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ORIGINAL RESEARCH

Gene–culture interactions: a multi-gene approach

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Abstract Previous studies have identified genetic variants linked to increased susceptibility to socio-cultural influences. These studies typically show that individuals with the more susceptible variant of a specific polymorphism exhibit social behavior more in accordance with surrounding cultural norms. Given limitations of the single gene approach, we propose to assess genetic susceptibility with a multi-gene index, composed of polymorphisms previously identified in gene–culture interaction studies. Specifically, we are interested in whether the combined susceptibility index moderates cultural differences in self-expression. In the present study, Americans and Koreans completed psychological and behavioral assessments of self-expression tendencies and provided DNA samples, which were genotyped for preselected *OXTR, 5HTR1A, SERT,* and *DRD4* polymorphisms. Results show that the genetic susceptibility index predicts a wider range of self-expression outcomes than what is predicted by individual polymorphisms. The findings underscore the importance of developing biologically and functionally informed models of genetic influence. Further the work demonstrates a model for examining the effects of multiple genes simultaneously and advances our understanding of how genetic and socio-cultural factors jointly contribute to shape social behaviors.

Keywords Culture · Genetics · Self-expression · Cultural neuroscience

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Introduction

A growing body of research has shown the interactive effects of genes and the environment on psychological outcomes (e.g., Bakermans-Kranenburg & van IJzendoorn 2011; Caspi et al. 2002, 2003; Taylor et al. 2006). The gene–environment (G × E) interaction framework proposes that environmental conditions may moderate the manifestation of the underlying genotype (Caspi et al. 2002, 2003). More recently, researchers have broadened the G × E conceptualization of "environment" beyond personal life experiences that differ in terms of quality (e.g., Belsky et al. 2007; Kim-Cohen & Gold 2009) to include the sociocultural context. Individuals carrying the variants associated with environmental susceptibility are proposed to show the greatest cultural divergence in behavioral tendencies like self-expression (Kim et al. 2010, 2011; see Kim & Sasaki 2014 for review).

While variation of single genes has been shown to moderate susceptibility to environmental influence, concerns have been raised about the reliability of using single target genes (Duncan & Keller 2011). Investigating the role of multiple genes had been proposed as a way to address this concern (e.g., Belsky et al. 2012, 2013; Docherty et al. 2011). Currently there is no clear multi-gene model for understanding increased social susceptibility. In the present study, we propose a polygenic approach to investigating gene–culture interactions. More specifically, we examine whether culture moderates the influence of genetic susceptibility assessed across multiple polymorphic sites on self-expressive tendencies. We predict that individuals at higher polygenic susceptibility would be more receptive to cultural input, and thus, would exhibit greater tendency to act in a culturally normative way.

Gene–culture interaction framework

Existing G × E research has shown that depending on genetic variation individuals may differ in their susceptibility to environmental inputs (Caspi et al. 2002, 2003). The G × E framework proposes that an individual may be genetically predisposed to a particular outcome, but that outcome will manifest phenotypically only under certain environmental conditions. Gene–environment interactions have been found across neurotransmitter systems with many genes, including the dopamine D_4 receptor gene (*DRD4*) (Bakermans-Kranenburg & van IJzendoorn 2006, 2011; Sasaki et al. 2013), oxytocin receptor gene (*OXTR*) (Chen et al. 2011), and monoamine oxidase A (*MAOA*) gene (Caspi et al. 2002; Foley et al. 2004; Kim-Cohen et al. 2006). For example, the adverse effects of childhood maltreatment were especially pronounced in children carrying the genotype of the *MAOA* gene linked with susceptibility (Caspi et al. 2002).

The gene–culture framework builds upon the G × E framework by expanding the notion of environment to include sociocultural factors, which can moderate the link between genetic variation and psychological outcomes. Culture, which comprises a mutually shared system of beliefs, values, and institutions, influences the development of psychology tendencies by defining norms and practices (Kitayama 2002; Markus & Kitayama 1991). G × C studies have highlighted the role of genes conceptualized as 'plasticity' genes with susceptible genotypes more

sensitive for better and for worse (Belsky et al. 2007). Variation of such genes may increase susceptibility to environmental input, including cultural influence.

A number of papers provide empirical evidence for the G × C framework. The *OXTR* rs53576 polymorphic region has been shown to moderate cultural differences in self-expressive behaviors, such as emotional support-seeking (Kim et al. 2010a) and emotional suppression (Kim et al. 2011). Similarly, variation in the serotonin 1A receptor gene (*5HTR1A*) polymorphism rs6295 moderated a cultural difference in holistic attention (Kim et al. 2010b). In addition, culture moderated the influence of serotonin transporter polymorphism (5-HTTLPR) on sensitivity to disappearance of facial expressions (Ishii et al. 2014a). The Exon 3 variable number tandem repeat (VNTR) polymorphism of the D_4 receptor gene (*DRD4*) moderates cultural divergence on the overarching independence–interdependence social orientation (Kitayama et al. 2014). Carrying the susceptibility genotype was associated with cultural divergence in social orientations, with genetically susceptible European Americans exhibiting greater independence while genetically susceptible Asian Americans exhibited greater interdependence. These studies demonstrate the explanatory power of the G × C approach, which provides a framework for understanding how genes may predispose people to susceptibility to cultural influence.

Genetic susceptibility index

In the present study, we propose a polygenic approach to combining variation at polymorphic regions within four genes: *OXTR, 5HTR1A, SERT,* and *DRD4*. The polymorphisms were selected on the basis of previous G × E and G × C results, which implicate these variants in susceptibility. Further, studies of the neurotransmitter systems associated with these genes provide behavioral and anatomical evidence for grouping these genes into a composite index.

OXTR encodes for the oxytocin receptor and is localized to human chromosome 3 (Gimpl & Fahrenholz 2001; Simmons et al. 1995). One variant, *OXTR* rs53576, is a single-nucleotide polymorphic site of the oxytocin receptor gene, located in intron 3 of the coding region (Gimpl & Fahrenholz 2001). Although its molecular mechanisms are unknown, *OXTR* rs53576 has been associated with differences in amygdala activation and in hypothalamic structure (Tost et al. 2010). Behaviorally, individuals homozygous for the G-allele of *OXTR* rs53576 show more sensitive parenting behavior (Bakermans-Kranenburg & van IJzendoorn 2008), more responsiveness to infant crying (Riem et al. 2011), more prosocial temperament (Tost et al. 2010), and greater empathic accuracy (Rodrigues et al. 2009).

5HTR1A and *SERT* are both involved in serotonin signaling. *5HTR1A* encodes for the serotonin HT_{1A} receptor (de Almedia & Mengod, 2008; Ito et al. 1999). We examined the role of the *5HTR1A* rs6295 [aka, C(-1019)G] polymorphism, which is located in the promoter region of the *5HTR1A* gene. The G-allele of the *5HTR1A* rs6295 prevents binding of repressor proteins, which increases gene expression and hence reduces serotonin levels, and has been linked to depression and neuroticism (Huang et al. 2004; Lemonde et al. 2003; Strobel et al. 2003).

SERT encodes for the serotonin transporter protein, which removes serotonin from the synaptic cleft. We examined the 5-HTTLPR polymorphic region located within the promoter region of the serotonin transporter gene (*SLC6A4*) comprising a short (S) allele and a long (L) allele version. The S-allele of 5-HTTLPR is linked to decreased 5-HTT mRNA expression resulting in higher serotonin concentrations in the synapse compared to the L-allele (Lesch et al. 1996). The S-allele of the serotonin transporter gene is implicated in increased negative emotion tendencies, including anxiety (Munafo et al. 2005; Sen et al. 2004), harm avoidance (Munafo et al. 2005), and fear conditioning (Lonsdorf et al. 2009).

DRD4 encodes for the dopamine D_4 receptor and contains a 48-base pair variable number tandem repeat (VNTR) in exon III, which ranges from 2- to 11-repeats (van Tol et al. 1992). The 2-/7-repeat versions reduce gene expression, compared to the 4-repeat version (Schoots & Van Tol 2003; see also Reist et al. 2007 and Wang et al. 2004 for evidence on similarity of 2- and 7- repeats). Behaviorally 2-/7-repeat variants of the *DRD4* VNTR polymorphism have been linked to increased novelty or sensation seeking (Ebstein et al. 1996), gambling (de Castro et al. 1997), risk taking (Kuhnen & Chiao 2009), decreased altruism (Bachner-Melman et al. 2005), and reduced sensitivity to fairness (Zhong et al. 2010).

Integrative approach

While the previous studies have shown some specificity in behavioral effects (e.g., oxytocin linked with socioemotional sensitivity), overall the genetic variants have all been linked to susceptibility to environment, including culture. Furthermore, studies focusing on the effects of the associated neurotransmitter systems have provided behavioral and anatomical reasoning for integrating the effects of these genes. Behaviorally, the neurotransmitter systems—dopamine, oxytocin, and serotonin—have all been implicated in social affiliative behaviors (e.g., Bartz et al. 2011; Knutson et al. 1998; Tamir & Mitchell 2012; Love 2014), including autism spectrum disorders, which are marked by impaired social communication skills (Anderson et al. 1990; Holden & Liu 2005; Modahl et al. 1992, 1998). Further, experimental manipulations, which alter signaling activity, have demonstrated the role of these neurotransmitter systems in social decision-making processes (Declerck et al. 2010; Mikolajczak et al. 2010; Sevy et al. 2006; Wood et al. 2006).

In addition, the neurotransmitter systems and target genes of interest are anatomically and functionally related within the brain, specifically within the hypothalamus. In the paraventricular nuclei (PVN) and supraoptic nuclei (SON) of the hypothalamus, oxytocin is synthesized and released. Dopamine D_4 receptors and serotonin HT_{1A} receptors are expressed in the hypothalamic PVN and SON regions and appear to modulate oxytocin neuronal activation. Stimulation of dopamine D_4 receptors (Succu et al. 2007) and serotonin HT_{1A} receptors (Jorgensen et al. 2003) increases oxytocin release. Together, the evidence supports grouping the genes on the basis of their behavioral, biological, and anatomical relationships.

The present work

The present study aims to test the G × C model using the genetic susceptibility index (GSI) based on polymorphisms from the four genes implicated in environmental susceptibility. More specifically, we examined the interaction between the GSI and culture (i.e., American and Korean participants) in shaping the tendencies of self-expression, which have been shown to differ between cultures with European Americans exhibiting greater expressive tendencies than Asians (e.g., Butler et al. 2009; Kim and Sherman 2007; Kim et al. 2008; Lee et al. 2009; Matsumoto et al. 2008).

We predicted a gene–culture interaction on expressive tendencies using the GSI. Among Americans, increased genetic susceptibility was predicted to be associated with greater expressive tendencies (i.e., less emotion suppression, greater valuation of self-expression, and more emotional support seeking), while Koreans were predicted to show the opposite pattern. Further we examined the relationship between genetic susceptibility and cognitive reappraisal, an emotion regulation strategy that is comparably used in both cultures (Gross & John 2003; Matsumoto et al. 2008). Given the lack of cultural difference, culture should not moderate the association between the GSI and cognitive appraisal use (for a relevant finding, see Kim et al. 2011). This allows us to examine whether the susceptibility score predicts psychological outcomes that do not differ across cultures, and thus, offers a contrasting case to the interactive prediction.

Moreover, we compared the results using the GSI with the results yielded using the single gene approach to see if the GSI yields overall more reliable results predicted by our theoretical framework. And finally, we sought to examine whether combining multiple genes provides the additional benefit of balancing cross-ethnic comparisons, which are often challenging with single genes due to ethnic differences in genotypic distributions.

Method

Participants

Participants included 100 Koreans (59 % female; $M_{age} = 22.4$) and 158 Americans (61 % female, $M_{age} = 19.3$, 47 East Asian Americans and 111 European Americans). East Asian American (i.e., those who identified themselves as from Korea, Japan, or China) and European American participants were recruited in the United States based on their self-categorized ethnicity. Korean participants were recruited in Korea on the basis of birth country and name at recruitment. Participants were recruited through the psychology department participant pool and class announcements. For participation, participants received either course credit or monetary compensation ($10 or 10,000₩ respectively).

Procedure and materials

As part of a larger collection of questionnaires,[1] participants completed the following measures on a computer: the Value of Expression Questionnaire, VEQ (Kim & Sherman 2007), the Emotion Regulation Questionnaire, ERQ (Gross & John 2003), and the Brief COPE (Carver 1997). The VEQ includes 11 items to assess the extent to which participants value self-expression on a 1 (*strongly disagree*) to 8 (*strongly agree*) scale ($\alpha_{U.S.} = 0.81$ and $\alpha_{Korea} = 0.76$). The ERQ includes 10 items to assess individual differences in two emotion regulation strategies: emotion suppression ($\alpha_{U.S.} = 0.736$ and $\alpha_{Korea} = 0.709$) and cognitive reappraisal ($\alpha_{U.S.} = 0.843$ and $\alpha_{Korea} = 0.818$), on a scale from 1 (*not at all*) to 7 (*very much*). Two items from the Brief Cope measured emotional support seeking with low anchor (I haven't been doing this at all) to high anchor (I've been doing this a lot), measured on 1–4 in the US ($r = 0.677$, $p < 0.001$) and 1–7 in Korea ($r = 0.596$, $p < 0.001$).[2] After completing the questionnaires, participants answered demographic questions and provided saliva samples for genotyping. All measures were originally developed in English and translated into Korean using the back-translation method.

In addition to the questionnaires described above, American participants completed behavioral tasks. The recruited participants were asked to bring a friend of the same ethnicity and gender. The average length of friendship was 18.8 months and did not differ by ethnicity, $t(156) = 1.000$, $p = 0.319$. Together, they went through a situation in which one member of the pair experienced a stressor. The main participant (support recipient) worked on a challenging cognitive task, while the friend (support provider) completed a simple questionnaire. The roles were supposedly randomly assigned; in fact, the main participant was always assigned to the support recipient role. The challenging task, which consisted of 20 items from the Remote Association Test, was described as predictive of performance on standardized tests relevant to graduate school (e.g., the GRE). The experimenter told the support recipient to solve the questions as accurately and quickly as possible and that they would be timed with a limit of 10 min. The support provider was instructed to complete a straightforward questionnaire described as not taking more than seven to eight minutes to complete, leaving several minutes for the friend to provide support. During the scenario, the interactions between the friendship pairs were recorded with a concealed video camera.

The ten-minute videotapes were coded by two undergraduate judges (from a team of six: three European American, two Asian American, and one Latino American), who were unaware of the study hypotheses and participants' genotypes. The judges counted and recorded the number of times emotional social support was sought (e.g., saying "I feel stressed") within thirty-second periods, which were summed to yield a total count of emotional support-seeking incidences over the 10 min

[1] Published results in Kim et al. 2011 and Sasaki et al. 2013 used the same data set.

[2] This discrepancy is due to programming error and thus, we standardized within each culture to put values on a comparable dimension. Given the standardization, we do not discuss the main effect of culture for this measure.

duration. Coders also provided an overall rating of emotional support seeking from 1 (not at all present) to 7 (strongly present). For rating emotional support seeking, intercoder correlations (r) among the coder pairs ranged from 0.749 to 0.900 (mean = 0.828). For counting incidences of emotional support seeking, intercoder correlations ranged 0.359–1.000 (mean = 0.715). Since reliability was high, the ratings and incidence counts were averaged for each pair.

Genotyping

Saliva samples were collected using an Oragene Saliva kit OG-500. DNA was extracted following the manufacturer recommendation (DNA Genotek, Ontario, Canada). DNA was quantified using A260/A280 ratio.

The *5HTR1A* rs6295 polymorphism was genotyped using a 5′ nuclease assay to discriminate between the two alleles (Taqman SNP Genotyping Assay C__11904666_10, Applied Biosystems Inc.). Polymerase chain reactions (PCR) were performed using 5-ml reaction volumes in 384-well plates with 5 ng of DNA. The standard protocol provided with the kit was followed. End point reads of fluorescence levels were obtained with an ABI 7900HT Sequence Detection System.

To identify the genotypes of the *5-HTTLPR* rs25531 polymorphism, the forward primer was labeled with 6FAM-5′-GGC GTTGCC GCT CTG AAT GC-3′, the reverse primer was unlabelled 5′-GAG GGA CTGAGC TGG ACA ACC AC-3′, which yielded 484-bp (short) and 527-bp (long) fragments. PCR was performed in a total volume of 25 µl, containing 50 ng of DNA; 1 µl of each primer (10 µM stock); 1.5 µl of (25 mM)MgCl2; 2 % DMSO (v/v); 2.5 U Amplitaq Gold DNA polymerase (Applied Biosystems, Foster City, California); 2ul of Deaza dNTP (2 mM each dATP, dCTP, dTTP, 1 mM dGTP, 1mM deaza dGTP). PCR cycling conditions consisted of (1) a 12 min denaturation at 94 °C; (2) 8 cycles for 30 s at 94 °C, varied annealing temperatures consisting of 30 s at 66 °C (2 cycles), then 65 °C (3 cycles), then 64 °C (3 cycles), followed by hybridization for 1 min at 72 °C; (3) 35 cycles with an annealing temperature of 63 °C and the same denaturation and hybridization parameters; and (4) a final extension for 20 min at 72 °C. The PCR products were electrophoresed on an ABI 3730 DNA analyzer (Applied Biosystems) with a LIZ1200 size standard (AppliedBiosystems). Data collection and analysis used Genemapper software (Applied Biosystems). Genotyping procedures for OXTR and DRD4 are described in detail in Kim et al. (2011; OXTR) and Sasaki et al. (2013; DRD4).

Genetic susceptibility index (GSI)

We created an index of genetic susceptibility to environmental input by averaging across the four candidate polymorphisms. To assign the score associated with variation for each polymorphism, we employed an additive model (Lewis 2002; Minelli et al. 2005), which assumes a monotonic increase in association with environment susceptibility, moving from zero to one and one to two copies of the relevant allele. The genes appear independent with the exception of *OXTR* and

DRD4 among European Americans, which are positively correlated (see Table 1). Since only one set of genes correlated in one group and because no evidence exists to determine the exact contributions of the separate polymorphisms to environmental susceptibility, we used an unweighted count of alleles averaging across the four genes (for a similar approach, see Belsky et al. 2012, 2013). For *SERT*, *5HTR1A*, and *OXTR*, the most susceptible homozygote based on existing literature was assigned a value of 2; the theoretically least susceptible homozygote was assigned a value of 0; heterozygotes were assigned a value of 1. For *SERT*, the following values were assigned: *s/s* (2), *s/l* (1), *l/l* (0); for *5HTR1A*: G/G (2), C/G (1), C/C (0); for *OXTR*: G/G (2), A/G (1), A/A (0). For *DRD4*,[3] participants were divided into individuals having two 2- or 7-repeat alleles (i.e., 2/2, 2/7, or 7/7 variants, valued as 2), at least one 2- or 7-repeat allele (valued as 1), and no 2- or 7-repeat allele (valued as 0). Thus, the overall genetic susceptibility index ranges from 2 to 0.

Results

Genotype distributions and GSI score

Consistent with previous studies (e.g., Chang et al. 1996; Chiao & Blizinsky 2010; Kim et al. 2010a), we found significant ethnic differences in the allelic distributions of the selected polymorphisms (see Table 2). However, with the GSI score, a one-way ANOVA comparing Koreans to East Asian Americans to European Americans revealed no significant differences between the cultural groups ($M_{\text{Korean}} = 0.995$, $SD_{\text{Korean}} = 0.030$; $M_{\text{Asian American}} = 0.913$, $SD_{\text{Asian American}} = 0.046$, $M_{\text{European American}} = 0.913$, $SD_{\text{European American}} = 0.029$), $F(2, 233) = 2.245$, $p = 0.108$. Further, there was no difference between the two cultural distributions, according to the two-sample Kolmogorov–Smirnov test ($D = 0.119$, $p = 0.3638$). In addition to the results described below using the GSI, additional moderated hierarchical regression analyses were run with each individual gene. Culture was entered at step 1, the GSI at step 2, and the interaction term at step 3. For the behavioral measures, which were collected only with Americans, regression analyses were run with the GSI in the first step, and no additional interactive or cultural effects.

Findings for culturally variant self-expression measures

To examine whether culture moderates the link between genetic susceptibility and an index of self-expression tendencies, we calculated an index of self-expressive

[3] Previous research has shown that the distribution of *DRD4* variants differs across ethnic groups (Chang et al. 1996). In Caucasian populations, individuals carrying the 7-repeat allele exhibit the greatest antisocial tendencies (Ebstein et al. 1996), while such tendencies are highest among 2-repeat allele carriers in East Asian populations (Zhong et al. 2010) or the 2- and 7-repeat alleles combined (Reist et al. 2007). Thus, we grouped the 2- and 7-repeat alleles together as susceptibility variants and treated all other alleles as non-susceptibility variants across our American and Korean participants (see also Kitayama et al. 2014; Sasaki et al. 2013 for the same grouping).

Table 1 Correlations among polymorphisms included in the gene composite index

	European Americans		Asian Americans		Koreans	
	r(N)	*p*	*r*(N)	*p*	*r*(N)	*p*
SERT–DRD4	−0.117(108)	0.227	−0.121(44)	0.432	−0.001(97)	0.989
SERT–OXTR	−0.084(106)	0.394	0.175(45)	0.250	−0.108(99)	0.285
SERT–HTR1A	−0.125(103)	0.209	0.119(43)	0.448	0.012(98)	0.904
DRD4–OXTR	−0.322(104)	0.001	−0.242(42)	0.123	−0.081(96)	0.431
DRD4–HTR1A	0.038(101)	0.706	0.198(40)	0.220	0.077(95)	0.459
OXTR–HTR1A	0.005(104)	0.963	−0.178(43)	0.254	0.103(98)	0.312

Given the distributional differences among the ethnic groups, we perform this analysis separately to avoid ethnic stratification

Table 2 Distributions of *OXTR*, *5HTR1A*, *SERT*, and *DRD4* polymorphism variants

				Between-culture effect $\chi^2(2)$	*p*
	OXTR			30.301	<0.001
	AA	AG	GG		
Korean (0.970)*	50	40	9		
American (0.522)	33	68	51		
	5HTR1A			12.024	0.002
	CC	CG	GG		
Korean (0.891)	5	38	55		
American (0.982)	25	67	55		
	SERT			50.751	<0.001
	L/L	S/L	S/S		
Korean (0.923)	4	33	63		
American (0.990)	44	79	34		
	DRD4			3.419	0.181
	No 2- or 7-	One 2 or 7-	Two 2- or 7′s		
Korean (0.995)	71	23	3		
American (1)	94	51	7		

* *Note* value in parentheses indicates Hardy–Weinberg equilibrium *p* value

tendencies and then conducted a moderated hierarchical regression analysis. The culturally variant self-expressive measures—value of expression, emotion suppression, and emotional support seeking—were combined into an index of self-expressive tendencies ($\alpha_{\text{Americans}} = 0.822$, $\alpha_{\text{Koreans}} = 0.812$). The culture variable (grouped to compare East Asian Americans and European Americans to Koreans)

Table 3 The main effects of culture for expression-related and coping outcomes

	Culture	N	Mean	Std. Error	Between-culture effect	
					t(df)	*p*
Value of expression	American	102	5.5590	0.08423		
	Korean	100	5.3484	0.08629		
					1.747(200)	0.082
Emotional suppression	American	158	3.3017	0.08038		
	Korean	100	3.7050	0.12021		
					2.900(256)	0.004
Cognitive reappraisal	American	158	5.0468	0.07004		
	Korean	100	4.8943	0.10305		
					0.064(256)	0.206
Incidences of emotional support seeking	American	146	2.3870	0.15811		
	Korean	NA	–	–		
					NA	
Rating of emotional support seeking	American	145	1.7092	0.04660		
	Korean	NA	–	–		
					NA	

Note Because emotional support seeking was standardized within each culture, we do not report mean levels here

was entered on step 1; the GSI on step 2; and the interaction term on step 3.[4] For cultural main effects, see Table 3. For results of regressions for each polymorphism, see Table 4.

At step 2, the main effect of the genetic susceptibility index was not significant, $\Delta R^2 = 0.000$, $F(1, 233) = 0.039$, $p = 0.843$. At step 3, the interaction was significant, $\Delta R^2 = 0.036$, $F(1, 232) = 8.752$, $p = 0.003$. Simple slope analysis showed that for Koreans, there was the predicted negative relationship between genetic susceptibility and the index of self-expressive tendencies, while for Americans, the relationship between genetic susceptibility and self-expressive tendencies was positive (see Fig. 1).

Behavioral emotional support seeking

We also examined actual support seeking among Americans. Because our Korean sample did not participate in the behavioral portion of the study, we looked at the simple relationship between the GSI and behavioral measures, considering it as the American half of the predicted interaction. We found a significant positive relationship between genetic susceptibility and the overall coder rating of emotion

[4] In all analyses, East Asian Americans' associations between GSI and expressive behavior outcomes statistically resembled those of European Americans, but not Koreans (see Kim et al. 2010b for the rationale for triangulation method). Thus we do not report separate analyses separating East Asian Americans from European Americans.

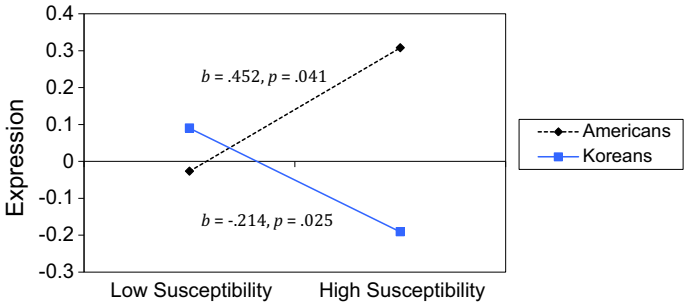

Fig. 1 Interaction between culture and genetic susceptibility on expression composite

seeking tendencies, $R^2 = 0.080$, $F(1, 127) = 11.115$, $p = 0.001$, and a marginal positive relationship between the genetic susceptibility index and the number of incidences of emotion support seeking, $R^2 = 0.027$, $F(1, 127) = 3.516$, $p = 0.063$.

Findings for cognitive reappraisal

To examine the link between genetic susceptibility and a non-culturally variant measure, we conducted similar moderated hierarchical regression analysis with cognitive reappraisal. We entered culture on step 1; GSI on step 2; and the interaction term on step 3. At step 2, the main effect of genetic susceptibility was statistically significant, $\Delta R^2 = 0.035$, $F(1, 233) = 8.467$, $p = 0.004$. At step 3, the interaction was not significant, as predicted, $\Delta R^2 = 0.005$, $F(1, 232) = 1.182$, $p = 0.278$ (see Table 4).

Discussion

Summary

The present study provides initial evidence of the benefits of applying a polygenic approach to gene–culture interactions. We found the predicted interactive effect between cultural context and the GSI with all outcome measures, such that polygenic predisposition to environmental susceptibility was associated with expressive-tendencies more consistent with cultural norms. For Americans, living in a cultural context emphasizing self-expression, individuals at higher genetic susceptibility valued self-expression more and suppressed emotion less, compared to less susceptible individuals. Koreans exhibited the reverse pattern, such that individuals at higher genetic susceptibility valued self-expression less and suppressed emotion more, compared to less susceptible individuals. As predicted for cognitive reappraisal, which does not differ between North American and East Asian cultures, the link between genetic susceptibility and reappraisal tendencies was not moderated by culture. Instead, for both Americans and Koreans, genetic susceptibility was associated with increased use of cognitive reappraisal coping

Table 4 Interaction of culture and each individual genetic polymorphism on expression-related and coping outcomes

		Gene			Gene x culture		
		ΔR^2	F(df)	p	ΔR^2	F(df)	p
Expression	OXTR	0.016	4.067(1, 248)	0.045	0.047	12.461(1, 247)	<0.001
	DRD4	0.000	0.033(1, 246)	0.856	0.001	0.344(1, 245)	0.558
	HTR1A	0.139	0.139(1, 242)	0.709	0.001	0.150(1, 241)	0.699
	SERT	0.000	0.124(1, 254)	0.725	0.001	0.214(1, 253)	0.644
	GSI	0.000	0.039(1, 233)	0.843	0.036	8.752(1, 232)	0.003
Cognitive reappraisal	OXTR	0.001	0.261(1, 248)	0.610	0.004	1.000(1, 247)	0.318
	DRD4	0.004	1.064(1, 246)	0.303	0.006	1.612(1, 245)	0.205
	HTR1A	0.008	2.032(1, 242)	0.155	0.026	6.461(1, 241)	0.012
	SERT	0.006	1.549(1, 254)	0.214	0.002	0.484(1, 253)	0.487
	GSI	0.035	8.467(1, 233)	0.004	0.005	1.182(1, 232)	0.278
Incidences of emotional support seeking	OXTR	0.011	1.496(1, 138)	0.223	–	–	–
	DRD4	0.022	3.061(1, 138)	0.082	–	–	–
	HTR1A	0.001	0.114(1, 133)	0.736	–	–	–
	SERT	0.000	0.005(1, 143)	0.942	–	–	–
	GSI	0.027	3.516(1, 127)	0.063	–	–	–
Rating of emotional support seeking	OXTR	0.016	2.182(1, 137)	0.142	–	–	–
	DRD4	0.045	6.557(1, 138)	0.012	–	–	–
	HTR1A	0.016	2.166(1, 132)	0.143	–	–	–
	SERT	0.001	0.079(1, 142)	0.779	–	–	–
	GSI	0.080	11.11(1, 127)	0.001	–	–	–

Note Because only data for Americans were available for behavioral measures of emotional support seeking, we do not report any interactive effects here

strategies. Given that cognitive reappraisal can be conceptualized as adjustment to emotional situations, those with greater environmental susceptibility may be more aware of their emotional situations and more able to easily adjust themselves to the situation. The pattern of findings supports the proposed contribution of multiple genes to environmental susceptibility. Increased polygenic susceptibility was linked to greater cultural divergence only for those self-expression outcomes known to differ between cultures.

Single gene versus polygenic approach

Our approach of combining the effects of multiple genetic polymorphisms has a number of important methodological and theoretical strengths. Although summing across the genetic variants did not substantially increase the effect sizes, we found a more consistent pattern of predicted findings with the GSI, compared to using single variants. With single genetic variants, the pattern of association between G × C and self-expression outcomes differed (e.g., suppression was predicted by *OXTR*, behavioral emotional support seeking with *DRD4*). The pattern may have seemed

inconsistent, if only considering the associations of single genes. The composite score consistently supported the predicted pattern, including with measures of actual behavior, which provides evidence for both specificity and generality of genetics in influencing social behaviors. For specific outcomes, the genetic variant showing the strongest effect may vary, suggesting the possibility of genetic specificity underlying social behaviors. At the same time, even when a specific gene is associated with an outcome (e.g., *OXTR* with value of expression), adding the effects of additional genes did not damper the association, except when the association with a single gene was theoretically unexpected (i.e., *5HTR1A* polymorphism on cognitive reappraisal). Concerns have been raised about inflated chances of false positives with the single target gene approach (Duncan and Keller 2011). In this case, the unexpected interactive effect may have been spurious. Indeed, the GSI did not show any interactive effect, possibly preventing a false positive effect. In addition, the results with the two measures of emotional support seeking appear consistent with the individual genetic polymorphisms. The *DRD4* polymorphism predicts behavioral support seeking in the lab situation, while the *OXTR* polymorphism appears to influence self-reported self-expressive tendencies (also see Kim et al. 2010a), including emotional support seeking items. We speculate a number of explanations for this seeming inconsistency. First, it could be that variation of *DRD4* is more closely linked to situations where immediate potential reward (i.e., emotional comfort and encouragement) is salient, while *OXTR* relates more to retrospective reflection in which the psychological focus is on the overall social relationship (see Sasaki et al. 2014 for discussion of genetic specificity). Second, while the exact strengths of relationships differ for each gene with the two measures, it is important to note that the relationships are directionally consistent, especially with the behavioral measures. Thus, we argue that both *OXTR* and *DRD4*, along with the other genetic variants, contribute to susceptibility, but the strength of the relationship differs from a situation to another situation and from a sample to another sample. In a way, this relatively weak reliability of the single target gene approach is precisely the issue that the present analysis aims to address. The GSI does not show the inconsistent result. Instead it predicts both the behavioral as well as self-reported emotional support seeking behavior, consistent with predictions and providing further justification for combining multiple genes.

A chief benefit of using multiple genes, like designing a scale measure with multiple items, may be increased reliability. In the case of scales, item responses include both random measurement error and true score variance (Spearman and Charles 1910; Brown 1910). Thus, aggregating across multiple items assessing the same underlying construct may effectively cancel out meaningless errors. The genetic variants included in our genetic susceptibility index link to similar underlying biological functions and psychological processes, which support increased environmental sensitivity. Moreover, aggregating polymorphisms reduces the multiple-testing problem of analyzing associations of individual polymorphisms (Docherty et al. 2011). In this study of polygenic G × E effects on mathematical ability, researchers found that individual variants increased the number of multiple tests ten-fold and had vastly reduced effect size, compared to a set of polymorphisms. In addition the use of multiple genetic variants provides the pragmatic

benefit of helping to reduce differences in allele distribution and frequencies between ethnic groups. Between the groups, the GSIs did not differ in their statistical distributions and also did not exhibit mean-level differences.

Theoretically, the lack of mean-level and distribution differences with the GSI has interesting implications, namely that ethnic groups probably do not differ in base genetic susceptibility. For example, we found that the susceptible *OXTR* variant was more common among Americans compared to Koreans, while the susceptible *SERT* variants was more common among Koreans. These differences in genetic distribution may lead to a speculation that groups differ in their genetic predisposition to environmental sensitivity (e.g., Way & Lieberman 2010). Of course, one gene may carry greater weight in conferring environmental sensitivity to a given cultural group. For example, among European Americans the *OXTR* gene may be more central to shape their susceptibility, while among East Asians it is the s allele of *SERT,* and this difference may influence the exact characteristics of their respective susceptibility. Nevertheless, the lack of cultural differences in the GSI suggests that no ethnic group is genetically more predisposed to environmental susceptibility compared to any other group.

Limitations and future directions

There are several limitations to this study. The findings are based on a relatively small sample size. In addition, we used a simple additive model to account for the contributions of multiple genetic variants. Additive models alone cannot account for more complicated interactive genetic phenomena like epistasis. In the study of genetic contributions to complex traits, researchers have asserted that genes do not generally act in a simple additive model, but rather through interacting networks (Colhoun et al. 2003). Future work could more fully account for the complexity of biological factors involved, including the possibility of gene–gene interactions. In addition, the current study focuses on self-expressive tendencies but this is just one component of the differences between the two cultures. The multi-gene approach could be applied to understanding a wider array of culturally variant tendencies (e.g., social dimensions like independence-interdependence; see Kitayama et al. 2014). Future testing of the applicability of the model to other domains of culture-specific tendencies is needed to further strengthen and revise the model.

Further, the selection of genetic variants was limited to polymorphisms previously implicated in environmental susceptibility by gene–culture interaction studies. To link genetic variation to biological processes, known neuroanatomical structures and functions could be leveraged to inform future selection. Sets of candidate genes might be identified through gene network analyses (e.g., Lee et al. 2012) or through correlations of brain mRNA expression levels (Janusonis 2014), which may suggest functional relationships among neurotransmitter receptors. In addition, including multiple genes from the same neurotransmitter signaling system could allow for the influence of variants to be combined and accounted for in a more sophisticated manner.

Conclusion

Our polygenic approach to G × C effects is complementary to single gene approaches, which may help identify possible variants of interest. Indeed, the gene–culture interaction framework has now been studied with several polymorphic sites and psychological outcomes (Ishii et al. 2014b; Kim et al. 2010a, b; Kitayama et al. 2014). However, since the brain is an interactive system, G × C which consider multiple genetic influences will likely be important in the future. Such research can leverage existing neuroscience knowledge of linkages between genes and move towards a more anatomically informed approach to studying the interplay between genes and the environment on psychological tendencies.

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References

Anderson, G., Horne, W., Chatterjee, D., & Cohen, D. (1990). The hyperserotonemia of autism. *Annuals of the New York Academy of Sciences, 600*, 331–342.

Bachner-Melman, R., Girsenko, I., Nemanov, L., Zohar, A. H., Dina, C., & Ebstein, R. P. (2005). Dopaminergic polymorphisms associated with self-report measures of human altruism: A fresh phenotype for the dopamine D_4 receptor. *Molecular Psychiatry, 10*, 333–335.

Bakermans-Kranenburg, M., & van IJzendoorn, M. (2006). Gene-environment interaction of the dopamine D4 receptor (DRD4) and observed maternal insensitivity predicting externalizing behavior in preschoolers. *Developmental Psychobiology, 48*(5), 406–409.

Bakermans-Kranenburg, M., & van IJzendoorn, M. (2008). Oxytocin receptor (OXTR) and serotonin transporter (5-HTT) genes associated with observed parenting. *Social Cognitive and Affective Neuroscience, 3*(2), 128–134.

Bakermans-Kranenburg, M., & van Ijzendoorn, M. (2011). Differential susceptibility to rearing environment depending on dopamine-related genes: New evidence and a meta-analysis. *Development and Psychopathology, 23*(01), 39–52.

Bartz, J., Zaki, J., Bolger, N., & Ochsner, K. (2011). Social effects of oxytocin in humans: context and person matter. *Trends in Cognitive Sciences, 15*(7), 301–309.

Belsky, J., Bakermans-Kranenburg, M., & Van IJzendoorn, M. (2007). For better and for worse differential susceptibility to environmental influences. *Current Directions in Psychological Science, 16*(6), 300–304.

Belsky, D., Moffitt, T., Baker, T., Biddle, A., Evans, J., Harrington, H., et al. (2013). Polygenic risk and the developmental progression to heavy, persistent smoking and nicotine dependence evidence from a 4-decade longitudinal study developmental progression of smoking behavior. *JAMA Psychiatry, 70*(5), 534–542.

Belsky, D. W., Moffitt, T. E., Houts, R., Bennett, G. G., Biddle, A. K., Blumenthal, J. A., et al. (2012). Polygenic risk, rapid childhood growth, and the development of obesity evidence from a 4-decade longitudinal study. *Archives of Pediatrics and Adolescent Medicine, 166*(6), 515–521.

Brown, W. (1910). SOME EXPERIMENTAL RESULTS IN THE CORRELATION OF MENTAL ABILITIES1. *British Journal of Psychology, 1904–1920, 3*(3), 296–322.

Butler, E., Lee, T., & Gross, J. (2009). Does expressing your emotions raise or lower your blood pressure? The answer depends on cultural context. *Journal of Cross-Cultural Psychology, 40*, 510–517.

Carver, C. (1997). You want to measure coping but your protocol's too long: Consider the Brief COPE. *International Journal of Behavioral Medicine, 4*, 92–100.

Caspi, A., McClay, J., Moffitt, T., Mill, J., Martin, J., Craig, I., et al. (2002). Role of genotype in the cycle of violence in maltreated children. *Science, 297*(5582), 851–854.

Caspi, A., Sugden, K., Moffitt, T., Taylor, A., Craig, I., Harrington, H., et al. (2003). Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. *Science, 301*(5631), 386–389.

Chang, F., Kidd, J., Livak, K., Pakstis, A., & Kidd, K. (1996). The worldwide distribution of allele frequencies at the human dopamine D_4 receptor locus. *Human Genetics, 98*, 91–101.

Chen, F., Kumsta, R., von Dawans, B., Monakhov, M., Ebstein, R., & Heinrichs, M. (2011). Common oxytocin receptor gene (OXTR) polymorphism and social support interact to reduce stress in humans. *Proceedings of the National Academy of Sciences, 108*(50), 19937–19942.

Chiao, J., & Blizinsky, K. (2010). Culture–gene coevolution of individualism–collectivism and the serotonin transporter gene. *Proceedings of the Royal Society B: Biological Sciences, 277*(1681), 529–537.

Colhoun, H., McKeigue, P., & Smith, G. (2003). Problems of reporting genetic associations with complex outcomes. *The Lancet, 361*(9360), 865–872.

de Castro, I. P., Ibanez, A., Torres, P., Saiz-Ruiz, J., & Fernandez-Piqueras, J. (1997). Genetic association study between pathological gam- bling and a functional DNA polymorphism at the D_4 receptor gene. *Pharmacogenetics, 7*, 345–348.

Declerck, C. H., Boone, C., & Kiyonari, T. (2010). Oxytocin and cooperation under conditions of uncertainty: the modulating role of incentives and social information. *Hormones and Behavior, 57*(3), 368–374.

Docherty, S. J., Kovas, Y., & Plomin, R. (2011). Gene–environment interaction in the etiology of mathematical ability using SNP sets. *Behavior Genetics, 41*(1), 141–154.

Duncan, L., & Keller, M. (2011). A critical review of the first 10 years of candidate gene-by-environment interaction research in psychiatry. *American Journal of Psychiatry, 168*(10), 1041–1049.

Ebstein, R., Novick, O., Umansky, R., Umansky, R., Priel, B., Osher, Y., et al. (1996). Dopamine D_4 receptor (D4DR) exon III polymorphism associated with the human personality trait of novelty seeking. *Nature Genetics, 12*, 78–80.

Foley, D., Eaves, L., Wormley, B., Silberg, J., Maes, H., Kuhn, J., et al. (2004). Childhood adversity, monoamine oxidase a genotype, and risk for conduct disorder. *Archives of General Psychiatry, 61*(7), 738–744.

Gimpl, G., & Fahrenholz, F. (2001). The oxytocin receptor system: structure, function, and regulation. *Physiological Reviews, 81*(2), 629–683.

Gross, J. J., & John, O. P. (2003). Individual differences in two emotion regulation processes: Implications for affect, relationships, and well-being. *Journal of Personality and Social Psychology, 85*, 348–362.

Holden, J. A., & Liu, X. (2005). The roles of dopamine and norepinephrine in autism: from behavior and pharmacotherapy to genetics. In M. L. Bauman & T. L. Kemper (Eds.), *The Neurobiology of Autism*. Baltimore: JHU.

Huang, Y. Y., Battistuzzi, C., Oquendo, M. A., Harkavy-Friedman, J., Greenhill, L., Zalsman, G., et al. (2004). Human 5-HT1A receptor C (−1019) G polymorphism and psychopathology. *The International Journal of Neuropsychopharmacology, 7*(4), 441–451.

Ishii, K., Kim, H., Sasaki, J., Shinada, M., & Kusumi, I. (2014a). Culture modulates sensitivity to the disappearance of facial expressions associated with the serotonin transporter polymorphism (5-HTTLPR). *Culture and Brain, 2*, 72–88.

Ishii, K., Kim, H. S., Sasaki, J., Shinada, M., & Kusumi, I (2014b). Culture modulates sensitivity to the disappearance of facial expressions associated with serotonin transporter polymorphism (5-HTTLPR). *Culture and Brain*, 1–17. doi:10.1007/s40167-014-0014-8.

Ito, H., Halldin, C., & Farde, L. (1999). Localization of 5-HT1A receptors in the living human brain using [carbonyl-11C] WAY-100635: PET with anatomic standardization technique. *Journal of Nuclear Medicine: Official Publication, Society of Nuclear Medicine, 40*(1), 102–109.

Janusonis, S. (2014). Functional associations among G protein-coupled neurotransmitter receptors in the human brain. *BMC Neuroscience, 15*(1), 16.

Jorgensen, H., Kjaer, A., Knigge, U., Moller, M., & Warberg, J. (2003). Serotonin stimulates hypothalamic mRNA expression and local release of neurohypophysial peptides. *Journal of Neuroendocrinology, 15*, 564–571.

Kim, H. S., & Sasaki, J. Y. (2014). Cultural neuroscience: Biology of the mind in cultural context. *Annual Review of Psychology, 64*, 487–514.

Kim, H. S., Sherman, D. K., Mojaverian, T., Sasaki, J. Y., Park, J., Suh, E. M., et al. (2011). Gene–culture interaction oxytocin receptor polymorphism (OXTR) and emotion regulation. *Social Psychological and Personality Science, 2*(6), 665–672.

Kim, H. S., Sherman, D. K., Sasaki, J. Y., Xu, J., Chu, T. Q., Ryu, C., et al. (2010a). Culture, distress, and oxytocin receptor polymorphism (OXTR) interact to influence emotional support seeking. *Proceedings of the National Academy of Sciences, 107*(36), 15717–15721.

Kim, H. S., Sherman, D. K., Taylor, S. E., Sasaki, J. Y., Chu, T. Q., Ryu, C., et al. (2010b). Culture, serotonin receptor polymorphism and locus of attention. *Social Cognitive and Affective Neuroscience, 5*(2–3), 212–218.

Kim, H. S., & Sherman, D. K. (2007). " Express yourself ": culture and the effect of self-expression on choice. *Journal of personality and social psychology, 92*(1), 1.

Kim, H. S., Sherman, D. K., & Taylor, S. E. (2008). Culture and social support. *American Psychologist, 63*(6), 518.

Kim-Cohen, J., Caspi, A., Taylor, A., Williams, B., Newcombe, R., Craig, I. W., et al. (2006). MAOA, maltreatment, and gene–environment interaction predicting children's mental health: New evidence and a meta-analysis. *Molecular Psychiatry, 11*(10), 903–913.

Kim-Cohen, J., & Gold, A. L. (2009). Measured gene–environment interactions and mechanisms promoting resilient development. *Current Directions in Psychological Science, 18*(3), 138–142.

Kitayama, S. (2002). Culture and basic psychological processes—toward a system view of culture: comment on Oyserman et al (2002). *Psychological Bulletin, 128*, 383–409.

Kitayama, S., Anthony, K., Yoon, C., Tompson, S., Huff, S., & Liberzon, I. (2014). The dopamine D4 receptor gene (DRD4) moderates cultural difference in independent versus interdependent social orientation. *Psychological Science, 25*(6), 1169–1177.

Knutson, B., Wolkowitz, O. M., Cole, S. W., Chan, T., Moore, E. A., Johnson, R. C., et al. (1998). Selective alteration of personality and social behavior by serotonergic intervention. *American Journal of Psychiatry, 155*(3), 373–379.

Kuhnen, C. M., & Chiao, J. Y. (2009). Genetic determinants of financial risk taking. *PLoS ONE, 4*, e4362.

Lee, T. L., Raygada, M. J., & Rennert, O. M. (2012). Integrative gene network analysis provides novel regulatory relationships, genetic contributions and susceptible targets in autism spectrum disorders. *Gene, 496*(2), 88–96.

Lee, E., Suh, E. M., Chu, T., Kim, H. S., & Sherman, D. K. (2009). Is emotion suppression that bad? Comparing the emotion suppression and subjective well-being link in two cultures. *Korean Journal of Social and Personality Psychology, 23*, 131–146.

Lemonde, S., Turecki, G., Bakish, D., Du, L., Hrdina, P. D., Bown, C. D., et al. (2003). Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide. *The Journal of Neuroscience, 23*(25), 8788–8799.

Lesch, K. P., et al. (1996). Association of anxiety-related traits with a polymorphism in the serotonin transporter gene regulatory region. *Science, 274*, 1527–1531.

Lewis, C. M. (2002). Genetic association studies: design, analysis and interpretation. *Briefings in Bioinformatics, 3*(2), 146–153.

Lonsdorf, T. B., Weike, A. I., Nikamo, P., Schalling, M., Hamm, A. O., & Öhman, A. (2009). Genetic gating of human fear learning and extinction possible implications for gene–environment interaction in anxiety disorder. *Psychological Science, 20*(2), 198–206.

Love, T. M. (2014). Oxytocin, motivation and the role of dopamine. *Pharmacology, Biochemistry and Behavior, 119*, 49–60.

Markus, H. R., & Kitayama, S. (1991). Culture and the self: Implications for cognition, emotion, and motivation. *Psychological Review, 98*(2), 224.

Matsumoto, D., Yoo, S. H., Nakagawa, S., & 37 members of the multinational study of cultural display rules. (2008). Culture, emotion regulation, and adjustment. *Journal of Personality and Social Psychology, 94*, 925–937.

Mikolajczak, M., Pinon, N., Lane, A., de Timary, P., & Luminet, O. (2010). Oxytocin not only increases trust when money is at stake, but also when confidential information is in the balance. *Biological Psychology, 85*(1), 182–184.

Minelli, C., Thompson, J. R., Abrams, K. R., Thakkinstian, A., & Attia, J. (2005). The choice of a genetic model in the meta-analysis of molecular association studies. *International Journal of Epidemiology, 34*(6), 1319–1328.

Modahl, C., Fein, D., Waterhouse, L., & Newton, N. (1992). Does oxytocin deficiency mediate social deficits in autism? *Journal of Autism and Developmental Disorders, 22*(3), 449–451.

Modahl, C., Green, L. A., Fein, D., Morris, M., Waterhouse, L., Feinstein, C., et al. (1998). Plasma oxytocin levels in autistic children. *Biological Psychiatry, 43*(4), 270–277.

Munafo, M. R., Clark, T., & Flint, J. (2005). Does measurement instrument moderate the association between the serotonin transporter gene and anxiety-related personality traits? A meta-analysis. *Molecular Psychiatry, 10,* 415–419.

Reist, C., Ozdemir, V., Wang, E., Hashemzadeh, M., Mee, S., & Moyzis, R. (2007). Novelty seeking and the dopamine D_4 receptor gene (DRD4) revisited in Asians: Haplotype characterization and relevance of the 2-repeat allele. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 144B*, 453–457.

Riem, M. M., Bakermans-Kranenburg, M. J., Pieper, S., Tops, M., Boksem, M. A., Vermeiren, R. R., et al. (2011). Oxytocin modulates amygdala, insula, and inferior frontal gyrus responses to infant crying: a randomized controlled trial. *Biological Psychiatry, 70*(3), 291–297.

Rodrigues, S. M., Saslow, L. R., Garcia, N., John, O. P., & Keltner, D. (2009). Oxytocin receptor genetic variation relates to empathy and stress reactivity in humans. *Proceedings of the National Academy of Sciences, 106*(50), 21437–21441.

Sasaki, J. Y., Kim, H. S., Mojaverian, T., Kelley, L. D., Park, I. Y., & Janušonis, S. (2013). Religion priming differentially increases prosocial behavior among variants of the dopamine D_4 receptor (DRD4) gene. *Social Cognitive and Affective Neuroscience, 8*(2), 209–215.

Sasaki, J. Y., Mojaverian, T., & Kim, H. S. (2014). Religion priming and an oxytocin receptor gene (OXTR) polymorphism interact to affect self-control in a social context. *Development and Psychopathology*. (in press)

Schoots, O., & van Tol, H. H. M. (2003). The human dopamine D_4 receptor repeat sequences modulate expression. *The Pharmacogenomics Journal, 3*(6), 343–348.

Sen, S., Burmeister, M., & Ghosh, D. (2004). Meta-analysis of the association between a serotonin transporter promoter polymorphism (5-HTTLPR) and anxiety-related personality traits. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 127*(1), 85–89.

Sevy, S., Hassoun, Y., Bechara, A., Yechiam, E., Napolitano, B., Burdick, K., et al. (2006). Emotion-based decision-making in healthy subjects: short-term effects of reducing dopamine levels. *Psychopharmacology (Berl), 188*(2), 228–235.

Simmons, C. F., Jr, Clancy, T. E., Quan, R., & Knoll, J. H. (1995). The oxytocin receptor gene (OXTR) localizes to human chromosome 3p25 by fluorescence in situ hybridization and PCR analysis of somatic cell hybrids. *Genomics, 26*(3), 623–625.

Spearman, C. (1910). Correlation calculated from faulty data. *British Journal of Psychology, 1904−1920, 3*(3), 271–295.

Strobel, A., Gutknecht, L., Rothe, C., Reif, A., Mössner, R., Zeng, Y., et al. (2003). Allelic variation in 5–HT1A receptor expression is associated with anxiety and depression–related personality traits. *Journal of Neural Transmission, 110*(12), 1445–1453.

Succu, S., Sanna, F., Melis, T., Boi, A., Argiolas, A., & Melis, M. (2007). Stimulation of dopamine receptors in the paraventricular nucleus of the hypothalamus of male rats induces penile erection and increases extra-cellular dopamine in the nucleus accumbens: Involvement of central oxytocin. *Neuropharmacology, 52*, 1034–1043.

Tamir, D. I., & Mitchell, J. P. (2012). Disclosing information about the self is intrinsically rewarding. *Proceedings of the National Academy of Sciences, 109*(21), 8038–8043.

Taylor, S. E., Way, B. M., Welch, W. T., Hilmert, C. J., Lehman, B. J., & Eisenberger, N. I. (2006). Early family environment, current adversity, the serotonin transporter promoter polymorphism, and depressive symptomatology. *Biological Psychiatry, 60*(7), 671–676.

Tost, H., Kolachana, B., Hakimi, S., Lemaitre, H., Verchinski, B. A., Mattay, V. S., et al. (2010). A common allele in the oxytocin receptor gene (OXTR) impacts prosocial temperament and human hypothalamic-limbic structure and function. *Proceedings of the National Academy of Sciences, 107*(31), 13936–13941.

van Tol, H. H., Wu, C. M., Guan, H. C., Ohara, K., Bunzow, J. R., Civelli, O., et al. (1992). Multiple dopamine D_4 receptor variants in the human population. *Nature, 358*, 149–152.

Wang, E., Ding, Y. C., Flodman, P., Kidd, J. R., Kidd, K. K., Grady, D. L., et al. (2004). The genetic architecture of selection at the human dopamine receptor D_4 (DRD4) gene locus. *American Journal of Human Genetics, 74*, 931–944.

Way, B. M., & Lieberman, M. D. (2010). Is there a genetic contribution to cultural differences? Collectivism, individualism and genetic markers of social sensitivity. *Social cognitive and affective neuroscience, 5*(2–3), 203–211.

Wood, R. M., Rilling, J. K., Sanfey, A. G., Bhagwagar, Z., & Rogers, R. D. (2006). Effects of tryptophan depletion on the performance of iterated prisoner's dilemma game in healthy adults. *Neuropsychopharmacology, 31*, 1075–1084.

Zhong, S., Israel, S., Shalev, I., Xue, H., Ebstein, R. P., & Chew, S. H. (2010). Dopamine D4 receptor gene associated with fairness preference in ultimatum game. *PLoS ONE, 5*, e13765.