A REEXAMINATION OF THE EFFECTS OF CULTURE AND DOPAMINE D4 RECEPTOR GENE INTERACTION ON SOCIAL ORIENTATION

Keiko ISHII 1, Takahiko MASUDA 2, Masahiro MATSUNAGA 3, Yasuki NOGUCHI 4, Hidenori YAMASUE 5, and Yohsuke OHTSUBO 6

1)Nagoya University, Japan
2)University of Alberta, Canada
3)Aichi Medical University, Japan
4)Kobe University, Japan
5)Hamamatsu University School of Medicine, Japan
6)University of Tokyo, Japan

The dopamine D4 receptor gene (DRD4) is associated with novelty-seeking and risk-taking behaviors that have had an adaptive value in the history of human migration. It also plays a role in moderating the extent to which people adhere to cultural norms and practices. The aim of this study was to replicate previous findings about how DRD4 polymorphism interacts with cultural differences in social orientation, which revealed Westerners’ emphasis on independence and East Asians’ emphasis on interdependence. Testing Japanese and European Canadian undergraduates (n = 784), we succeeded in replicating these previous findings: the Canadian students were more independent, whereas the Japanese students were more interdependent. However, none of the interaction effects between culture and DRD4 were significant. Implications for candidate gene research investigating gene–environment and gene–culture interactions are discussed.

Dopamine is an important neurotransmitter that controls various functions, including locomotor activity, cognition, emotion, appetitive and motivational behaviors, and endocrine regulation. DRD4, one of the five subtypes of dopamine receptors that have been identified and characterized, is abundant in the frontal lobe and is linked to novelty- seeking and impulsive behaviors (Benjamin et al., 1996; Ebstein et al., 1996). The DRD4 gene has several polymorphisms, including 48 base-pair variable number tandem repeat (VNTR) polymorphism in exon 3 with 2 to 11 repeat units (Ding et al., 2002). The most frequent VNTR alleles are 2-, 4-, and 7-repeats. Compared with individuals with the 4R allele, individuals with the 7R and 2R alleles are more likely to exhibit greater sensitivity to rewards (Nikolova et al., 2011), increased novelty-seeking (Ebstein et al., 1996), and a greater risk-taking tendency (Kuhnen & Chiao, 2009).

There are regional variations in the allelic frequency of DRD4 polymorphism among populations. The most common allele is the 4R, which can be found across all regions of the world; the next most common is the 7R allele, which is quite common in Americans but rare in East and South Asians; the third most common is the 2R allele, which is quite common in East and South Asians but rare in Americans (Chang et al., 1996). Chen et al. (1999) demonstrated that these variations are related to migration history. The proportion of the 7R allele was positively associated with migratory distances. Also, it was higher in nomadic populations than in sedentary populations (see also Eisenberg et al., 2008). The association between the 7R allele and migration distance was also supported by Matthews and Butler (2011) that performed a strict test controlling neutral genetic processes. Chen et al. (1999) proposed that the 7R allele, which is linked to greater novelty-seeking, exploratory impulses, and risk-taking tendencies, was eventually selected by migration because its associated behaviors were adaptive for unfamiliar environments. Moreover, the behavioral tendencies were also more adaptive and selected in nomadic groups, which were often faced with challenging environments, than in settled groups that primarily practiced agriculture. This proposal is in line with the idea of gene–culture co-evolution (Richerson & Boyd, 2008), which similarly holds that behavioral traits such as novelty-seeking, exploratory impulses, and risk-taking tendencies are adaptive to the challenging environments that migration entails, which may have led to the genetic selection of the 7R allele for the migration process.

In addition, Kitayama et al. (2016) have recently suggested that a factor that initially differentiated East and West in terms of culture was the former's history of farming rice versus the latter's history of farming wheat, two forms of agriculture that differ in their respective emphases on interdependence fostered by intense cooperation and coordination; the authors argued that dopaminergic system genes may play a significant role in establishing the cultural norms that facilitate these forms of subsistence through reinforcement-based learning. Given that a history of rice farming makes cultures more collectivistic and interdependent whereas a history of wheat farming makes cultures more individualistic and independent (Talhelm et al., 2014), dopaminergic system genes may be associated with the extent to which people adhere to cultural norms that emphasize interdependence versus those that emphasize independence. Kitayama et al. (2014) asked European Americans and East Asians to report their independent and interdependent orientations on multiple scales and showed that cultural differences in independent versus interdependent orientation were more pronounced in those carrying either 2R or 7R alleles of DRD4 polymorphism than those having neither the 2R nor 7R allele (the cultural differences in independent vs. interdependent orientation disappeared in those having neither the 2R nor 7R allele).

The findings of Kitayama et al. (2014) are in line with both the concept of gene–environment interaction, which holds that individuals' susceptibility to the environment is moderated by genetic variation (Belsky et al., 2007, 2009; Obradović & Boyce, 2009; Way & Taylor, 2010), and that of gene–culture interaction, which expands on the gene–environment interaction framework to include cultural norms and practices as components of the environment (Kim & Sasaki, 2014; Sasaki & Kim, 2017). In this context, individuals who carry the 7R and 2R alleles of DRD4 polymorphism are more environmentally susceptible than noncarriers (Bakermans-Kranenburg & van IJzendoorn, 2006; Sasaki et al., 2013).

To corroborate the association they earlier identified between dopaminergic system genes and cultural acquisition, Kitayama et al. further demonstrated that (a) interdependent self-construal was inversely associated with the gray-matter volume of the orbitofrontal cortex (OFC) and the medial prefrontal cortex (mPFC; Kitayama et al., 2017; Yu et al., 2019); (b) cultural differences in the-gray matter volume of prefrontal regions, including OFC and mPFC, were moderated by DRD4, with cultural difference emphasized more in 7R-/2R-allele carriers than in 7R-/2R-allele noncarriers (Yu et al., 2019); and (c) the gray-matter volume of the temporoparietal junction (TPJ), which is associated with perspective-taking, was greater among East Asians than European Americans, and that cultural difference was emphasized more in 7R-/2R-allele carriers than in 7R-/2R-allele noncarriers (Kitayama et al., 2020).

Taken together, DRD4 polymorphism moderated cultural differences in the gray- matter volume of brain regions, which are associated with the extent to which individuals adhere to cultural values. However, its moderation of cultural differences in independent versus interdependent orientation has not been fully examined after Kitayama et al. (2014). Given that research on gene–environment interaction using candidate genes has been criticized for its limited statistical power due to relatively small sample size and small effect size (Duncan & Keller, 2011) and increasing concern about the replicability of findings (Jern et al., 2017), an attempt to replicate the findings of Kitayama et al. (2014) with a larger sample size would be worth investigating.1

In the present study, we investigated the interplay of culture and DRD4 polymorphism in cultural orientation (i.e., independence vs. interdependence). Kitayama et al. (2014) tested about 200 students of European ancestry who were born and raised in the United States, and about 200 East Asian students who were born in an East Asian country and had spent no more than 10 years in the United States. They administered a series of questionnaires and focused on the following scales related to cultural orientation: for independence, the independent subscale of the self-construal scale (Singelis, 1994), the general self-efficacy scale (Schwarzer et al., 1999), the self-esteem scale (Rosenberg, 1965), and the value of expression questionnaire (Kim & Sherman, 2007); and for interdependence, the interdependent subscale of the self-construal scale (Singelis, 1994) and the analysis-holism scale (Choi et al., 2007).

In this study, we analyzed data about Japanese and Canadian students (about 800 data in total) as part of an exploratory cross-cultural project that sought to investigate how cultures and genes would interact in the manifestation of various psychological tendencies, including self, personality traits, emotion, cognition, and interpersonal behaviors (see Ishii et al., 2021, and Matsunaga et al., 2018, for some of the results regarding gene–culture interaction in this project). Therefore, the scales used in this study were not identical to those in Kitayama et al. (2014), although measures of self- construal, self-esteem, and holistic thinking were included and analyzed, as described in the method section. We also included the measures of the behavioral inhibition system/behavioral activation system (BIS/BAS) and the Big Five personality traits. Given cultural differences in approach/avoidance motivations (Hamamura et al., 2009), it can be expected that Japanese would show higher scores of BIS than Canadians, whereas Canadians would show higher scores of BAS than Japanese. A recent study testing American and Japanese nonstudent adults found cultural differences in BIS/BAS consistent with this expectation (Chuang et al., 2021). Based on the results of a large- scale survey of the Big Five traits across 56 nations (Schmitt et al., 2007), extraversion, openness to experience, agreeableness, and conscientiousness would be lower in Japanese than in Canadians, whereas the trend would be reversed in the case of neuroticism. In addition to the cultural differences in BIS/BAS and the Big Five traits, given a positive association between the 7R and 2R alleles of DRD4 and novelty-seeking (Benjamin et al., 1996; Ebstein et al., 1996), some effects of DRD4 polymorphism on BIS/BAS and the Big Five traits (particularly, extraversion) might be expected. Moreover, it has been unclear whether the expected cultural differences in BIS/BAS and the Big Five traits are moderated by DRD4 polymorphism. Thus, we included the measures of BIS/BAS and the Big Five traits to replicate the cultural differences and exploratorily investigate the effects of DRD4 polymorphism.

Additionally, the testing sites and languages used differed between the two studies: Kitayama et al. (2014) tested European Americans and East Asians in an American university by administering the questionnaires in English, whereas in this study, we tested European Canadians in a Canadian university and Japanese in a Japanese university by administering the questionnaires in their native languages (i.e., English for Canadians, Japanese for Japanese). Given the influence of host cultures and languages on self- construal, self-esteem, and thinking style (Kitayama et al., 1997, 2003; Ross et al., 2002), the results for East Asian participants in Kitayama et al. (2014) might be influenced by the participants' daily communication and practices within an American culture and should thus be interpreted with caution. Furthermore, because this study was conducted with a larger sample size than that of Kitayama et al. (2014), it can be read as a stricter and more statistically stable test on the moderation effect of DRD4 polymorphism on cultural differences in social orientation. If the moderation effect is adequately strong, European Canadians' emphasis on independence and Japanese' emphasis on interdependence would be more pronounced for 7R-/2R-allele carriers than for 7R-/2R-allele noncarriers.

METHOD

Participants and Procedures

This study involved the participation of 416 Japanese undergraduates at Kobe University (217 females and 198 males, one unidentified; Mage = 19.47, SD = 1.24) and 368 European Canadian undergraduates at the University of Alberta (248 females and 119 males, one unidentified; Mage = 19.46, SD = 2.17) who were recruited through a psychology subject pool at each institution. According to a power analysis with G*Power 3.1, we needed at least 674 participants to detect a small/medium effect size ($f = .15$), which was computed on the basis of effect size ($\eta p2 = .024$) regarding the culture and DRD4 interaction reported by Kitayama et al. (2014), with 95% power for an F-test (fixed effects analysis of variance [ANOVA]), when the significance level was set to 0.025 (= 0.05/2 tested hypotheses [the main effect of culture and its interaction with DRD4]). The ethics committees at Kobe University and the University of Alberta approved this research. The participants provided a written informed consent at the beginning of the study. All responses were confidential.

We administered questionnaires to the Japanese and Canadian participants on a wide range of topics, such as self, emotion, cognition, and interpersonal behaviors. Measures used were translated and back- translated between Japanese and English to ensure cross-cultural equivalence. The following measures were relevant to this research.

Independence and interdependence. We used a 20-item self-construal scale that Park and Kitayama (2014) developed by selecting items from Singelis (1994) and Takata (1999), broken down into 10 items regarding independent self-construal (e.g., "I always try to have my own opinions.") and 10 items regarding interdependent self-construal (e.g., "I am concerned about what people think of me."). Participants were presented with each item and rated their agreement on a 7-point scale (1 = strongly disagree, 7 = strongly agree). This scale is conceptually identical to the Singelis (1994) self-construal scale used by Kitayama et al. (2014). For independent self-construal, Cronbach's α was .72 for Japanese and .71 for Canadians; for interdependent self-construal, Cronbach's α was .67 for Japanese and .60 for Canadians.

Dialectical thinking. We assessed the participants' dialectical self by using a 32-item dialectical self scale (Spencer-Rodgers et al., 2001), which included such statements as "When I hear two sides of an argument, I often agree with both. Participants were presented with each item and rated their agreement on a 7-point scale (1 = strongly disagree, 7 = strongly agree). The dialectical self scale is one of the representative scales to measure Easterners and Westerners' ways of thinking as well as the analysis-holism scale (Choi et al., 2007) used by Kitayama et al. (2014; see Zhang & Tsai, 2014, for details). Cronbach's α was .78 for Japanese and .82 for Canadians.

Self-esteem. Participants were asked to indicate through a 6-point Likert-type scale the extent to which they agreed (1 = "strongly disagree" to 6 = "strongly agree") with each of the 10 items (e.g., "On the whole, I am satisfied with myself.") on the Rosenberg self-esteem scale (Rosenberg, 1965), which Kitayama et al. (2014) also used. Cronbach's α was .89 for Japanese and .92 for Canadians.

BIS/BAS. The BIS/BAS scale (Carver & White, 1994) consists of 7 items related to BIS, which measure response to threats (e.g., "Criticism or scolding hurts me quite a bit.") and 13 items related to BAS, which measure reward-seeking behavior (e.g., "I'm always willing to try something new if I think it will be fun."). Participants rated their agreement with each item on a 4-point Likert scale (1 = very false for me, 4 = very true for me). We used the Japanese version of the scale (Takahashi et al., 2007) for the Japanese participants. For BIS, Cronbach's α was .82 for Japanese and .79 for Canadians; for BAS, Cronbach's α was .81 for Japanese and .79 for Canadians.

Big Five personality traits. The Big Five personality traits (neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness) were measured using the NEO Five-Factor Inventory (Costa & McCrae, 1992), with 12 items for each trait and a scoring system ranging from 0 to 48. We used the Japanese version of the scale (Shimonaka et al., 1999) for the Japanese participants. Cronbach's α for neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness was .84, .80, .69, .70, and .79 for Japanese and .87, .81, .72, .81, and .84 for Canadians, respectively.

Genotyping. Nail samples were collected from which genomic DNA was extracted using ISOHAIR kits (Nippon Gene Co., Ltd., Tokyo, Japan). The DRD4 polymorphism was amplified by PCR using the primers 5’-GCGACTACGTGGTCTACTCG and 5’-AGGACCCTCATGGCCTTG (Lichter et al., 1993) in a volume of 25 µl solution containing 100 ng of genomic DNA, 0.4 mM Deoxynucleotide Triphosphates (dNTPs), 0.2 µM of each primer, 1.25 U of Takara LA Taq polymerase (Takara Bio Inc., Kusatsu, Japan), and GC buffer I (Takara Bio Inc., Kusatsu, Japan). Initial denaturation at 95 ˚C for 5 min was followed by 40 cycles of denaturation at 95 ˚C for 20 s, annealing at 57 ˚C for 20 s, and extension at 72 ˚C for 1 min.

RESULTS

Genotype Distribution

Twenty-seven participants (21 Canadians and 6 Japanese) whose alleles were undetermined were excluded in the following analysis. The final sample size was thus 757 (410 Japanese and 347 European Canadians). The 4R/4R allele of DRD4 was the most common among Canadians (n = 164, 47.3%) and Japanese (n = 286, 69.8%). The frequencies of carriers of at least one 2R allele and carriers of at least one 7R allele were 15.3% and 33.1% for Canadians, and 18.8% and 2.0% for Japanese, respectively. Consistent with previous research (Kitayama et al., 2014; Sasaki et al., 2013; Yu et al., 2019), the next most common DRD4 polymorphism in Canadians was the 7R allele, whereas for Japanese it was the 2R allele. The distribution of the main alleles (4R/4R [n = 164], 4R/7R [n = 79], and 7R/7R [n = 18] in Canadians; 2R/2R [n = 5], 2R/4R [n = 67], and 4R/4R [n = 286] in Japanese) was not different from that predicted by the Hardy–Weinberg equilibrium in either cultural group, which was $\chi 2(1) = 3.69$, $p = .055$ for Canadians, and $\chi 2(1) = 0.22$, $p = .64$ for Japanese.

Considering the functional and evolutionary similarities between the 2R and 7R alleles of DRD4 (Reist et al., 2007) and following previous research (Kitayama et al., 2014; Sasaki et al., 2013; Yu et al., 2019), we grouped carriers of at least one 2R or 7R allele together and compared them with noncarriers of these alleles (i.e., carriers of 4R and infrequent alleles [e.g., 3R and 5R]) in the analysis. In total, there were 246 7R-/2R- allele carriers (161 Canadians and 85 Japanese) and 511 7R-/2R-allele noncarriers (186 Canadians and 325 Japanese).

Culture–DRD4 Interaction

For each measure, we performed an ANOVA with two between-subject variables: culture (Canada and Japan) and DRD4 (7R-/2R-allele carriers and 7R-/2R-allele noncarriers). We set the significance level to 0.025 (= 0.05/2 tested hypotheses [the main

Table 1. Descriptive Statistics for the Measures for Each Cultural Group

Measure	Canadians		Japanese		Cultural difference
	M	*SD*	*M*	*SD*	
Independence	3.84	0.52	3.15	0.61	$F(1, 753) = 226.49, p < .001, \eta_p^2 = .23$
Interdependence	3.44	0.50	3.69	0.49	$F(1, 753) = 37.43, p < .001, \eta_p^2 = .05$
Dialectical thinking	3.87	0.61	4.54	0.53	$F(1, 753) = 218.74, p < .001, \eta_p^2 = .23$
Self-esteem	4.27	0.97	3.57	0.93	$F(1, 752) = 85.48, p < .001, \eta_p^2 = .10$
BIS	3.12	0.55	3.13	0.58	$F(1, 752) = 0.16, p = .70, \eta_p^2 = .0002$
BAS	3.08	0.36	3.00	0.42	$F(1, 752) = 11.11, p < .001, \eta_p^2 = .01$
Neuroticism	26.49	8.74	30.88	7.70	$F(1, 753) = 45.49, p < .001, \eta_p^2 = .06$
Extraversion	29.80	6.64	24.34	7.25	$F(1, 753) = 104.95, p < .001, \eta_p^2 = .12$
Openness	29.93	6.07	28.81	6.11	$F(1, 753) = 4.30, p = .04, \eta_p^2 = .01$
Agreeableness	31.63	7.00	28.88	5.78	$F(1, 753) = 28.37, p < .001, \eta_p^2 = .04$
Conscientiousness	30.32	7.22	25.14	6.80	$F(1, 753) = 83.80, p < .001, \eta_p^2 = .10$

Note. BIS = behavioral inhibition system; BAS = behavioral activation system.

Table 2. Descriptive Statistics for the Measures for DRD4 7R-/2R-Allele Noncarriers and Carriers

Measure	Noncarriers		Carriers		The main effect of DRD4
	M	*SD*	*M*	*SD*	
Independence	3.40	0.66	3.62	0.65	$F(1, 753) = 0.18, p = .67, \eta_p^2 = .0002$
Interdependence	3.60	0.51	3.51	0.50	$F(1, 753) = 0.20, p = .66, \eta_p^2 = .0003$
Dialectical thinking	4.30	0.65	4.10	0.67	$F(1, 753) = 0.02, p = .90, \eta_p^2 = .00002$
Self-esteem	3.83	0.99	4.02	1.04	$F(1, 752) = 0.08, p = .78, \eta_p^2 = .0001$
BIS	3.11	0.58	3.16	0.54	$F(1, 752) = 1.62, p = .20, \eta_p^2 = .002$
BAS	3.04	0.40	3.04	0.39	$F(1, 752) = 1.01, p = .31, \eta_p^2 = .001$
Neuroticism	29.11	8.25	28.37	8.91	$F(1, 753) = 0.70, p = .40, \eta_p^2 = .001$
Extraversion	26.52	7.58	27.52	7.25	$F(1, 753) = 1.53, p = .22, \eta_p^2 = .002$
Openness	29.26	6.11	29.45	6.13	$F(1, 753) = 0.05, p = .83, \eta_p^2 = .0001$
Agreeableness	29.77	6.39	30.90	6.70	$F(1, 753) = 0.40, p = .53, \eta_p^2 = .0005$
Conscientiousness	26.87	7.36	28.86	7.48	$F(1, 753) = 0.69, p = .40, \eta_p^2 = .0009$

Note. DRD4 = the dopamine D4 receptor gene; BIS = behavioral inhibition system; BAS = behavioral activation system.

Table 3. Mean Scores for the Measures and Interaction of Culture and DRD4

	Noncarriers				Carriers				
	Canadians		Japanese		Canadians		Japanese		Culture × DRD4
Measure	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	
Independence	3.82	0.50	3.16	0.62	3.88	0.55	3.14	0.57	$F(1, 753) = 0.61, p = .43$
Interdependence	3.45	0.50	3.69	0.50	3.42	0.50	3.68	0.46	$F(1, 753) = 0.07, p = .80$
Dialectical thinking	3.87	0.61	4.54	0.53	3.86	0.60	4.55	0.54	$F(1, 753) = 0.03, p = .87$
Self-esteem	4.27	0.96	3.58	0.92	4.27	0.99	3.54	0.94	$F(1, 752) = 0.07, p = .79$
BIS	3.09	0.56	3.12	0.59	3.16	0.53	3.16	0.55	$F(1, 752) = 0.11, p = .74$
BAS	3.07	0.35	3.02	0.42	3.09	0.37	2.93	0.40	$F(1, 752) = 3.58, p = .059$
Neuroticism	26.18	8.51	30.79	7.62	26.85	9.00	31.24	8.03	$F(1, 753) = 0.03, p = .87$
Extraversion	29.89	6.54	24.59	7.47	29.70	6.78	23.38	6.28	$F(1, 753) = 0.83, p = .36$
Openness	30.15	5.80	28.75	6.23	29.68	6.38	29.01	5.65	$F(1, 753) = 0.54, p = .46$
Agreeableness	31.35	6.88	28.86	5.92	31.95	7.13	28.92	5.27	$F(1, 753) = 0.28, p = .60$
Conscientiousness	29.90	7.15	25.13	6.91	30.81	7.29	25.16	6.38	$F(1, 753) = 0.60, p = .44$

Note. DRD4 = the dopamine D4 receptor gene; BIS = behavioral inhibition system; BAS = behavioral activation system.

effect of culture and its interaction with DRD4]). Table 1 shows descriptive statistics for the measures for each cultural group. Cultural differences in the measurements of independence and interdependence were significant in the predicted direction as shown in Table 1. There were also cultural differences in BIS/BAS and the Big Five traits in the expected direction, although the cultural difference was not significant in either BIS or openness (Table 1). On the other hand, neither the main effect of DRD4 (Table 2) nor the interaction effect of culture and DRD4 (Table 3) was significant.

DISCUSSION

In this study we attempted to replicate the findings of Kitayama et al. (2014) regarding the interaction between culture and DRD4 polymorphism, using different scales of social orientation and testing samples with different cultural backgrounds. We set the sample size of this research that had adequate power to detect the interaction effect of culture and DRD4 polymorphism reported by Kitayama et al. (2014), following suggestions on conducting candidate gene research (e.g., Dick et al., 2015). However, we found no evidence of an interaction effect of culture and DRD4 polymorphism on social orientation, which is inconsistent with the findings of Kitayama et al. (2014). Given that the proportion of attempts to replicate the findings of previous gene–environment interaction studies that attained significance is less than 25% (Duncan & Keller, 2011), the results of this study would be unexceptional. Rather, they suggest a caveat that the previous findings are based on small samples and may be false. Further follow-up studies with larger sample sizes having sufficient power, which incorporate multiple measurements of social orientation (see Na et al., 2010) and adopt a more appropriate measurement to capture individual differences in self-construal in diverse cultural contexts (Vignoles et al., 2016) are needed to find consistent results of the interaction between culture and DRD4 polymorphism and reach a credible conclusion.

We should hasten to add that this failure of replication does not deny the proposition of the association between dopaminergic system genes and cultural acquisition made by Kitayama and colleagues. Rather, it suggests that researchers need to test the effects of genetic variants by employing different and appropriate methods. For instance, the inconsistent findings on the culture and DRD4 polymorphism interaction on independence and interdependence orientations might partly result from some issues regarding the self- construal scale used. Indeed, the reliability of the self-construal scale in this study was somewhat low. Vignoles et al. (2016) suggested that both independence and interdependence are multifaceted, such as self-reliance and self-expression (independence) and dependence on others and harmony (interdependence), and proposed a seven-dimensional model of self-construal in which independence and interdependence are mutually exclusive within each of the seven domains (e.g., making decisions, looking after oneself, communicating with others, and so on). They developed a new scale to capture the seven dimensions in various cultural contexts. Adopting the newly developed scale may enable researchers to find reliable relationships between DRD4 polymorphism and individual differences in self-construal across cultures, which the existing scale failed to detect. Additionally, researchers are encouraged to use not only self-reporting measures but also behavioral measures and neural processes; indeed, Kitayama and colleagues (Kitayama et al., 2020; Yu et al., 2019) have adopted neuro-imaging techniques and examined the relationships among interdependence, DRD4, and the gray-matter volume of brain regions (e.g., OFC). Future work that clarifies the neural pathways underlying cultural differences in social orientation and assesses how genetic variants affect the neural pathways will help strengthen the proposition. For example, Ma et al. (2014) tested Chinese participants and found that associations between interdependent self-construal and neural activities in the regions related to self-reflection (e.g., mPFC and TPJ) were moderated by serotonin transporter polymorphisms. Although Ma et al. (2014) neither tested participants from Western cultures nor examined the moderation effect of DRD4 polymorphism, expanding research in this direction will be fruitful for understanding of the interplay between culture and the brain.

Furthermore, our failure to replicate previous findings does not devalue studies that examine the effects of genetic variants cross-culturally with sufficient sample sizes. Montag et al. (2020) argued that one way to improve candidate gene studies might be “the establishment of molecular genetic research groups or collaborations with local investigators in different areas of the world in order to be able to replicate findings across different ethnic groups” (p. 169). This proposed initiative would have significant implications for the assessment of gene–environment interaction research. If the moderation effects of genes on the association between environments (e.g., childhood adversity) and social behaviors appear in a similar way across cultures, even if the allele frequencies are different cross-culturally, researchers will be able to assess the genetic effects as valid. In line with the statement by Montag et al. (2020), we have demonstrated in both Canada and Japan that the trend that childhood adversity had a negative effect on general trust was significant only for individuals with the AA genotype of oxytocin receptor gene polymorphism, despite a skewed distribution of the A and G alleles between the two cultures (Zheng et al., 2020).

Because of the replication issue of candidate gene studies, genome-wide association studies (GWAS) have been conducted as an alternative, evidence from which has been steadily accumulating. One advantage of GWAS is the ability to discover new genetic variants that have not been addressed. Using the GWAS methodology, researchers may find further novel candidate genes that are associated with the history of out-of-Africa migration and cultural acquisition. However, GWAS need huge sample sizes to detect significant results because of an exceedingly small significance threshold set to control for alpha error inflation. Alternatively, in the context of the history of out-of-Africa migration, archive data on worldwide genetic variants with frequencies such as the 1000- genome project may be useful for finding new candidate genes. Indeed, by using the 1000-genome project database, Royo et al. (2018) found an association between signal regulatory protein beta-1 (SIRPB1) copy-number polymorphism and the history of migration.

The present study includes some limitations that must be addressed in future work, in addition to the ones we have already mentioned. First, because the study relied on self-reporting measures, it is unclear whether and to what extent gene and culture interact to influence the actual behaviors corresponding to independence and interdependence. Second, we failed to examine the influence of gene–gene interactions that might have caused the null finding of interaction between culture and DRD4 polymorphism. Further investigation that includes other gene variants of the dopaminergic system (e.g., the dopamine D2 receptor

[DRD2], ankyrin repeat and kinase domain containing 1 [ANKK1], catechol-O-methyltransferase [COMT], and dopamine transporter [SLC6A3] genes) will be needed. Third, as in Kitayama et al. (2014), we tested only undergraduates. To generalize the findings, future work will need to test nonstudent adults and investigate a gene–culture interaction effect controlling confounding variables that might have an impact on cultural orientation, such as socioeconomic status (see Ishii & Eisen, 2020, for a review) and residential mobility (see Choi & Oishi, 2020, for a review).

In conclusion, although our study successfully replicated cultural differences regarding independence versus interdependence, we failed to find any interaction between culture and DRD4 polymorphism, which is inconsistent with Kitayama et al. (2014). Given the current controversial status of candidate gene approach, this null finding from a stricter and more statistically stable test implies the need for future research on gene–culture (and gene–environment) interaction. Future research employing multiple methods, including an examination of the neural pathways underlying social orientation and a search for new candidate genes, will enhance our understanding of behavioral traits associated with the history of migration and cultural acquisition.

AUTHOR’S CONTRIBUTION

K.I., T.M., M.M., Y.N., H.Y., and Y.O. designed research. K.I., T.M., and Y.O. performed research. K.I. and M.M. analyzed data. K.I. wrote the paper.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be constructed as a potential conflict of interest.

REFERENCES

Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (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. https://doi.org/10.1002/dev.20152

Belsky, J., Bakermans-Kranenburg, M. J., & van IJzendoorn, M. H. (2007). For better and for worse: Differential susceptibility to environmental influences. Current Directions in Psychological Science, 16(6), 300–304. https://doi.org/10.1111/j.1467-8721.2007.00525.x

Belsky, J., Jonassaint, C., Pluess, M., Stanton, M., Brummett, B., & Williams, R. (2009). Vulnerability genes or plasticity genes? Molecular Psychiatry, 14(8), 746–754. https://doi.org/10.1038/mp.2009.44 Benjamin, J., Li, L., Patterson, C., Greenberg, B. D., Murphy, D. L., & Hamer, D. H. (1996). Population and familial association between the D4 dopamine receptor gene and measures of novelty seeking.
Nature Genetics, 12(1), 81–84. https://doi.org/10.1038/ng0196-81
Carver, C. S., & White, T. L. (1994). Behavioral inhibition, behavioral activation, and affective responses to
impending reward and punishment: The BIS/BAS Scales. Journal of Personality and Social Psychology, 67(2), 319–333. https://doi.org/10.1037/0022-3514.67.2.319
Chang, F. M., Kidd, J. R., Livak, K. J., Pakstis, A. J., & Kidd, K. K. (1996). The world-wide distribution of
allele frequencies at the human dopamine D4 receptor locus. Human Genetics, 98(1), 91–101. https://doi.org/10.1007/s004390050166
Chen, C., Burton, M., Greenberger, E., & Dmitrieva, J. (1999). Population migration and the variation of
dopamine D4 receptor (DRD4) allele frequencies around the globe. Evolution and Human Behavior,
20(5), 309–324. https://doi.org/10.1016/S1090-5138(99)00015-X
Choi, H., & Oishi, S. (2020). The psychology of residential mobility: A decade of progress. Current
Opinion in Psychology, 32, 72–75. https://doi.org/10.1016/j.copsyc.2019.07.008
Choi, I., Koo, M., & Choi, J. A. (2007). Individual differences in analytic versus holistic thinking. Personality and Social Psychology Bulletin, 33(5), 691–705. https://doi.org/10.1177/0146167206298568 Chuang, R., Ishii, K., Kim, H. S., & Sherman, D. K. (2021). Swinging for the fences versus advancing the runner: Culture, motivation, and strategic decision making. Social Psychological and Personality
Science. Advance online publication. https://doi.org/10.1177/1948550621999273
Costa, P. T., & McCrae, R. R. (1992). Revised NEO Personality Inventory (NEO-PI-R) and NEO Five-
Factor Inventory (NEO-FFI) professional manual. Psychological Assessment Resources.
Dick, D. M., Agrawal, A., Keller, M. C., Adkins, A., Aliev, F., Monroe, S., Hewitt, J. K., Kendler, K. S., & Sher, K. J. (2015). Candidate gene–environment interaction research: Reflections and recommendations.
Perspectives on Psychological Science, 10(1), 37–59. https://doi.org/10.1177/1745691614556682 Ding, Y. C., Chi, H. C., Grady, D. L., Morishima, A., Kidd, J. R.,

Kidd, K. K., Flodman, P., Spence, M. A., Schuck, S., Swanson, J. M., Zhang, Y. P., & Moyzis, R. K. (2002). Evidence of positive selection acting at the human dopamine receptor D4 gene locus. Proceedings of the National Academy of Sciences, 99(1), 309–314. https://doi.org/10.1073/pnas.012464099

Duncan, L. E., & Keller, M. C. (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. https://doi.org/10.1176/appi.ajp.2011.11020191

Ebstein, R. P., Novick, O., Umansky, R., Priel, B., Osher, Y., Blaine, D., Bennett, E. R., Nemanov, L., Katz, M., & Belmaker, R. H. (1996). Dopamine D4 receptor (D4DR) exon III polymorphism associated with the human personality trait of Novelty Seeking. Nature Genetics, 12(1), 78–80. https:// doi.org/10.1038/ng0196-78

Eisenberg, D. T., Campbell, B., Gray, P. B., & Sorenson, M. D. (2008). Dopamine receptor genetic polymorphisms and body composition in undernourished pastoralists: An exploration of nutrition indices among nomadic and recently settled Ariaal men of northern Kenya. BMC Evolutionary Biology, 8, Article 173. https://doi.org/10.1186/1471-2148-8-173

Glazer, J., King, A., Yoon, C., Liberzon, I., & Kitayama, S. (2020). DRD4 polymorphisms modulate reward positivity and P3a in a gambling task: Exploring a genetic basis for cultural learning. Psychophysiology, 57(10), Article e13623. https://doi.org/10.1111/psyp.13623

Hamamura, T., Meijer, Z., Heine, S. J., Kamaya, K., & Hori, I. (2009). Approach—avoidance motivation and information processing: A cross-cultural analysis. Personality and Social Psychology Bulletin, 35(4), 454–462. https://doi.org/10.1177/0146167208329512

Henn, B. M., Cavalli-Sforza, L. L., & Feldman, M. W. (2012). The great human expansion. Proceedings of the National Academy of Sciences, 109(44), 17758–17764. https://doi.org/10.1073/pnas.1212380109

Ishii, K., & Eisen, C. (2020). Socioeconomic status and cultural differences. In Oxford Research Encyclopedia of Psychology. Oxford University Press. https://doi.org/10.1093/acrefore/9780190236557.013.584

Ishii, K., Masuda, T., Matsunaga, M., Noguchi, Y., Yamasue, H., & Ohtsubo, Y. (2021). Do culture and oxytocin receptor polymorphisms interact to influence emotional expressivity? Culture and Brain, 9(1), 20–34. https://doi.org/10.1007/s40167-020-00091-5

Jern, P., Verweij, K. J., Barlow, F. K., & Zietsch, B. P. (2017). Reported associations between receptor genes and human sociality are explained by methodological errors and do not replicate. Proceedings of the National Academy of Sciences, 114(44), E9185–E9186. https://doi.org/10.1073/pnas.1710880114

Kim, H. S., & Sasaki, J. Y. (2014). Cultural neuroscience: Biology of the mind in cultural context. Annual Review of Psychology, 65, 487–514. https://doi.org/10.1146/annurev-psych-010213-115040

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), 1–11. https://doi.org/10.1037/0022- 3514.92.1.1

Kitayama, S., Duffy, S., Kawamura, T., & Larsen, J. T. (2003). Perceiving an object and its context in different cultures: A cultural look at new look. Psychological Science, 14(3), 201–206. https:// doi.org/10.1111/1467-9280.02432

Kitayama, S., King, A., Hsu, M., Liberzon, I., & Yoon, C. (2016). Dopamine-system genes and cultural acquisition: The norm sensitivity hypothesis. Current Opinion in Psychology, 8, 167–174. https:// doi.org/10.1016/j.copsyc.2015.11.006

Kitayama, S., King, A., 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. https://doi.org/10.1177/0956797614528338

Kitayama, S., Markus, H. R., Matsumoto, H., & Norasakkunkit, V. (1997). Individual and collective processes in the construction of the self: Self-enhancement in the United States and self-criticism in Japan. Journal of Personality and Social Psychology, 72(6), 1245–1267. https://doi.org/10.1037/ 0022-3514.72.6.1245

Kitayama, S., Yanagisawa, K., Ito, A., Ueda, R., Uchida, Y., & Abe, N. (2017). Reduced orbitofrontal cortical volume is associated with interdependent self-construal. Proceedings of the National Academy of Sciences, 114(30), 7969–7974. https://doi.org/10.1073/pnas.1704831114

Kitayama, S., Yu, Q., King, A. P., Yoon, C., & Liberzon, I. (2020). The gray matter volume of the temporoparietal junction varies across cultures: A moderating role of the dopamine D4 receptor gene (DRD4). Social Cognitive and Affective Neuroscience, 15(2), 193–202. https://doi.org/10.1093/scan/nsaa032

Kuhnen, C. M., & Chiao, J. Y. (2009). Genetic determinants of financial risk taking. PLOS ONE, 4(2),
Article e4362. https://doi.org/10.1371/journal.pone.0004362

Lichter, J. B., Barr, C. L., Kennedy, J. L., van Tol, H. H., Kidd, K. K., & Livak, K. J. (1993). A hypervariable segment in the human dopamine receptor D4 (DRD4) gene. Human Molecular Genetics, 2(6), 767–773. https://doi.org/10.1093/hmg/2.6.767

Ma, Y., Wang, C., Li, B., Zhang, W., Rao, Y., & Han, S. (2014). Does self-construal predict activity in the
social brain network? A genetic moderation effect. Social Cognitive and Affective Neuroscience,

9(9), 1360–1367. https://doi.org/10.1093/scan/nst125

Matsunaga, M., Masuda, T., Ishii, K., Ohtsubo, Y., Noguchi, Y., Ochi, M., & Yamasue, H. (2018). Culture and cannabinoid receptor gene polymorphism interact to influence the perception of happiness. PLOS ONE, 13(12), Article e0209552. https://doi.org/10.1371/journal.pone.0209552

Matthews, L. J., & Butler, P. M. (2011). Novelty-seeking DRD4 polymorphisms are associated with human migration distance out-of-Africa after controlling for neutral population gene structure. American Journal of Physical Anthropology, 145(3), 382–389. https://doi.org/10.1002/ajpa.21507

Montag, C., Ebstein, R. P., Jawinski, P., & Markett, S. (2020). Molecular genetics in psychology and personality neuroscience: On candidate genes, genome wide scans, and new research strategies. Neuroscience & Biobehavioral Reviews, 118, 163–174. https://doi.org/10.1016/j.neubiorev.2020.06.020 Na, J., Grossmann, I., Varnum, M. E., Kitayama, S., Gonzalez, R., & Nisbett, R. E. (2010). Cultural differences are not always reducible to individual differences. Proceedings of the National Academy of Sciences, 107(14), 6192–6197. https://doi.org/10.1073/pnas.1001911107

Nikolova, Y. S., Ferrell, R. E., Manuck, S. B., & Hariri, A. R. (2011). Multilocus genetic profile for dopamine signaling predicts ventral striatum reactivity. Neuropsychopharmacology, 36(9), 1940–1947. https://doi.org/10.1038/npp.2011.82

Obradović, J., & Boyce, W. T. (2009). Individual differences in behavioral, physiological, and genetic sensitivities to contexts: Implications for development and adaptation. Developmental Neuroscience, 31(4), 300–308. https://doi.org/10.1159/000216541

Park, J., & Kitayama, S. (2014). Interdependent selves show face-induced facilitation of error processing: Cultural neuroscience of self-threat. Social Cognitive and Affective Neuroscience, 9(2), 201–208. https://doi.org/10.1093/scan/nss125

Reist, C., Ozdemir, V., Wang, E., Hashemzadeh, M., Mee, S., & Moyzis, R. (2007). Novelty seeking and the dopamine D4 receptor gene (DRD4) revisited in Asians: Haplotype characterization and relevance of the 2-repeat allele. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 144(4), 453–457. https://doi.org/10.1002/ajmg.b.30473

Richerson, P. J., & Boyd, R. (2008). Not by genes alone: How culture transformed human evolution. University of Chicago Press. https://doi.org/10.7208/chicago/9780226712130.001.0001

Rosenberg, M. (1965). Society and the adolescent self-image. Princeton University Press. https:// doi.org/10.1515/9781400876136

Ross, M., Xun, W. E., & Wilson, A. E. (2002). Language and the bicultural self. Personality and Social Psychology Bulletin, 28(8), 1040–1050. https://doi.org/10.1177/01461672022811003

Royo, J. L., Valls, J., Acemel, R. D., Gómez-Marin, C., Pascual-Pons, M., Lupiañez, A., Gomez-Skarmeta, J. L., & Fibla, J. (2018). A common copy-number variant within SIRPB1 correlates with human Out- of-Africa migration after genetic drift correction. PLOS ONE, 13(3), Article e0193614. https:// doi.org/10.1371/journal.pone.0193614

Sasaki, J. Y., & Kim, H. S. (2017). Nature, nurture, and their interplay: A review of cultural neuroscience. Journal of Cross-Cultural Psychology, 48(1), 4–22. https://doi.org/10.1177/0022022116680481 Sasaki, J. Y., Kim, H. S., Mojaverian, T., Kelley, L. D. S., Park, I. Y., & Janušonis, S. (2013). Religion priming differentially increases prosocial behavior among variants of the dopamine D4 receptor (DRD4) gene. Social Cognitive and Affective Neuroscience, 8(2), 209–215. https://doi.org/10.1093/scan/nsr089

Schmitt, D. P., Allik, J., McCrae, R. R., & Benet-Martínez, V. (2007). The geographic distribution of Big Five personality traits: Patterns and profiles of human self-description across 56 nations. Journal of Cross-Cultural Psychology, 38(2), 173–212. https://doi.org/10.1177/0022022106297299

Schwarzer, R., Mueller, J., & Greenglass, E. (1999). Assessment of perceived general self-efficacy on the Internet: Data collection in cyberspace. Anxiety, Stress, & Coping, 12(2), 145–161. https://doi.org/10.1080/10615809908248327

Shimonaka, Y., Nakazato, K., Gondo, Y., & Takayama, M. (1999). Nihon-ban NEO-PI-R, NEO-FFI shiyo manyuaru [NEO-PI-R, NEO-FFI manual for the Japanese version] (revised and enlarged ed.). Tokyo Shinri.

Singelis, T. M. (1994). The measurement of independent and interdependent self-construals. Personality and Social Psychology Bulletin, 20(5), 580–591. https://doi.org/10.1177/0146167294205014

Spencer-Rodgers, J., Srivastava, S., & Peng, K. (2001). The dialectical self scale [Unpublished data]. Takahashi, Y., Yamagata, S., Kijima, N., Shigemasu, K., Ono, Y., & Ando, J. (2007). Gray's temperament model: Development of Japanese version of BIS/BAS scales and a behavior genetic investigation using the twin method. Japanese Journal of Personality, 15(3), 276–289. https://doi.org/10.2132/ personality.15.276

Takata, T. (1999). Developmental process of independent and interdependent self-construal in Japanese culture: Cross-cultural and cross-sectional analyses. Japanese Journal of Educational Psychology, 47(4), 480–489. https://doi.org/10.5926/jjep1953.47.4_480

Talhelm, T., Zhang, X., Oishi, S., Shimin, C., Duan, D., Lan, X., & Kitayama, S. (2014). Large-scale psychological differences within China explained by rice versus wheat agriculture. Science, 344(6184), 603–608. https://doi.org/10.1126/science.1246850

Timmermann, A., & Friedrich, T. (2016). Late Pleistocene climate drivers of early human migration. Nature, 538(7623), 92–95. https://doi.org/10.1038/nature19365

Vignoles, V. L., Owe, E., Becker, M., Smith, P. B., Easterbrook, M. J., Brown, R., González, R., Didier, N., Carrasco, D., Cadena, M. P., Lay, S., Schwartz, S. J., Des Rosiers, S. E., Villamar, J. A., Gavreliuc, A., Zinkeng, M., Kreuzbauer, R., Baguma, P., Martin, M., . . . Bond, M. H. (2016). Beyond the 'East–West' dichotomy: Global variation in cultural models of selfhood. Journal of Experimental Psychology: General, 145(8), 966–1000. https://doi.org/10.1037/xge0000175

Way, B. M., & Taylor, S. (2010). The serotonin transporter promoter polymorphism is associated with cortisol response to psychosocial stress. Biological Psychiatry, 67(5), 487–492. https://doi.org/ 10.1016/j.biopsych.2009.10.021

Yu, Q., Abe, N., King, A., Yoon, C., Liberzon, I., & Kitayama, S. (2019). Cultural variation in the gray matter volume of the prefrontal cortex is moderated by the dopamine D4 receptor gene (DRD4). Cerebral Cortex, 29(9), 3922–3931. https://doi.org/10.1093/cercor/bhy271

Zhang, Y. L., & Tsai, J. L. (2014). The assessment of acculturation, enculturation, and culture in Asian- American samples. In L. T. Benuto, N. S. Thaler, & B. D. Leany (Eds.), Guide to psychological assessment with Asians (pp. 75–101). Springer. https://doi.org/ 10.1007/978-1-4939-0796-0_6

Zheng, S., Masuda, T., Matsunaga, M., Noguchi, Y., Ohtsubo, Y., Yamasue, H., & Ishii, K. (2020). Oxytocin receptor gene (OXTR) and childhood adversity influence trust. Psychoneuroendocrinology, 121, Article 104840. https://doi.org/10.1016/ j.psyneuen.2020.104840

(Manuscript received 30 January, 2021; Revision accepted 14 May, 2021; Released online in J-STAGE as advance publication 21 July, 2021)