ORIGINAL RESEARCH

Culture modulates sensitivity to the disappearance of facial expressions associated with serotonin transporter polymorphism (5-HTTLPR)

Keiko Ishii · Heejung S. Kim · Joni Y. Sasaki · Mizuho Shinada · Ichiro Kusumi

Abstract   The present research investigated an association between the serotonin transporter polymorphism (5-HTTLPR) and sensitivity to the disappearance of facial expressions cross-culturally and found, for the first time, that cultural norms and practices modulate the association. Participants watched both happy-to-neutral and sad-to-neutral movies and judged the point at which the emotional expressions disappeared. As predicted, the results showed that Japanese with the s/s genotype detected the disappearance of facial expressions (particularly the disappearance of smiles) with greater perceptual efficiency than did those with s/l and l/l genotypes, whereas such a tendency was not found in Americans. This suggests that people with the s/s genotype of 5-HTTLPR are more sensitive to environmental changes, but only when the change is culturally important, compared to people with the long allele. Moreover, Asian Americans' pattern was much more similar to European Americans than to Japanese, supporting the idea that the differences between cultural groups are indeed due to different cultural experiences.

K. Ishii (✉)
Department of Psychology, Faculty of Letters, Kobe University, 1-1 Rokkodai-cho, Nada-ku, Kobe 657-8501, Japan
e-mail: ishii@lit.kobe-u.ac.jp

H. S. Kim
Department of Psychological and Brain Sciences, University of California, Santa Barbara, CA, USA

J. Y. Sasaki
Department of Psychology, York University, Toronto, ON, Canada

M. Shinada
Department of Social Psychology, Faculty of Letters, University of Tokyo, Tokyo, Japan

I. Kusumi
Department of Psychiatry, Graduate School of Medicine, Hokkaido University, Sapporo, Japan

There is a growing body of research showing that one's psychological tendency may emerge as a result of an interaction between genetic and environmental factors, and that certain genes may be associated with greater plasticity or susceptibility to the environment (see Belsky et al. 2007, 2009; Obradovic and Boyce 2009; Way and Taylor 2010). Broadening the idea of gene–environment interactions, researchers have proposed gene–culture interactions that include culturally specific norms and practices as environmental factors (Kim and Sasaki 2014). Recent studies have suggested that certain genes of greater plasticity or susceptibility to the environment foster a more culture-specific way of behaving. Thus, people with particular genotypes are likely to respond more strongly to culture-specific norms and practices and show more culturally contingent tendencies of behaviors, compared to those with other genotypes (Kim et al. 2010a, b, 2011). The present study focuses on a gene in the serotonin-transporter-linked polymorphic region (5-HTTLPR) and examines the possibility that culture interacts with 5-HTTLPR to impact emotional processing, specifically the sensitivity to detecting changes in the emotional state of another person.

5-HTTLPR and emotional processing

The serotonin transporter (5-HTT) plays an important role in regulating serotonergic neurotransmission, which contributes to cognition and emotional states, including mood and anxiety (Hariri and Holmes 2006). Studies have shown that individuals carrying a short (s) versus long (l) allele of this 5-HTT gene-linked polymorphic region (5-HTTLPR) are different in the extent to which the gene is expressed. Having the short allele is associated with reduction in brain 5-HTT binding (Heinz et al. 2000), which may be linked to emotional processing. Pioneering work by Lesch et al. (1996) showed that individuals carrying one or two copies of the short allele of 5-HTTLPR are higher in the NEO personality inventory factor of neuroticism (Costa and McCrae 1997) than those who are homozygous for the long allele of 5-HTTLPR. Moreover, compared to those with the l/l genotype, short allele carriers are more likely to attend to fear-relevant stimuli (Osinsky et al. 2008), exhibit greater amygdala activity in response to angry and fearful faces (Hariri et al. 2002), have disorganized attachment (Caspers et al. 2009), experience anxious mood (Gunthert et al. 2007), and avoid risk taking (Kuhnen and Chiao 2009). These features relate to harm avoidance and sensitivity to threat, which would be adaptive in an environment where intra-group competition levels are elevated (Dobson and Brent 2013). Furthermore, recent studies have suggested that 5-HTTLPR influences sensitivity to various emotional stimuli, showing greater neural activation to both negative and positive stimuli, compared to neutral stimuli (e.g., Beevers et al. 2009; Canli et al. 2005, 2008).

Other studies focusing on the relationship between stress and psychological state have also shown that compared to long allele carriers, people who are homozygous for the short allele of 5-HTTLPR appear to be more environmentally sensitive, demonstrating greater plasticity or susceptibility to environmental inputs (Caspi et al. 2003; Taylor et al. 2006; see Obradovic and Boyce 2009; Way and Taylor 2010 for review). In particular, these studies show that compared to long allele carriers, individuals with the s/s genotype are at greater risk for psychological disorders (e.g., depression) when they experience stressful life events or harsh family environment, whereas their risk for psychological disorders is actually lower when they have positive and supportive social environments.

These gene–environment interaction studies usually frame "environments" as personal experiences with distress or supportiveness and examine their impact on one's well-being and psychological health. More recent research on gene–culture interactions (Kim et al. 2010a, b, 2011; see Kim and Sasaki 2014 for review) has proposed a model including cultural norms and practices in the notion of environment. In the model, culture is conceptually different from environment in at least two ways. First, the model frames "culture" as a collective-level phenomenon including collectively shared norms, values, and daily practices. Second, assuming that cultural differences reflect each cultural group's adaptation to the cultural environment, the model examines not only one's well-being and psychological health, but also normative behaviors and psychological tendencies. The gene–culture interaction model considers a genetic basis for the susceptibility to environment and addresses the extent to which culture moderates the association between genes and behavioral and psychological tendencies.

The present study builds on earlier studies on gene–culture interaction, and aims to extend it by including different aspects of the environment. That is, in addition to culture, we varied a more situational aspect of the environment—valence of emotional cues. From a gene–environment interaction perspective, there are a few studies showing that people with different genotypes may differ in their sensitivity in responding to even fleeting situational cues (Sasaki et al. 2013). By adding culture as another variable in which the situational cues take place, the present study aims to test whether culture modulates the link between a gene and emotional processing, particularly sensitivity to negative and positive emotional stimuli. Consistent with previous findings, we expected that individuals with the s/s genotype of 5-HTTLPR would respond more strongly to emotional stimuli than would those with long alleles. However, based on the gene–culture interaction framework, we expected that environmentally sensitive individuals would respond most strongly to different aspects of emotional events, depending on the norms and practices of the broader cultural context.

Cultural differences in sensitivity to the disappearance of facial expressions

Culture is conceptualized as a collective-level phenomenon that is composed of both socially shared meanings such as ideas and beliefs and scripted behavioral patterns of norms and practices (Kitayama and Uskul 2011). While every human lives within

a cultural system, the core values, beliefs, and practices vary drastically from one culture to another. One of the primary domains in which cultures differ is in how people view the self. Culturally divergent views of the self are characterized as relatively independent and separate from other people in Western cultural contexts, and as more interdependent and connected with others in Eastern cultural contexts (Markus and Kitayama 1991).

Researchers have proposed that control and efficacy are emphasized as a way to maintain the independent view of self in Western cultures, whereas adjustment and connectedness are often emphasized as ways to maintain the interdependent view of self in East Asian cultures (Morling et al. 2002; Weisz et al. 1984). Although it brings benefits to social relationship maintenance, emphasis on adjustment and connectedness could also produce negative outcomes in East Asian cultures. For example, East Asians and Asian Americans tend to experience higher social anxiety than European Americans (Norasakkunkit and Kalick 2002; Okazaki 1997). Also, Japanese are higher in level of attachment-related anxiety and avoidance than European Americans (Ishii et al. 2011).

There also is a cultural difference in the extent to which a person may be concerned about other people approving of his or her behaviors (Suh et al. 1998). Depending on culture, a person may be more or less vigilant to non-verbal signs implying that one is falling short of other's expectations or undermining social harmony. One example is the gradual disappearance of a smile, which should be a dynamic cue indicating that expectations have been violated. Using the morph movie paradigm (Niedenthal et al. 2000), Ishii et al. (2011) examined cultural differences in sensitivity to the disappearance of facial expressions between European Americans and Japanese. The results showed that compared to European Americans, Japanese judged the disappearance of smiles faster. That is, Japanese were particularly vigilant to signs of the disappearance of a smile. On the other hand, there was no cultural difference in detecting the disappearance of others' frowns. This suggests that the disappearance of others' negative expressions should not pose a threat to social relationships or require either Japanese or Americans to adjust their behavior.

The Ishii et al. (2011) study suggests that Japanese respond more quickly to the disappearance of smiles, reflecting cultural norms and practices that emphasize concerns about other people's approval. In contrast, in a North American cultural context, concerns about others' approval are relatively less emphasized. Building on this study, we raised the question of how cultural norms and practices emphasizing the importance of social approval modulate the association between 5-HTTLPR and processing of emotional cues. To answer this question, by using the task developed by Ishii et al. (2011), we examined an association between 5-HTTLPR and response to the disappearance of positive and negative facial emotions in two cultures that differ in their emphasis on concerns about social approval. It is important to note that the stimuli in the current study differ from emotional stimuli in previous studies involving genes. Rather than measuring the degree of reactivity to unambiguous and static emotional cues (e.g., Hariri et al. 2002), the current task measures sensitivity to changes in emotional cues. Thus, this study provides a novel way of examining environmental sensitivity.

The present study

This study builds on the framework of gene–culture interactions by examining 5-HTTLPR and cultural differences in sensitivity to the disappearance of positive and negative facial expressions. North Americans and Japanese were exposed to happy-to-neutral and sad-to-neutral movies and were instructed to determine the offset of the initial facial expression. Replicating the Ishii et al. (2011) study, we expected an interaction between culture and facial expressions.

Moreover, we also expected an interaction between culture and genotypes of 5-HTTLPR. If 5-HTTLPR is associated with sensitivity to emotional stimuli (e.g., Canli et al. 2005, 2008), then the association should vary between cultures that differ in their relative emphasis on social approval. More specifically, we predicted that the s/s genotype of 5-HTTLPR would lead people to respond more quickly to the disappearance of facial expressions, compared to the s/l or l/l genotypes in Japanese culture, where people are more vigilant to social approval and disapproval. Moreover, this genetic difference would be particularly pronounced in the case of smiles disappearing because it represents a disappearance of social approval, a potentially threatening social cue. In contrast, in North American culture, where vigilance to social approval is not a culturally fostered behavior and is even at times discouraged (cf. Kim and Markus 1999), 5-HTTLPR genotype may not impact how quickly people respond to the disappearance of facial expressions. In sum, we predicted that Japanese with the s/s genotype would judge the disappearance of facial expressions faster than would those with s/l and l/l genotypes. In contrast, we expected that the difference between genotypes would be negligible in North Americans.

For triangulation purposes we included a group of East Asian Americans who were raised in North American culture. In so doing, we also tested whether cultural experiences in North America or shared genetic attributes with East Asians influenced their responses, following the triangulation method used in previous studies (e.g., Kim et al. 2010a, b, 2011).

Method

Participants and procedure

One hundred and ninety-six American undergraduates [146 European Americans (90 females, 53 males, and 3 gender not specified), 47 East Asian American undergraduates (34 females and 13 males), and 3 who did not report their ethnicity] and 153 Japanese undergraduates (94 females, 57 males, and 2 gender not specified) participated in the study. Only Asian American participants who indicated that they were originally from East Asian cultures (i.e., China, Korea, Japan, and Taiwan) were included.[1] Eleven out of the East Asian American participants were not born in the U.S., but have lived there since their childhood ($M = 15.45$ years,

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[1] The ethnic backgrounds were as follows: Chinese (24), Korean (15), Japanese (7), and Taiwanese (1).

$SD = 3.05$ years). The remaining East Asian American participants were born and raised in the U.S. American students were recruited in the U.S. and received course credit or $10, while Japanese students were recruited in Japan and paid 1000 yen ($\sim$$10). Participants were tested individually on laboratory computers.

After filling out a consent form, participants were initially asked to perform the morph movie task (Niedenthal et al. 2000) according to the procedure used by Ishii et al. (2011). Following two practice trials, participants completed 32 trials watching morph movies that depicted a target person's happy or sad facial expression gradually fading. On each trial, they first watched a complete movie once. Then they watched it again and, by pressing a key, indicated the point at which they thought the target person was no longer expressing the initial emotion. They could fine-tune their stopping point by pressing another set of keys, and when they were satisfied with their judgment, they pressed a final answer key and began the next trial.

Morph movie task stimuli

The morph movie task program was developed on Microsoft Visual Basic 6. A set of 32 movies [= 4 people × 2 genders × 2 ethnicities (European Americans and Japanese) × 2 emotions (happiness to neutral and sadness to neutral)] developed by Ishii et al. (2011) were used for the morph movie task. Ishii et al. (2011) developed the set by initially selecting pictures of 4 females and 4 males from each culture, which were perceived to express one of three emotions (happy, sad, or neutral) by both Japanese and European American raters. Using a digital morphing program (FantaMorph Version 3; http://www.fantamorph.com/), 100-frame digital movies were produced in which either a happy or a sad expression changed to a neutral expression for the same individual's face. The image size was 170 × 225 pixels, and the length of each movie was 8.33 s (i.e., 12 frames per a second). Example still shots from the movies are shown in Fig. 1. Ishii et al. (2011) showed that there was no cultural difference in the relative intensity of happy and sad expressions perceived compared to neutral expressions, although the intensity of happiness was perceived to be larger than the intensity of sadness overall, suggesting no cultural difference in terms of perceived intensity of emotional expression for the set of pictures used.

Genotyping

Saliva samples were collected with the Oragene collection device (Genotek). Per manufacturer recommendations, the samples were kept at room temperature prior to DNA extraction. DNA was extracted as per manufacturer recommendation (DNA Genotek, Ontario, Canada). DNA was quantitated using A260/A280 ratio, and 5-HTTLPR was identified using the following protocol. Briefly, 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. Polymerase chain reaction (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) MgCl$_2$, 2 % DMSO (v/v), 2.5 U Amplitaq Gold

Fig. 1 Example still shots from morph movies (*top* happy-to-neutral Japanese movie, *bottom* sad-to-neutral Caucasian movie)

DNA polymerase (Applied Biosystems, Foster City, CA, USA), and 2 μL of Deaza dNTP (2 mM each dATP, dCTP, dTTP, 1 mM dGTP, 1 mM deaza dGTP). Cycling conditions consisted of: (1) an initial 12 min denaturation at 94 °C, (2) 8 cycles with denaturation 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).

Results

Genotype distribution

Consistent with previous studies indicating greater prevalence of s carriers of 5-HTTLPR in East Asian regions (Chiao and Blizinsky 2010; Gelernter et al. 1997), the frequency of s allele carriers was higher in Japanese (93 s/s, 54 s/l, and 3 l/l) than in Americans (50 s/s, 81 s/l, and 57 l/l), including East Asian Americans, $\chi^2(2, N = 338) = 63.46$, $p < 0.0001$. Moreover, the frequency of s allele carriers in East Asian Americans (17 s/s, 20 s/l, and 6 l/l) was higher than in European Americans (33 s/s, 61 s/l, and 51 l/l), $\chi^2(2, N = 188) = 8.59$, $p < 0.02$, and lower than in Japanese, $\chi^2(2, N = 193) = 14.16$, $p < 0.001$. The distribution of genotypes did not deviate significantly from Hardy–Weinberg equilibrium in all cultural groups (Japanese: $\chi^2(1) = 2.34$, $p = 0.13$, European American: $\chi^2(1) = 3.07$, $p = 0.08$, East Asian American: $\chi^2(1) = 0.001$, $p = 0.97$).

Morph task

Eleven participants were excluded from the following analyses because either their genotypes were undetermined or their ethnicities were not reported. The data from

the remaining 338 participants were analyzed. Because proportion of individuals with l/l genotype in Japan was quite small ($n = 3$), we initially analyzed American (including East Asian Americans) and Japanese data by classifying participants with s/l genotype as l carriers and combining their data with the data of participants with l/l genotypes.[2] We then compared East Asian American data to European American and Japanese data to test whether differences in genetic attributes influenced their responses (see the "Supplemental analysis" section below).

To test our hypotheses, the offset frames were first log-transformed (base e) because the distribution was negatively skewed. We then computed relevant means for each participant across both ingroup and outgroup faces in each of the expression conditions (i.e., smile vs. frown expression) and performed an ANOVA on the log-transformed means with three between-subject variables (culture of participant: Americans vs. Japanese, genotype: s/s vs. s/l–l/l, and gender: female vs. male) and one within-subject variable (expression: smile vs. frown and ethnicity of face: Caucasian vs. Asian). As expected, the two-way interaction between culture of participant and expression was significant, $F(1, 325) = 4.63$, $p < 0.05$, $\eta^2 = 0.01$. Moreover, the two-way interaction between culture of participant and genotype was significant, $F(1, 325) = 6.43$, $p < 0.05$, $\eta^2 = 0.02$. The culture-by-genotype interaction was also qualified by a significant 3-way interaction with facial expression, $F(1, 325) = 5.37$, $p < 0.05$, $\eta^2 = 0.02$. However, planned pairwise comparisons showed that neither differences between genotypes in Japanese and Americans nor differences between genotypes in the judgment for the disappearance of smile and frown faces were significant with one exception.[3] No gender effect was found.

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[2] For Americans, we examined the s/s genotype separately from s/l and l/l genotypes. Those results indicated a linear pattern showing that people with the s/s genotype were slower to detect the disappearance of smiles than those with s/l and l/l genotypes. Please see footnote 5 for the details of the results.

[3] When response to ingroup and outgroup faces were included, both Japanese and Americans judged the offset of smile faces (Japanese: $M = 4.32$, $SD = 0.17$, Americans: $M = 4.29$, $SD = 0.24$) significantly faster than that of frown faces (Japanese: $M = 4.38$, $SD = 0.12$, Americans: $M = 4.33$, $SD = 0.15$), $t(325) = 5.12$, $p < 0.0001$, $d = 0.57$, 95 % CI [0.04, 0.08] for Japanese, $t(325) = 4.04$, $p < 0.0001$, $d = 0.45$, 95 % CI [0.02, 0.06] for Americans. However, the significant interaction between culture and expression indicates that the tendency is stronger in Japanese than in Americans. As for the effect of genotype, 5-HTTLPR genotype did not impact how quickly people respond to the disappearance of facial expressions in Japanese (s/s genotype ($M = 4.34$, $SD = 0.16$), s/l–l/l genotypes ($M = 4.37$, $SD = 0.12$), $t(325) = 1.39$, $p = 0.17$, $d = 0.15$, 95 % CI [-0.01, 0.09]. Rather, Americans with s/s genotype ($M = 4.35$, $SD = 0.14$) tended to respond slower to the disappearance of facial expressions than did those with s/l–l/l genotypes ($M = 4.30$, $SD = 0.22$), $t(325) = 1.90$, $p = 0.058$, $d = 0.21$, 95 % CI [0, 0.10]. In addition, in the offset of smile faces the impact of 5-HTTLPR genotype was not found in Japanese (s/s genotype ($M = 4.30$, $SD = 0.18$), s/l–l/l genotypes ($M = 4.34$, $SD = 0.14$), $t(325) = 1.43$, $p = 0.15$, $d = 0.16$, 95 % CI [-0.02, 0.10]), whereas Americans with s/s genotype ($M = 4.35$, $SD = 0.16$) were significantly slower compared to those with s/l–l/l genotypes ($M = 4.27$, $SD = 0.25$), $t(325) = 3.01$, $p < 0.01$, $d = 0.33$, 95 % CI [0.03, 0.14]. In the judgment for the offset of frown faces, the impact of 5-HTTLPR genotype was not found regardless of cultures (Japanese: s/s genotype ($M = 4.37$, $SD = 0.13$), s/l–l/l genotypes ($M = 4.40$, $SD = 0.10$), $t(325) = 1.01$, $p = 0.31$, $d = 0.11$, 95 % CI [-0.03, 0.09], American: s/s genotype ($M = 4.34$, $SD = 0.13$), s/l–l/l genotypes ($M = 4.33$, $SD = 0.16$), $t(325) = 0.43$, $p = 0.67$, $d = 0.05$, 95 % CI [-0.04, 0.07]).

This result might be interpreted in terms of cultural differences in daily frequency of exposure to cultural outgroup members. Ishii et al. (2011) found that people process expressions displayed by ingroup faces with greater efficiency than outgroup faces in the morph task, which is consistent with findings of an ingroup advantage in recognizing emotional expressions (e.g., Elfenbein and Ambady 2002). Because North American participants were recruited from a West coast university where Asians and Asian Americans make up a sizeable minority of the student body, daily frequency of exposure to Asians' facial expressions in the group of Americans should be higher compared to the daily frequency of exposure to European Americans' facial expressions in the group of Japanese. This difference in daily frequency of exposure to cultural outgroup faces might mask expected differences by culture and gene in processing the disappearance of facial expressions. We thus compared response to cultural ingroup faces (i.e., Japanese faces for Japanese and Caucasian faces for Americans) between Japanese and Americans to test our predictions again.

As expected, the two-way interaction between culture of participant and expression was significant, $F(1, 325) = 19.15$, $p < 0.0001$, $\eta^2 = 0.05$. Although Japanese ($M = 4.29$, $SD = 0.19$) judged the offset of smile faces faster than did Americans ($M = 4.30$, $SD = 0.21$), the difference was not significant, $t(325) = 0.69$, $p = 0.49$, $d = 0.08$, 95 % CI [-0.02, 0.05]. However, Japanese judged the offset of smile faces ($M = 4.29$, $SD = 0.19$) significantly faster than that of frown faces ($M = 4.38$, $SD = 0.12$), $t(325) = 6.91$, $p < 0.0001$, $d = 0.77$, 95 % CI [0.06, 0.11], consistent with Ishii et al. (2011). The difference between judgments was marginally significant in Americans (smile: $M = 4.30$, $SD = 0.21$; frown: $M = 4.32$, $SD = 0.15$), $t(325) = 1.76$, $p = 0.079$, $d = 0.20$, 95 % CI [0, 0.04].

In addition, as expected, the two-way interaction between culture of participant and genotype was significant, $F(1, 325) = 7.46$, $p < 0.05$, $\eta^2 = 0.02$. Regardless of facial expression, participants with s/s genotype ($M = 4.32$, $SD = 0.17$) judged the offset somewhat faster than did those with s/l or l/l genotypes ($M = 4.36$, $SD = 0.14$) among Japanese, $t(325) = 1.69$, $p = 0.092$, $d = 0.19$, 95 % CI [0, 0.10], whereas participants with the s/s genotype ($M = 4.35$, $SD = 0.13$) judged the offset somewhat slower than did those with s/l and l/l genotypes ($M = 4.30$, $SD = 0.20$) among Americans, $t(325) = 1.73$, $p = 0.085$, $d = 0.19$, 95 % CI [0, 0.09].

The culture-by-genotype interaction was also qualified by a significant 3-way interaction with facial expression, $F(1, 325) = 5.93$, $p < 0.05$, $\eta^2 = 0.02$. The mean untransformed offset of smile and the mean untransformed offset of frown between the two cultural groups in the two genotypes are shown in Fig. 2. Japanese with the s/s genotype ($M = 4.27$, $SD = 0.20$) judged the offset of smile faces faster than did those with s/l or l/l genotypes ($M = 4.33$, $SD = 0.16$), $t(325) = 1.88$, $p = 0.061$, $d = 0.21$, 95 % CI [0, 0.11], whereas there was no difference in the offset of frown faces between the s/s and s/l–l/l genotypes (s/s: $M = 4.37$, $SD = 0.12$; s/l–l/l: $M = 4.40$, $SD = 0.10$), $t(325) = 1.13$, $p = 0.26$, $d = 0.13$, 95 % CI [-0.02, 0.09]. Americans with the s/s genotype ($M = 4.36$, $SD = 0.13$) judged the offset of smile faces significantly slower than did those with s/l or l/l

genotypes ($M = 4.28$, $SD = 0.23$), $t(325) = 2.81$, $p < 0.01$, $d = 0.31$, 95 % CI [0.02, 0.14], whereas there was no difference in the offset of frown faces between the s/s and s/l–l/l genotypes (s/s: $M = 4.33$, $SD = 0.14$; s/l–l/l: $M = 4.32$, $SD = 0.15$), $t(325) = 0.25$, $p = 0.70$, $d = 0.03$, 95 % CI [−0.05, 0.06].[4]

Supplemental analysis

Because Japanese and North Americans differ not only in terms of culture but also in the makeup of genes other than the gene examined in the present study, gene–gene interactions (Kaufman et al. 2006) are a potential alternative explanation for the present results. Thus, following the triangulation methods used in previous research (e.g., Kim et al. 2010a, b, 2011), we compared East Asian American participants and European Americans to examine the role of cultural exposure.

For the American data, we performed an ANOVA on the means with three between-subject variables (ethnicity of participant: European Americans vs. East Asian Americans, genotype: s/s vs. s/l–l/l, and gender: female vs. male) and two within-subject variables (expression: smile vs. frown and ethnicity of face: Caucasian vs. Asian). The interaction between expression and genotype was marginally significant, $F(1, 177) = 2.99$, $p = 0.086$, $\eta^2 = 0.02$. Importantly, the interaction was not qualified by ethnicity of participant ($F < 1$, $p > 0.70$). Thus, regardless of ethnicity of participant, Americans with the s/s genotype tended to judge the offset of smile faces slower than did those with s/l or l/l genotypes (s/s genotype: $M = 4.35$, $SD = 0.15$; s/l or l/l genotypes: $M = 4.28$, $SD = 0.25$ for European Americans, s/s genotype: $M = 4.35$, $SD = 0.18$; s/l or l/l genotypes: $M = 4.23$, $SD = 0.29$ for East Asian Americans). None of the interactions with ethnicity of participant were significant.[5]

As mentioned above, the frequency of s allele carriers in East Asian Americans was significantly lower than in Japanese. Thus, the group of East Asian Americans in the current study may not be ideal for testing whether East Asian Americans'

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[4] Cultural differences in each genotype were also tested. Japanese with s/s genotype judged the offset of smile faces significantly faster than Americans with the same genotype, $t(325) = 3.05$, $p < 0.01$, $d = 0.34$, 95 % CI [0.03, 0.15]. In contrast, there was no cultural difference among people with s/l or l/l genotypes in judgments for the offset of smile faces, $t(325) = 1.57$, $p = 0.12$, $d = 0.17$, 95 % CI [−0.01, 0.10]. Americans with s/l or l/l genotypes judged the offset of frown faces faster than Japanese with s/l or l/l genotypes, $t(325) = 2.84$, $p < 0.01$, $d = 0.32$, 95 % CI [0.02, 0.13], whereas there was no cultural difference among people with s/s genotype, $t(325) = 1.26$, $p = 0.21$, $d = 0.14$, 95 % CI [−0.02, 0.10].

[5] Although proportion of individuals with l/l genotype in East Asian Americans was very small ($n = 6$), for American data, to see potential differences between s/l and l/l genotypes and the influence of ethnicity of faces, we also performed a 3 (genotype: s/s, s/l, and l/l) × 2 (ethnicity of participant) × 2 (gender) × 2 (expression) × 2 (ethnicity of face) ANOVA on the means to see differences among the three genotypes. The interaction between expression and genotype was marginally significant, $F(2, 173) = 2.37$, $p = 0.096$, $\eta^2 = 0.02$. The responses of people with s/l genotype were between those with s/s and l/l genotypes. For smile faces, individuals with the s/s genotype ($M = 4.35$, $SD = 0.16$) judged the offset significantly slower than those with s/l ($M = 4.27$, $SD = 0.27$, $t(173) = 2.42$, $p < 0.05$, $d = 0.37$, 95 % CI [0.02, 0.15]) and l/l genotypes ($M = 4.26$, $SD = 0.24$, $t(173) = 2.41$, $p < 0.05$, $d = 0.37$, 95 % CI [0.02, 0.16]), whereas there was no significant difference for frown faces (s/s: $M = 4.34$, $SD = 0.13$, s/l: $M = 4.32$, $SD = 0.16$, l/l: $M = 4.34$, $SD = 0.15$, $ts = 0.68$ and 0.08, $ds = 0.10$ and 0.01, 95 % CI [−0.04, 0.09] and [−0.07, 0.07]). Importantly, the expression × genotype interaction was not qualified by either ethnicity of participant or ethnicity of face ($Fs < 1$, $ps > 0.30$).
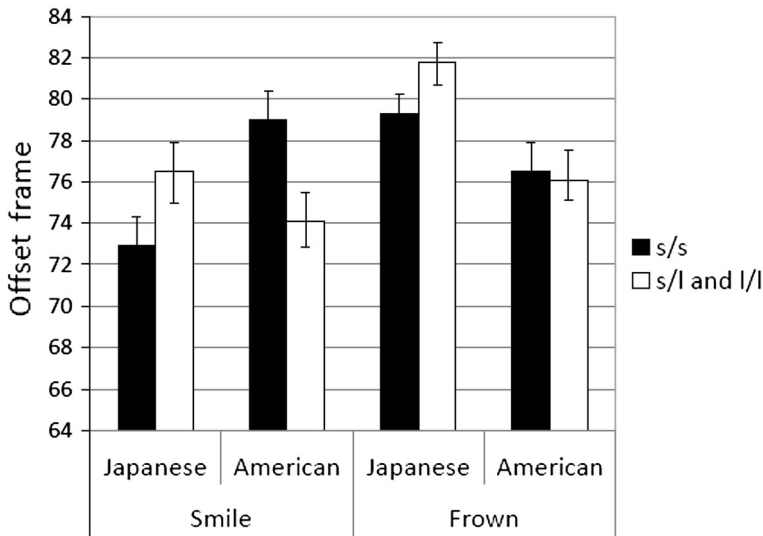
Fig. 2 Means of untransformed offset frames of smile and frown faces (*y* axis) judged by Americans and Japanese with s/s and s/l and l/l genotypes

shared genetic attributes with Japanese influence their responses. Nevertheless, for exploratory purposes, we compared Japanese and East Asian Americans in an ANOVA on the means for cultural ingroup faces (Japanese faces for Japanese and American faces for East Asian Americans) with three between-subject variables (culture of participant, gender, genotype: s/s and s/l–l/l) and one within-subject variable (facial expression). The two-way interaction between culture of participant and expression was marginally significant, $F(1,183) = 3.40$, $p = 0.067$, $\eta^2 = 0.02$. While Japanese judged the offset of smile faces faster ($M = 4.29$, $SD = 0.19$) than that of frown faces as mentioned above ($M = 4.38$, $SD = 0.12$), there was no difference in judgments between smile ($M = 4.30$, $SD = 0.22$) and frown faces ($M = 4.32$, $SD = 0.16$) among East Asian Americans, $t(183) = 0.97$, $p = 0.33$, $d = 0.14$, 95 % CI [−0.02, 0.07]. The three-way interaction among culture of participant, genotype and expression was also marginally significant, $F(1, 183) = 3.61$, $p = 0.059$, $\eta^2 = 0.02$. As mentioned above, Japanese with the s/s genotype ($M = 4.27$, $SD = 0.20$) judged the offset of smile faces faster than did those with s/l or l/l genotypes ($M = 4.33$, $SD = 0.16$), whereas there was no difference in the offset of frown faces between the s/s and s/l–l/l genotypes (s/s: $M = 4.37$, $SD = 0.12$; s/l–l/l: $M = 4.40$, $SD = 0.10$). East Asian Americans with the s/s genotype ($M = 4.37$, $SD = 0.12$) judged the offset of smile faces significantly slower than did those with s/l or l/l genotypes ($M = 4.25$, $SD = 0.26$), $t(183) = 2.26$, $p < 0.05$, $d = 0.33$, 95 % CI [0.02, 0.22], whereas there was no difference in the offset of frown faces between the s/s and s/l–l/l genotypes (s/s: $M = 4.30$, $SD = 0.17$; s/l–l/l: $M = 4.34$, $SD = 0.16$), $t(183) = 0.70$, $p = 0.48$, $d = 0.10$, 95 % CI [−0.07, 0.14]. These results show

that East Asian American pattern of interactions is more similar to those of European Americans than those of Japanese.[6]

In summary, as predicted, Japanese with s/s genotype tended to judge the disappearance of facial expressions faster than did those with s/l and l/l genotypes. In contrast, the tendency was not found in Americans. Moreover, the difference between genotypes in Japanese was clear in judgments of the disappearance of smiles. Furthermore, East Asian Americans' pattern was much more similar to European Americans than to Japanese, suggesting that the differences between cultural groups are indeed due to different cultural experiences.

Discussion

To our knowledge, the present study offers the first evidence of modulation of culture in the association between 5-HTTLPR and processing of emotional change. Overall, the results were consistent with our hypotheses based on gene–culture interactions with 5-HTTLPR. As predicted, we found a significant interaction between culture and 5-HTTLPR such that Japanese with the s/s genotype of 5-HTTLPR tended to detect the disappearance of facial expressions with greater

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[6] We also compared East Asian American participants to European Americans and Japanese in a 3 (culture of participant) $\times$ 2 (gender) $\times$ 2 (genotype) $\times$ 2 (facial expression) ANOVA on the means for cultural ingroup faces (Japanese faces for Japanese and American faces for European Americans and East Asian Americans). The culture-by-expression interaction was significant, $F(2, 321) = 7.97$, $p < 0.001$, $\eta^2 = 0.04$. The difference between judgments for smile and frown faces was not significant in either European Americans (smile: $M = 4.30$, $SD = 0.21$; frown: $M = 4.32$, $SD = 0.15$), $t(321) = 1.38$, $p = 0.17$, $d = 0.15$, 95 % CI [-0.01, 0.04] or East Asian Americans (smile: $M = 4.30$, $SD = 0.22$; frown: $M = 4.32$, $SD = 0.16$), $t(321) = 0.97$, $p = 0.33$, $d = 0.11$, 95 % CI [-0.02, 0.07]. In contrast, Japanese judged the offset of smile faces ($M = 4.29$, $SD = 0.19$) significantly faster than that of frown faces ($M = 4.38$, $SD = 0.12$), $t(321) = 6.91$, $p < 0.0001$, $d = 0.77$, 95 % CI [0.06, 0.11]. The culture-by-genotype interaction was also significant, $F(2, 321) = 3.61$, $p < .05$, $\eta^2 = 0.02$. Participants with the s/s genotype judged the offset of expressions somewhat slower than did those with s/l and l/l genotypes among both European Americans ($M = 4.35$, $SD = 0.13$ vs. $M = 4.30$, $SD = 0.19$) and East Asian Americans ($M = 4.34$, $SD = 0.15$ vs. $M = 4.30$, $SD = 0.22$), although these differences were not statistically significant, $t(321) = 1.54$, $p = 0.12$, $d = 0.17$, 95 % CI [-0.01, 0.11] and $t(321) = 0.86$, $p = 0.39$, $d = 0.10$, 95 % CI [-0.05, 0.13]. In contrast, participants with s/s genotype ($M = 4.32$, $SD = 0.17$) judged the offset of expressions somewhat faster than did those with s/l or l/l genotypes ($M = 4.36$, $SD = 0.14$) among Japanese, $t(321) = 1.69$, $p = 0.092$, $d = 0.19$, 95 % CI [0, 0.10]. The three-way interaction among culture of participant, genotype and expression was marginally significant, $F(1, 321) = 2.53$, $p = 0.081$, $\eta^2 = 0.01$. European Americans with the s/s genotype ($M = 4.36$, $SD = 0.13$) judged the offset of smile faces significantly slower than did those with s/l or l/l genotypes ($M = 4.29$, $SD = 0.23$), $t(321) = 2.02$, $p < 0.05$, $d = 0.23$, 95 % CI [0, 0.14], whereas there was no difference in the offset of frown faces between the s/s and s/l or l/l genotypes (s/s: $M = 4.34$, $SD = 0.13$; s/l–l/l: $M = 4.32$, $SD = 0.15$), $t(321) = 0.70$, $p = 0.48$, $d = 0.08$, 95 % CI [-0.04, 0.09]. East Asian Americans with the s/s genotype ($M = 4.37$, $SD = 0.12$) also judged the offset of smile faces significantly slower than did those with s/l or l/l genotypes ($M = 4.25$, $SD = 0.26$), $t(321) = 2.18$, $p < 0.05$, $d = 0.24$, 95 % CI [0.01, 0.22], whereas there was no difference in the offset of frown faces between the s/s and s/l–l/l genotypes (s/s: $M = 4.30$, $SD = 0.17$; s/l–l/l: $M = 4.34$, $SD = 0.16$), $t(321) = 0.67$, $p = 0.50$, $d = 0.07$, 95 % CI [-0.07, 0.14]. In contrast, Japanese with the s/s genotype ($M = 4.27$, $SD = 0.20$) judged the offset of smile faces faster than did those with s/l or l/l genotypes ($M = 4.33$, $SD = 0.16$), $t(321) = 1.88$, $p = 0.061$, $d = 0.21$, 95 % CI [0, 0.11], whereas there was no difference in the offset of frown faces between the s/s and s/l–l/l genotypes (s/s: $M = 4.37$, $SD = 0.12$; s/l–l/l: $M = 4.40$, $SD = 0.10$), $t(321) = 1.13$, $p = 0.26$, $d = 0.13$, 95 % CI [-0.02, 0.09].

perceptual efficiency than did those with s/l or l/l genotypes, reflecting cultural norms and practices that emphasize concerns about others' expectations and disruption of harmony, whereas the tendency was not found in North Americans from cultures that do not foster, and may in fact discourage, vigilance to social approval. The present study supports the idea of gene–culture interactions by providing evidence that people with the s/s genotype of 5-HTTLPR are more sensitive to environmental changes than those with the long allele, but only when the environmental change is culturally important.

Importantly, the difference between genotypes in Japanese was evident only in certain situations, when they judged the disappearance of smiles, demonstrating how culture provides meaning to particular social situations (Leung and Cohen 2011). This finding reflects the importance in Japanese culture of detecting particular non-verbal signs such as the disappearance of smiles, which represent that one is falling short of others' expectations or undermining social harmony. In contrast, as an unexpected finding, compared to Americans with s/l or l/l genotypes, those with the s/s genotype tended to judge the offset of facial expressions slower, and the tendency was clear in the judgment of the disappearance of smile faces. It may be the case that although s/s carriers are more sensitive to social events (Way and Taylor 2010) and more reactive to unambiguously negative emotional stimuli in all cultures (e.g., Hariri et al. 2002), the sensitivity to change may be a more culture-specific tendency. It appears that Americans with the s/s genotype were *less* sensitive to emotional change from positive/negative to neutral. While Japanese cultures tend to urge people to adjust themselves to expectations from others, American cultures tend to emphasize the individual's independence from social influence and concerns about others' approval (Kim and Markus 1999; Markus and Kitayama 1994; Suh et al. 1998). Moreover, European Americans are less likely than East Asians to believe that events are constantly changing, and thus they tend to undermine the probability for change in the trend of some event (Ji et al. 2001). Given the features of American cultures, we speculate that Americans with the s/s genotype may be more susceptible to this culturally prescribed tendency than Americans with s/l or l/l genotypes, by ironically showing less sensitivity to the disappearance of facial expressions, particularly the disappearance of smiles. However, these unexpected findings should be interpreted cautiously, and future research will be needed to directly test this intriguing possibility.

Gene–environment interactions and gene–culture interactions have been found with many target genes. For example, gene–culture interactions have been found with an oxytocin receptor polymorphism (OXTR) (Kim et al. 2010a, 2011), a serotonin receptor polymorphism (5-HTR1A) (Kim et al. 2010b) and the dopamine D4 receptor polymorphism (DRD4) (Kitayama et al. in press). Gene–environment interactions have also been found with 5-HTTLPR (Caspi et al. 2003; Taylor et al. 2006), DRD4 (Bakermans-Kranenburg et al. 2008; Sasaki et al. 2013), monoamine oxidase A gene (MAOA) (Caspi et al. 2002), and OXTR (Chen et al. 2011), among others. These studies, including the current one, may raise interesting questions about the specificity of these polymorphisms in producing outcomes in particular psychological domains, such as socio-emotional processes and cognitive processes, and their possible overlaps and interactions. Such findings suggest that although

different genes may sensitize people to slightly different aspects of environments, there may be complex overlaps in their biological, psychological, and social functions. One way to address this question is to take a polygenic approach and consider a set of genes in conjunction with each other, which will be a crucial next step.

While we used classification by short versus long alleles of 5-HTTLPR, research has suggested that the long allele of 5-HTTLPR has two variants, one of which (L_G) is very similar to the short allele in terms of transcriptional activity and lower in the amount of 5-HT than the other (L_A) (Hu et al. 2006). Future research should consider using this triallelic classification to address the way culture modulates the association between genes and psychological tendencies.

In future research, it will also be important to examine hypotheses based on gene–culture interactions by using not only self-report and behavioral measures, but also neural activities. Relevant to emotional processing examined in the current study, Muhlberger et al. (2011) found that sensitivity to the disappearance of smiles was associated with strong activity in the left amygdala and the left insula. Although the Muhlberger et al. (2011) study was not a cross-cultural investigation, the association between sensitivity to the disappearance of smiles and neural activities might be modulated by culture and genes. Given the current findings, Japanese with the s/s genotype of 5-HTTLPR may show stronger activity in the left amygdala and the left insula than do those with s/l or l/l genotypes when judging the disappearance of smiles, whereas such a difference between genotypes may be weaker in Americans. Such investigations will demonstrate more directly the extent to which 5-HTTLPR interacts with cultural factors to impact psychological tendencies, including underlying brain activities.

Moreover, our results showed that responses by East Asian Americans did not differ from those of European Americans. These current findings are consistent with those of Kim et al. (2010a, b, 2011) focusing on an oxytocin receptor polymorphism (OXTR rs53576) and a serotonin 1A receptor polymorphism (5-HTR1A). As a consequence, East Asian Americans differed from Japanese in terms of the pattern of differences between genotypes in the judgment for the disappearance of smiles. These results suggest that assimilation into a host culture (i.e., North American culture for Asian Americans) may influence the association between 5-HTTLPR and corresponding psychological tendencies. Thus, it would be informative to precisely test the possibility that Asian Americans' identification with their host culture (i.e., North American culture) and their heritage culture (i.e., East Asian culture) may play a role in the relationship between 5-HTTLPR and individual psychological process, thereby forming a basis for cultural change and persistence.

Finally, there are some limitations to the current study, which should be taken into account. Because the distributions of genotypes were skewed and varied across cultures, the present results should be interpreted cautiously. Moreover, although we found that the expected key interactions including culture $\times$ genotype in the judgment for the disappearance of facial expressions were significant, our findings on genetic differences in the judgment for the disappearance of facial expressions in Japanese are marginally significant. These small effects could potentially be due to the skewed distributions of genotypes and different daily frequency to culturally

matching ingroup and outgroup members. Furthermore, because the frequency of s allele carriers between East Asian Americans and Japanese was different, it is possible that the difference is explained by gene–gene interactions rather than, or perhaps in addition to, cultural moderation of the genetic effect. Further investigations with a larger sample to resolve these limitations are needed to confirm external validation of the current results.

In conclusion, the present research is in line with approaches in cultural neuroscience (e.g., Chiao and Ambady 2007; Chiao and Blizinsky 2010; Han and Northoff 2008; Kim and Sasaki 2014, Mrazek et al. 2013), which demonstrate whether and to what extent cultural factors influence brain mechanisms and contribute to an understanding of gene–culture interactions, as well as how culture and genes influence each other in processes of gene–culture co–evolution, which makes up and develops cultural norms and practices. The present research goes beyond previous work by providing the first empirical evidence of a gene–culture interaction with 5-HTTLPR that uses a behavioral measure of emotional processing. Because most of the previous work on gene–environment interactions has been done in Western cultures, less is known about how genes and culture interact and to what extent cultural interpretations of the environment influence the association between genes and behavioral responses to the environmental input. Our findings demonstrate that the cultural importance of social approval moderates the association between 5-HTTLPR and judgments of the disappearance of positive emotional expressions, thus filling a gap in the literature by illuminating a role of culture as an important modulator of the association between 5-HTTLPR and emotional processing. We believe that the present research will help shed light on further investigations by examining the relations among culture, genes, and human behaviors.

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