lower lifetime prevalence of major depression disorder. In the mediation regression analysis where both A allelic frequency of OXTR rs53576 and collectivistic cultural values were included as predictors of global lifetime prevalence of major depression disorder across the 12 nations, the collectivistic cultural values was a significant predictor ($\beta = -1.42$, $p < 0.05$, Table 6 and Fig. 4) whereas the effect of A allele frequency changed significantly (from $\beta = -0.72$ to $\beta = 0.63$; Sobel test $Z = -2.67$, $p < 0.01$, Table 6 and Fig. 4). The results suggest that the collectivistic cultural values significantly mediate the relationship between A allelic frequency and lifetime prevalence of major depression disorder.

Similarly, when Suh's index of collectivistic cultural values were used in the mediation analysis, frequency of A allele carriers of OXTR rs53576 was a significant positive predictor of collectivistic cultural values ($\beta = 0.94$, $p < 0.001$) and a negative predictor of lifetime prevalence of major depression disorder ($\beta = -0.72$, $p < 0.001$). The collectivistic cultural value was also a significant negative predictor of lifetime prevalence of major depression disorder ($\beta = -0.82$, $p = 0.001$). In the mediation regression where both A allelic frequency and Suh's index were included as predictors of global lifetime prevalence of major depression disorder across the 12 nations, collectivistic cultural value remained a reliable predictor ($\beta = -1.45$, $p < 0.05$), whereas the effect of A allele frequency changed significantly (from $\beta = -0.72$ to $\beta = 0.66$; Sobel test $Z = -2.61$, $p < 0.01$). These results suggest that A allelic frequency of OXTR rs53576 predicts lifetime prevalence of major depression disorder through collectivistic cultural values.

Discussion

The current work first showed evidence for the association between collectivistic cultural values and A allelic frequency of OXTR rs53576. There are more A allele carriers in nations that are more strongly dominated by collectivistic cultural values. This is similar to the association between S allelic frequency of 5-HTTLPR and collectivistic cultural values (Chiao and Blizinsky 2010). The association between collectivistic cultural values and A allelic frequency of OXTR rs53576 across nations stands when using different indexes of cultural values and when socioeconomic and health factors are controlled. This association is also evident when S allelic frequency of 5-HTTLPR is controlled.

Similar to the previous research (Chiao and Blizinsky 2010), our analyses showed positive correlations between contemporary (and historical) pathogen prevalence and collectivistic cultural values. Moreover, these associations are fully mediated by A allelic frequency of OXTR rs53576. Thus the mediating role of A allelic frequency of OXTR rs53576 here is similar to that of S allelic frequency of 5-HTTLPR. Previous behavioral genetics studies have shown an association between polymorphisms of 5-HTTLPR and depression (Pezawas et al. 2005). Moreover, the frequency of 5-HTTLPR S allele carriers who are more sensitive to negative emotion predicts decreased prevalence of mood disorder owing to collectivistic cultures (Chiao and Blizinsky 2010). Similarly, the current work found that the frequency of OXTR rs53576 A allele carrier with lower emotional sensitivity can predict the global prevalence of major depression disorder, and this association is mediated by collectivistic cultural values. It has been shown that OXTR rs53576 predicts symptoms of depression and anxiety across individuals (Thompson et al. 2014; McQuaid et al. 2013). The present work provides macro-scale evidence that cultural values play an adaptive role in buffering genetically vulnerable populations from a potentially increasing epidemiological prevalence of mental health disorders. In addition, genetic selection of OXTR rs53576 A allele within collectivistic cultures can explain the decreased prevalence of mood disorders like depression. Taken together, our results highlight the importance of genetic factors in explaining cultural differences, and how variation in cultural and genetic factors can interact to produce mental illness across the globe.

There has been biological evidence for the association between the serotonergic system and the oxytocinergic system. For example, both serotonin and oxytocin modulate affiliative responses to partners and offsprings (Emiliano et al. 2007). Both the serotonergic and oxytonergic system genes were associated with parenting (Bakermans-Kranenburg and Van IJzendoorn 2008), empathy (Luo et al. under review; Gyurak et al. 2013) and depressive symptoms (Pezawas et al. 2005; Thompson et al. 2011; McQuaid et al. 2013). In addition, Lee et al. (2003) found that serotonin stimulates hypothalamus to release oxytocin as precursor molecule. Galfi et al. (2005) further showed that the serotonergic system directly influences oxytocin secretion in rats. Moreover, serotonergic fibers have preferential input to oxytonergic regions in macaques and other animals (Emiliano et al. 2007). These findings indicate interactions between the oxytonergic and serotonergic systems in the brain. However, to date, it remains unclear how the two genes related to the

oxytonergic and serotonergic systems, OXTR and 5-HTTLPR, interact with each during evolution. Increasing evidence suggests that A compared to G allele carriers tend to exhibit lower emotional sensitivity such as empathy, emotional support seeking and maternal sensitivity (Rodrigues et al. 2009; Kim et al. 2010; Saphire-Bernstein et al. 2011; Bakermans-Kranenburg and Van IJzendoorn 2008; Walum et al. 2012). Our findings suggest a possibility that cultural values of individualism and collectivism are adaptive and may weaken the risks of genetic vulnerability (i.e., S allele carriers of 5-HTTLPR) for negative emotions (e.g., anxiety) through the selection of low emotional sensitivity genes (G allele carriers of OXTR rs53576). This, however, should be clarified in future research.

The present study is not without limitations. For example, our existing knowledge of cultural and genetic variation is limited as we examined data from only 12 nations. The results of the current work should be examined in future research when data from additional countries from Africa and the Middle East are reported. It is important to test the role of OXTR rs53576 in the association between 5-HTTLPR, pathogen prevalence, and cultural values across more countries and larger samples. In addition, causal inferences cannot be determined based correlational data reported in this study. Therefore, although the results of mediation analyses imply directionality, future studies are required to involve genotyping, behavioral priming of individualism-collectivism, and depression patients in order to advance out understanding of the causal links between genetic makeup, cultural value, and pathogen prevalence.

In summary, the current findings suggest significant relationships between cultural values of individualism-collectivism and allelic variation of OXTR rs53576, as well as the interplay between these variables in predicting prevalence of major depression disorder. The results reported in our study highlight the importance of culture-gene co-evolutionary theory in studying the predictive factors behind human's mental states and social behaviors. Future research should examine other specific genetic polymorphisms that may be associated with different dimensions of cultural values, as well as environment-culture-gene interactions that influence the psychological and neural processes underlying complex human behavior (Chiao and Blizinsky 2010; Chudek and Henrich 2011; Kim and Sasaki 2014).

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