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DRD4 polymorphisms modulate reward positivity and P3a in a gambling task: Exploring a genetic basis for cultural learning

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Abstract

Prior work shows that people respond more plastically to environmental influences, including cultural influences, if they carry the 7 or 2-repeat (7/2R) allelic variant of the dopamine D4 receptor gene (*DRD4*). The 7/2R carriers are thus more likely to endorse the norms and values of their culture. So far, however, mechanisms underlying this moderation of cultural acquisition by *DRD4* are unclear. To address this gap in knowledge, we tested the hypothesis that *DRD4* modulates the processing of reward cues existing in the environment. About 72 young adults, preselected for their *DRD4* status, performed a gambling task, while the electroencephalogram was recorded. Principal components of event-related potentials aligned to the Reward-Positivity (associated with bottom-up processing of reward prediction errors) and frontal-P3 (associated with top-down attention) were both significantly more positive following gains than following losses. As predicted, the gain-loss differences were significantly larger for 7/2R carriers than for noncarriers. Also, as predicted, the cultural backgrounds of the participants (East Asian vs. European American) did not moderate the effects of *DRD4*. Our findings suggest that the 7/2R variant of *DRD4* enhances (a) the detection of reward prediction errors and (b) controlled attention that updates the context for the reward, thereby suggesting one possible mechanism underlying the *DRD4* × Culture interactions.

KEYWORDS

DRD4, event-related potential, gene × culture interactions, reward processing

1 | INTRODUCTION

In social and behavioral sciences, as well as in society at large, culture has long been conceptualized as separate from and even antagonistic to, biology (Geertz, 1973; Gould, 1996). This long-standing dichotomy is evident, for example, in a sharp distinction between nature (biology) and nurture (culture). However, this dichotomy has begun to be seriously challenged. Most notably, several investigations have shown pronounced Gene × Culture interactions such that cultural differences in beliefs and values, as well as their cognitive, emotional, behavioral, and neural manifestations, are moderated by certain polymorphic gene variants (Kim & Sasaki, 2014; Kitayama et al., 2014; Kitayama, King, Hsu, Liberzon, & Yoon, 2016). This Culture × Genotype interaction effect has been consistently observed for a varying number tandem repeat (VNTR) variant in the exon III of the dopamine D4 receptor gene (*DRD4*) (Belsky & Pluess, 2009; Kitayama et al., 2014, 2016; Kitayama, Yu, King, Yoon, & Liberzon, 2019; Sasaki, 2013; Silveira et al., 2016; Tompson et al., 2018; Yu et al., 2018). The Culture × *DRD4* interaction pattern, observed in these studies, may result if the VNTR

polymorphic variants of *DRD4* modulate reward processing, thereby changing the degree to which culturally sanctioned behaviors are acquired through reinforcement-based learning. This possibility, however, has so far remained untested. Here, we addressed this gap by utilizing an event-related potential (ERP) gambling paradigm and testing the hypothesis that the *DRD4* polymorphisms modulate both bottom-up and top-down ERP components of reward processing.

1.1 | Culture × *DRD4* interactions

Prior work shows that European Americans are more independent or individualistic, and simultaneously, less interdependent or collectivistic, compared to East Asians (Kitayama & Uskul, 2011; Markus & Kitayama, 1991). This cultural difference is observed not only in beliefs in independence or interdependence of the self (Singelis, 1994), but also in cognitive (Nisbett, Peng, Choi, & Norenzayan, 2001), emotional (Kitayama, Karasawa, & Mesquita, 2006), and motivational behaviors (Heine, Lehman, Markus, & Kitayama, 1999) that support the respective beliefs.

More recent work has built on the previous cultural evidence and shown that the psychological differences between European Americans and East Asians are more pronounced for the carriers of alleles of *DRD4* that are linked to increased reward processing (7- or 2-repeat variants) than for those who do not carry them (Kitayama et al., 2014). Several other studies offer converging evidence (Sasaki et al., 2013; Silveira et al., 2016; Tompson et al., 2018). Of importance, the cultural variation extends to the cortical volume of specific brain regions. For example, the gray matter volume of a region implicated in the formation of preferences and attitudes, the orbitofrontal cortex (OFC), is larger for European Americans than for Asians (Chee, Zheng, Goh, Park, & Sutton, 2011). This cultural variation is similarly moderated by *DRD4* (Kitayama et al., 2019; Yu et al., 2018). Further, a growing body of literature shows that children up to 10 years old carrying these alleles of *DRD4* are more responsive to parenting, a particular form of environmental influence that mediates the acquisition of culture (Bakermans-Kranenburg & Ijzendoorn, 2011; Belsky & Pluess, 2009).

Currently, little is known about the mechanisms for the Culture × *DRD4* interactions. However, it stands to reason that they may result, in part, from an effect *DRD4* would have on reward processing. Dopamine is the key neurotransmitter involved in both the bottom-up, striatal functions (Berridge, Robinson, & Aldridge, 2009), and the top-down, prefrontal functions (Durstewitz, Seamans, & Sejnowski, 2000; Miller & Cohen, 2001). Of importance, the dopamine D4 receptors are known to be inhibitory. They inhibit neural systems connected to them, including reward processing systems. Moreover, Wang et al. (2004) provide evidence that the 7 or 2-repeat (7/2R) allele of *DRD4* is associated with reduced D4 receptor activity. In combination, the 7/2R allele of *DRD4* may disinhibit the activity of the reward processing systems by reducing the D4 receptor activity (which is thought to inhibit these systems). Consistent with this expectation, prior work consistently shows that the 7R variant of this gene is associated with increased striatal neural activity (Forbes et al., 2009; Nikolova, Ferrell, Manuck, & Hariri, 2011). Although this work does not test the 2R variant of *DRD4* because this allele is relatively rare among European American samples that are tested, Wang et al. (2004) show that this variant is similar to the 7R allele in its ability to reduce D4 receptor activity (thereby, increasing reward processing).

1.2 | Reward processing

Reward processing requires two overarching components. One component is bottom-up (Rauss & Pourtois, 2013). Prior work shows that phasic increases or decreases in mesencephalic dopamine signaling directly follow outcomes that are better or worse than expected (Fiorillo, Tobler, & Schultz, 2003). These violations in reward expectation, called reward prediction errors (Holroyd & Coles, 2002), guide the selection of adaptive actions to maximize future rewards.[1] The computation of these errors has been localized to striatal regions and their cortical extensions in the OFC (Haber & Knutson, 2010). This striatal/OFC function of reward monitoring is useful for building habits on a trial-and-error basis. It is thought to be ancient in origin. It, indeed, is shared with all vertebrate species. As noted, the neuroimaging studies (Forbes et al., 2009; Nikolova et al., 2011) show that the 7R variant of *DRD4* is associated with the increased striatal activity.

However, the bottom-up component may not be sufficient to learn complex reward contingencies anchored in values, beliefs, and other cultural meanings. Indeed, scholars have hypothesized that there is a second component of reward processing that conveys higher-order predictions to lower levels of processing, which is contrastingly cognitive and top-down

[1]Prediction error signaling implies reward signals are compared to higher order reward expectations. When these expectations are violated, these violations are used to integrate and update future predictions at larger timescales (Grossberg, 2009). This process is called bottom-up top signify the direction of the flow of information from the rewards received to the higher-order expectations used to evaluate the rewards to update themselves. More generally, our theoretical account is consistent with predictive coding theories, which propose an interactive account of bottom-up and top-down processing that both involve ascending and descending connections between lower and higher levels of functioning (Rauss & Pourtois, 2013). While bottom-up processes only communicate with neighboring levels, top-down processes involve information transfer that skip two or more levels of the hierarchy to flexibly override bottom-up processes. This mutual interdependence and constant interaction between bottom-up and top-down processes is likely required to reliably and quickly adapt to rapidly changing environments and integrate higher order reward contingencies over larger timescales.

(Rauss & Pourtois, 2013; Rougier, Noelle, Braver, Cohen, & O'Reilly, 2005). In particular, individuals may formulate hypotheses or models of their surrounding environments and to control learning such that rewards received (or not received) are coded cognitively and incorporated into abstract representations of the surrounding environments (Saez, Set, & Hsu, 2014). These representations are updated continuously to predict future rewards that are contingent on complex stimulus cues and events in the environment. An increasing body of research shows that the higher-order cognitive functions are subserved by a variety of prefrontal regions, including the OFC (Fellows, 2011; O'Doherty, 2011), dorsolateral prefrontal cortex (Heatherton & Wagner, 2011; Ochsner et al., 2004), and medial prefrontal cortex (Qin et al., 2011; van der Meer, Costafreda, Aleman, & David, 2010). These prefrontal regions are involved in top-down attentional processes and abstract working memory representations (Corbetta & Shulman, 2002).

1.3 | Electroencephalogram gambling paradigm

One hitherto unexplored method in investigating the effect of *DRD4* on reward processing is to test electrocortical responses within a gambling paradigm. In this paradigm, participants are to choose between two options. They will receive either gain or loss feedback shortly afterward. Upon reward feedback to a choice made in each gamble, two event-related potential (ERP) components are elicited that are of direct relevance to the current hypothesis.

First, the reward-positivity (RewP) is a frontocentral positive deflection following gain (vs. loss) feedback (Miltner, Braun, & Coles, 1997). The RewP is thought to track reward prediction errors by signaling greater positivity when an outcome has gone better than expected and is an essential component of reinforcement learning (Holroyd & Coles, 2002; Holroyd, Pakzad-Vaezi, & Krigolson, 2008). In addition to the anterior cingulate cortex, the striatal reward networks have been linked to the RewP (Foti, Weinberg, Dien, & Hajcak, 2011). For consistency, we use the term RewP to refer to the difference between gains and losses, unless specified otherwise.

Second, directly following the RewP, another positive peak appears approximately 300–500 ms postfeedback, called the P3 (Donchin & Coles, 1988). The P3 is thought to reflect top-down attention that updates the cognitive representations of the context in which rewards are delivered. Of interest, the P3 can be separated into an earlier, frontal component (P3a) associated with top-down focused attentional control, and a later, parietal component (P3b) involved in updating working memory (Polich, 2007). Of the two, the earlier P3a is likely modulated by prefrontal dopamine variation, while the P3b is related to variation in temporal-parietal norepinephrine (Polich & Criado, 2006).

1.4 | Present research

In the current work, we tested whether the two signature electrocortical markers of reward processing (RewP and P3) would be moderated by *DRD4* VNTR status. We anticipated that the carriers of the 7/2-repeat allele of *DRD4* would show increases in reward processing, as revealed in a greater magnitude of both RewP and P3a following gain (vs. loss) feedback. Moreover, the purported increases in reward processing are thought to be a mechanism for the Culture × *DRD4* effects observed in previous work. Hence, the upregulation of reward processing during feedback evaluation was expected to be common across cultures. To examine this possibility, we tested both European Americans and comparable East Asian sojourners in the U.S. The participants were recruited such that approximately half in both groups carried the 7/2R variant of *DRD4*, whereas the remaining half did not.

In addition, our earlier work showed that the magnitude of RewP in the gambling paradigm could be attenuated by incidental exposure to a face image (called face priming) (Hitokoto, Glazer, & Kitayama, 2016). This effect was evident in the two cultural groups tested in the current work, European Americans and East Asian sojourners in the US. Our subsidiary aim was to replicate this finding. We, thus, included face priming in the design of the current work.

2 | METHOD

2.1 | Participants

Prior Western work on *DRD4* compared the carriers of the 7R allele of this gene with those who do not carry this allele. This work ignores the 2R allele because this allele is rare in Western samples. In East Asian samples, the 7R allele is relatively rare, but the 2R allele is more common. Since the two alleles are similar in their ability to inhibit D4 receptor activity (thereby increasing reward processing) (Wang et al., 2004), the carriers of the 7R and 2R alleles were combined to form a carrier group. This group was compared against a group of participants who do not carry either of the alleles, following a recommendation by Reist et al. (2007) as well as prior work (Kitayama et al., 2014, 2019; Tompson et al., 2018; Yu et al., 2018).

In the current work, participants were recruited from a larger pool of participants established in prior work ($n = 635$). All these participants had been genotyped for *DRD4*. We recruited both East Asians and European Americans such that there were approximately equal numbers of the carriers of the 7/2R allele and the noncarriers of it. Given the attrition of participants from the original pool, we tried to recruit as many participants as possible by the end of the school year in 2016. This effort yielded 82 participants. Forty-one participants

were European Americans who were born and raised in the U.S. (31 females and 10 males; age range 18–23 years; mean age 20.4 years), and 41 were East Asians who were born in an East Asian country (i.e., China, Japan, Korea, and Taiwan) and had lived in the U.S. for less than 10 years (30 females and 11 males; age range 18–27 years; mean age 21.4 years). The *DRD4* carrier status was divided nearly equally within each cultural group. Each participant was paid a total of $60.00 USD for the two-hour session. The participants provided their written informed consent in accordance with the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of the University of Michigan.

Ten participants were excluded due to excessive artifact rejection of greater than 50% of total trials in either the gain or loss condition (1), recent concussion or serious head trauma in the past 30 days (1), a history of seizures (1), current medication use (6), and an outlier with ERP amplitudes greater than 5 standard deviations from the mean (1). For medication use, participants were excluded if they self-reported currently using prescription drugs previously found to modulate reward-related neural activity including antidepressants (3 participants), stimulants (2 participants), and acne medication containing isotretinoin (1 participant). Following prior work recommending a minimum of 20 trials in each condition to measure the RewP (Marco-Pallares, Cucurell, Münte, Strien, & Rodriguez-Fornells, 2011), all remaining participants retained well over 20 trials in gain ($M = 45.61$, $SD = 4.20$) and loss ($M = 49.39$, $SD = 4.47$) conditions. After removal, 72 participants were retained for analysis (52 females, mean age 20.9): 23 East Asian 4R, 16 East Asian 7/2R, 18 European American 4R, and 15 European American 7/2R (see Table S1 for additional sample information).

The resulting sample size was sufficient to assure 80% power to attain the main effect of *DRD4*, which is hypothesized to be medium in size based on prior neuroimaging (Forbes et al., 2009) and electrophysiological evidence (Heitland et al., 2012).[1] Note that while we did not predict any Culture × *DRD4* interaction, the current sample size was not sufficient to detect this interaction that might be present.[2] Thus, caution is warranted because even if the predicted null interaction were borne out, it could merely be due to insufficient power.

2.2 | Procedure

Participants completed a modified two-choice door task, while the electroencephalogram (EEG) was recorded. The trial structure is shown in Figure 1. On each trial, a fixation cross was presented for 500 ms. Next, two adjacent rectangles were presented with either a schematic neutral face or scrambled image centered between them until the participant responded. Participants were instructed to look at but ignore these "distracter figures" which disappeared after 90 ms. As noted, we included these figures to test a face priming effect observed in prior work (Hitotoko et al., 2016). These figures were either a schematic face image or a scrambled face image. When participants made a choice between the two rectangles, a phrase, "The result is …," was shown for 1,000 ms right above the two rectangles, after which the two rectangles turned either green with "+50" appearing in the inside (gain feedback), or red with "−50" appearing in the inside (loss feedback). The feedback was presented on the screen for 1,500 ms. After an 800 ms interval, the next trial started with the presentation of a fixation cross. The task consisted of 16 trials per block with six blocks for a total of 96 trials. Between blocks, participants received a break and proceeded when ready with a button press.

The gambling task was preceded by 16 practice trials. No points could be gained or lost during the practice. During the gambling task, gains and losses were pseudo-randomized. About 75% of the trials in each block were predetermined to contain equal numbers of gains and losses, while the remaining 25% contained a random result. Participants began the task with 5,000 points. They had been told that they may earn a monetary bonus ($1.00 on average) if they earned greater than 5,000 points (mean final score = 5,141). This bonus was intended to keep the participants engaged in the task. All participants completed an additional modified Eriksen-Flanker task that was counterbalanced and not reported here. All saliva and genotyping were completed prior to the current study when participants first enrolled as part of the larger research project (see Kitayama et al., 2014 for details).

2.3 | Genotyping

As reported in Kitayama et al. (2014), an Oragene saliva kit (OG-500) was used for saliva collection (DNA Genotek, Kanata, Ontario, Canada). Genomic DNA was extracted using a high-capacity membrane-based column

[2]Specifically, Forbes et al. (2009) and Heitland et al. (2012) are arguably close, although not identical, to our current paradigm. Forbes tested *DRD4*, with the bold signal activity of the ventral striatum in response to emotional stimuli as the outcome variable of choice. The effect size for the *DRD4* main effect was $R^2 = 0.092$. Heitland et al. (2012) tested RewP in a gambling task. Their gene of interest, however, was not *DRD4*. They focused on DAT1. The effect size for the DAT1 was $\eta_p^2 = 0.10$. By an effect size of $\eta_p^2 = 0.10$, we estimated the power of 0.80, with the current sample of $N = 72$ at $p = .05$. Unlike the *DRD4* main effect, our current sample was under-powered to detect the *DRD4* x Culture interaction. Using the effect size of $\eta_p^2 = 0.062$ for the *DRD4* x Culture interaction reported in a recent study focusing on neural dependent variables (Yu et al., 2018), the observed power for our $N = 72$ sample at $p = .05$ was estimated to be 0.57.

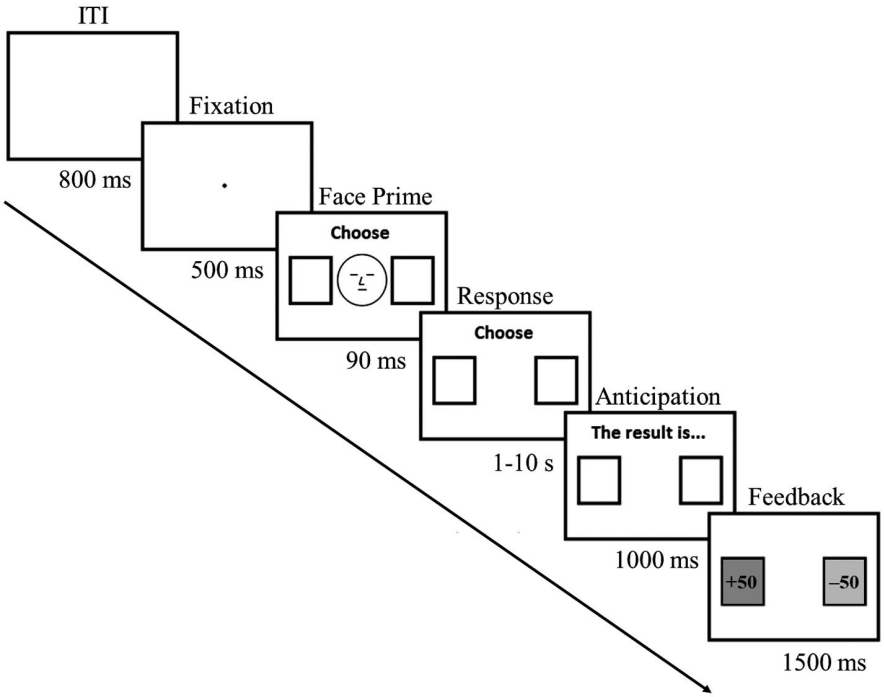

FIGURE 1 Trial structure for the gambling paradigm. First, a fixation dot is presented. Next, two boxes appear with the word "Choose" along with a brief neural face-prime. After a response, the words "The result is …" are presented followed by gain and loss feedback indicated by a green "+50" or a red "−50"

(QuickGene810, AutoGen, Inc., Holliston, MA) and was quantitated using an A260/A280 ratio with a NanoDrop spectrophotometer (ThermoScientific, Inc., Wilmington, DE) and agarose gel electrophoresis. The *DRD4* VNTR polymorphism was amplified, with 0.2 μM of *DRD4* forward primer 5′-GCGACTACGTGGTCTACTCG and 0.2 μM of *DRD4* reverse primer 5′-AGGACCCTCATGGCCTTG (Lichter et al., 1993), using the Roche GC-Rich PCR System amplification buffer (Roche Applied Science, Inc., Mannheim, Germany) and 20 ng of genomic DNA in a volume of 25 μl. The samples were heated in a Stratagene thermocycler (Life Technologies, Inc., Grand Island, NY) at 95°C for 3 min, then cycled 40 times at 95°C for 20 s, 57°C for 20 s, and 72°C for 1 min, followed by 72°C for 3 min. Polymerase chain reaction products were separated and visualized on a 2% agarose gel (type 1-A, Sigma, St. Louis, MO) stained with ethidium bromide.

Among the 72 participants that were included in the ERP analysis, frequencies of the *DRD4* VNTR alleles were: for European American participants, 12% 2R, 9% 3R, 42% 4R, 33% 7R, and 3% 8R; for East Asian participants, 41% 2R, 3% 3R, 54% 4R, 3% 5R, and 0% 7R. As per suggested by previous work, carriers of 7R and 2R alleles were compared (15 European Americans and 16 East Asians) with noncarriers of these alleles (mostly 4R/4R, together with more infrequent variants including the 3R, 5R, and 8R alleles; 18 European Americans and 23 East Asians).

2.4 | Questionnaires

Immediately following the EEG session, participants completed a series of questionnaires administered for exploratory analyses. These included the mood and anxiety symptom questionnaire (MASQ) (Clark & Watson, 1991), the Penn State worry questionnaire (PSWQ) (Meyer, Miller, Metzger, & Borkovec, 1990), and the BIS/BAS scale (behavioral activation and behavioral inhibition; Carver & White, 1994). In addition, a modified version of the self-construal scale (Park & Kitayama, 2012) was administered to measure scores for interdependent and independent self-construal.

2.5 | EEG recording

Continuous EEG was recorded using a 32-channel BioSemi ActiveTwo System (BioSemi, Amsterdam, Netherlands) in accordance with the 10/20 system along with two mastoid electrodes. Four electrooculogram (EOG) electrodes were placed 1 cm from the eyes (above and beneath the left eye and to the right and left of both eyes). Impedances were kept below 10 and 20 kOHM for scalp/mastoid and facial electrodes, respectively. Data were digitized online at 512 Hz and the common mode sense active electrode and driven right leg passive electrode formed the ground during data acquisition in lieu of an online reference. Offline, data were resampled to 256 Hz, re-referenced to the average of both mastoids, and bandpass filtered with 0.1 and 30 Hz cutoffs. Next trials were epoched from 200 ms prefeedback stimulus to 800 ms following feedback presentation. Baseline correction was performed using the 200 ms prestimulus window. Blink artifacts were corrected for vertical EOG using the method developed by Gratton, Coles, and Donchin (1983). Automatic artifact rejection then identified and removed those trials where any scalp electrode exceeded a voltage threshold of 200 μV

within a 200 ms window using 100 ms steps that moved across the length of each epoch. Trials were also rejected if any scalp electrode fluctuated more than 50 μV between two successive sampling points or if any scalp electrode had little to no activity (±0.5 μV) over a 500 ms interval within each epoch. All offline analyses were performed using EEGLAB (Delorme & Makeig, 2004) and ERPLAB (Lopez-Calderon & Luck, 2014) toolboxes for MatLab.

2.6 | ERP analysis

From visual inspection of the raw waveforms and their scalp topographies, we identified two ERP components with peak latencies and scalp distributions consistent with the RewP and P3 (see Figure 2a). First, the RewP was quantified as the mean activity ±50 ms around the peak latency of the gain-loss difference wave (230–330 ms) at electrode site FCz where this difference was maximal. Following Luck (2014), we utilized a different wave approach to measure the RewP. This approach can help mitigate component overlap with the preceding P2 and subsequent P3. Each of these components displays separate scalp topographies, covary with distinct neuroanatomical correlates, and may reflect unique psychological processes (see Glazer, Kelley, Pornpattananangkul, Mittal, & Nusslock, 2018 for review).

Second, following prior work (Polich, 2007), we quantified this combined P3 time window from visual inspection as ±50 ms around electrode CPz where the average voltage across gains and losses was maximal (330–430 ms). From the raw waveform alone, however, the two subcomponents within P3 (P3a and P3b) were not discernable because both components are positive deflections that partially overlap in time. In fact, the P3a partially overlaps in time with both the P3b and the preceding RewP, making it difficult to determine when the RewP ends and the P3b begins. As a result, most studies measure both components using a single P3 time window at parietal electrode sites (Polich, 2007). To address this issue, we followed earlier work (Foti et al., 2011; Foti, Hajcak, & Dien, 2009; Sambrook & Goslin, 2016; see Polich, 2007, for a review), and utilized temporospatial principal component analysis (PCA) (Dien, 2010) to separate the RewP, P3a, and P3b.

The temporospatial PCA (Dien, 2012) involved an initial temporal PCA using Promax rotation. This procedure extracted nine factors. It was followed by a spatial PCA using infomax rotation. This second procedure extracted six factors using average scree plots. Factors to the left of the scree

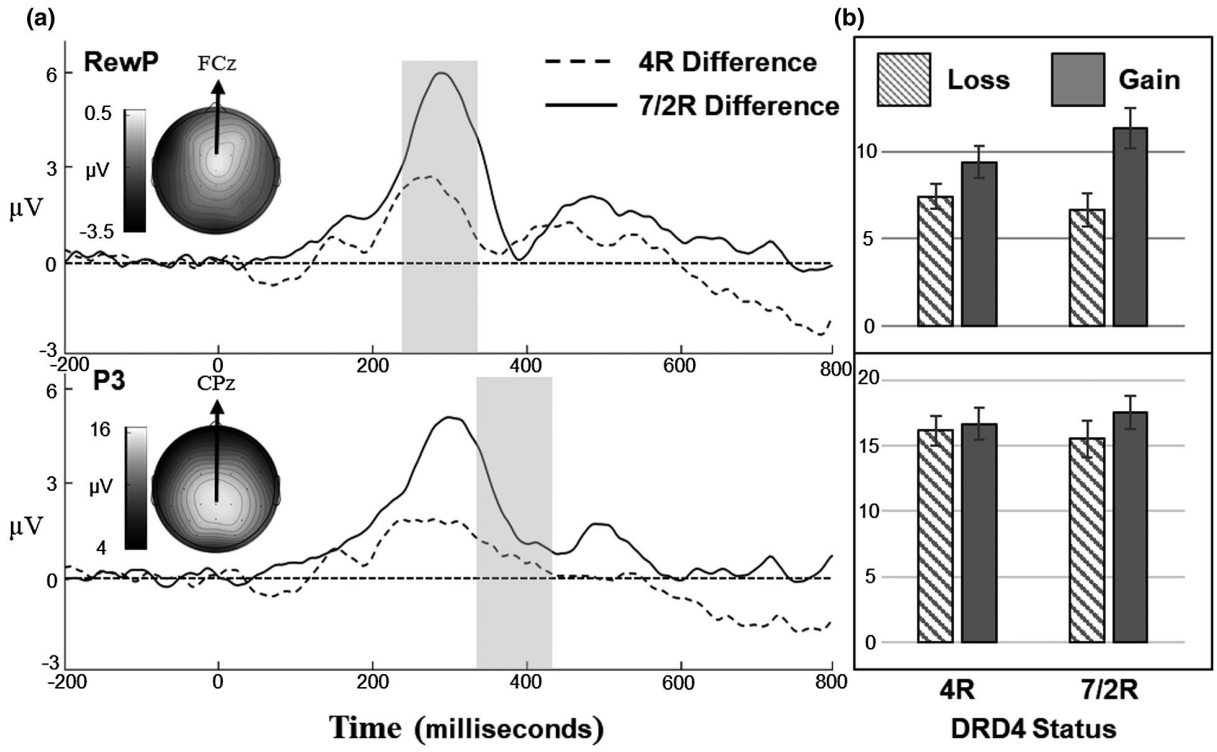

FIGURE 2 Principal components extracted from the raw ERP waveform. (a) Principal component gain-loss difference waves separated for 7/2R (solid lines) and 4R (dashed lines) carriers. Shaded regions indicate the measurement time window for the P2 at CPz (top), RewP at Cz (middle-top), P3a at FCz (middle-bottom), and the P3b at CPz (bottom). Scalp maps display the average voltage of each component across all 32 electrodes. (b) Mean amplitudes for each principal component separated by gains (solid bars) and losses (dashed bars) for 4R (left) and 7/2R (right) carriers. All error bars are standard error

plot "elbow" were retained after which eigenvalues level off. Factors were reconstructed through conversion to microvolts, following Dien (2010). Specifically, factor loadings were rescaled to microvolts by multiplying correlation factor loadings with the standard deviations of the variables. This operation converted the factor loadings into microvolt unit covariance loadings. Both the temporal-spatial PCAs used covariance matrix and Kaiser normalization and yielded a total of 54 factors (9 temporal factors × 6 spatial factors). The total variance from the 54 factors reached 90%.

To isolate components of interest, factors with fluctuations of less than 1 μV were excluded. Nine factors remained and accounted for 82% of the total variance in the data. The visual inspection identified four factors consistent with the latency and scalp distribution of well-established ERP components that are commonly associated with reward feedback (Dien, Beal, & Berg, 2005): P2 at CPz, RewP at Cz, P3a at FCz, and P3b at CPz, as illustrated in Figure 3a. Factor scores were quantified by taking the mean activity ±50 ms around their peak (P2 at 191 ms, RewP at 266 ms, P3a at 320 ms, and

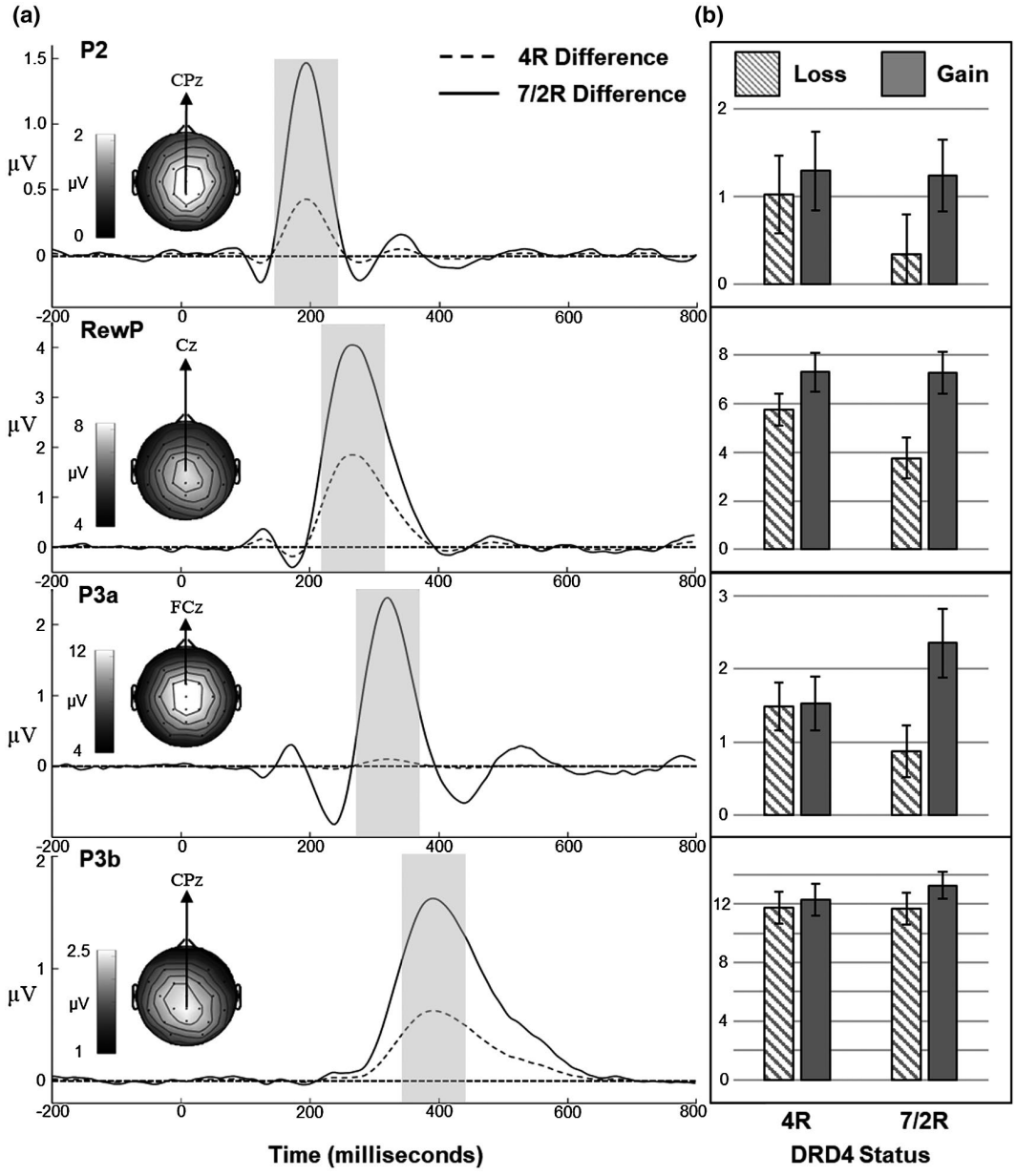

FIGURE 3 RewP and P3 ERP components measured in the raw ERP waveform. A: Raw waveform gain-loss difference waves separated for 7/2R (solid lines) and 4R (dashed lines) carriers. Shaded regions indicate the measurement time window for the RewP at FCz (top) and the P3 at CPz (bottom). Scalp maps display the average voltage of each component across all 32 electrodes. B. Mean amplitudes for the RewP at FCz (top) and P3 and CPz (bottom) separated by gains (solid bars) and losses (dashed bars) for 4R (left) and 7/2R (right) carriers. All error bars are standard error

P3b at 391 ms) at the electrode site where peak amplitude was maximal. The PCs of primary theoretical focus are RewP and P3a. Each PC was subjected to a separate Outcome × *DRD4* status × Culture ANOVA. For comparison, we extracted the RewP, P3a, and P3b from the raw waveforms using the mean activity ±50 ms around the same peak latencies and electrode sites identified in the PCA analysis.

3 | RESULTS

3.1 | Self-report data

The means of the self-report scales are shown in Table 1. The reliabilities, also reported in the same table, were mostly satisfactory. As can be seen, there were no significant effects of *DRD4* status on any of the scales (*ps* > .29). Unlike in prior work (Kitayama et al., 2014), we found no significant Culture × *DRD4* interaction on either independent or interdependent self-construal, likely due to substantially reduced sample size, which made our work insufficiently powered to detect the effect observed in Kitayama et al. (2014). In addition, none of the scale scores were significantly associated with any of the ERP or PCA difference waves (*ps* > .06). The sole exception was found for anxious arousal, which was significantly associated with RewP ($r = .26$, $p = .029$) and P2 ($r = .24$, $p = .043$) principal component difference waves. However, the anxious arousal scale exhibited a kurtosis of 3.60, where two participants who scored over three standard deviations above the mean appear to be driving this relationship.

3.2 | ERP data

Raw waveform difference waves are illustrated in Figure 2a separated by *DRD4* status. The RewP is clearly discernible, with the peak of the gain-loss difference wave observed at 280ms postfeedback around FCz. RewP was quantified as the average amplitude between 230 and 320ms postfeedback at FCz. In the raw waves, the P3a and P3b were merged into a single P3 time window around 380ms postfeedback. P3 was quantified as the average amplitude between 320 and 420ms postfeedback at electrode CPz. Condition-wise mean amplitudes are illustrated in Figure 2b. The RewP and P3 gain-loss difference waves were subjected to separate 2 × 2 ANOVAs (*DRD4* Status × Culture).

For the RewP, an ANOVA revealed the difference wave was significantly greater than zero ($F(1, 68) = 48.02$, $p < .001$, $\eta_p^2 = 0.41$), showing a more positive RewP for gains over losses ($M = 3.13$, $SD = 4.14$). Importantly, there was a significant main effect of *DRD4* status ($F(1, 68) = 8.00$, $p < .01$, $\eta_p^2 = 0.11$), revealing a greater RewP difference wave for the 7/2R carriers ($M = 4.65$, $SD = 4.29$) than for the noncarriers ($M = 1.97$, $SD = 3.65$). This effect was not qualified by culture ($p > .25$). Likewise, the P3 difference wave was significantly greater than zero ($F(1, 68) = 7.46$, $p < .01$, $\eta_p^2 = 0.10$), showing greater positivity for gains over losses ($M = 1.18$, $SD = 3.89$). However, the main effect of *DRD4* status was not significant for the P3 ($p = .10$). There were no other significant effects for the P3 (*ps* > .36). Finally, neither ERP difference wave was related to self-construal scores (*ps* > .34).

Next, we performed a temporospatial principal component analysis (PCA) on ERP signals. Four principal components (PCs) we extracted (P2 at CPz, RewP at Cz, P3a at FCz, and P3b at CPz) are illustrated in Figure 3a separated by *DRD4* status. Condition-wise mean amplitudes are illustrated in Figure 3b. The gain-loss difference waves for the RewP, P3a, and P3b PCs were subjected to separate 2 × 2 ANOVAs (*DRD4* Status × Culture).

In convergence with the raw wave analysis, the ANOVA on the RewP PC revealed the difference wave was significantly greater than zero ($F(1, 68) = 30.64$, $p < .001$, $\eta_p^2 = 0.31$), showing a more positive RewP PC for gains over losses ($M = 2.30$, $SD = 3.68$). Furthermore, there was a significant main effect of *DRD4* status ($F(1, 68) = 4.48$, $p = .038$, $\eta_p^2 = 0.06$). The gain-loss difference was significantly larger for 7/2R carrier group ($M = 3.32$, $SD = 3.71$) than for the noncarrier group ($M = 1.52$, $SD = 3.51$). This

TABLE 1 Averages and standard deviations for self-report measures for 4R and 7/2R carriers. *p* value (right) calculated from independent *t*-tests performed separately for each self-report measure to test differences between *DRD4* status groups

	4R		7/2R			
Questionnaire	***M***	***SD***	***M***	***SD***	***p***	***α***
Independent SC	4.85	0.55	4.98	0.72	.40	.71
Interdependent SC	4.89	0.56	4.78	0.91	.56	.81
Anhedonic depression	2.47	0.66	2.48	0.69	.95	.92
Anxious arousal	1.41	0.28	1.45	0.41	.65	.76
PSWQ	2.84	0.63	2.74	0.58	.50	.55
Behavioral activation	3.20	0.34	3.18	0.42	.80	.78
Behavioral inhibition	3.06	0.60	3.00	0.64	.71	.84

effect was not qualified by culture ($p > .18$). Likewise, the P3a PC difference wave was significantly greater than zero ($F(1, 68) = 9.81$, $p < .01$, $\eta_p^2 = 0.13$), showing a greater positivity for gains over losses ($M = 0.75$, $SD = 2.34$). Importantly, unlike the P3 window extracted from the raw ERP waveform, there was a significant main effect of *DRD4* status for P3a ($F(1, 68) = 8.81$, $p < .01$, $\eta_p^2 = 0.12$). The 7/2R group ($M = 1.64$, $SD = 2.22$) showed a greater gain-loss difference than the 4R group ($M = 0.07$, $SD = 2.22$). This effect was not qualified by culture ($p > .18$).

For the P3b PC, the difference wave was significantly greater than zero ($F(1, 68) = 5.25$, $p = .025$, $\eta_p^2 = 0.07$) with gains showing a greater positivity than losses ($M = 0.94$, $SD = 3.61$). However, the main effect of *DRD4* status was not significant for the P3b ($p > .3$). There were no other significant effects for any of the PCs ($ps > .13$) except for the P2.[3] Finally, none of the PC difference scores were related to self-construal scores ($ps > .28$).

For comparison, we extracted the RewP, P3a, and P3b components from the raw waveforms using the mean activity ±50 ms around the same peak latencies and electrode sites identified in the prior PCA analysis. As with the PCs, the gain-loss difference waves for each of these three components were entered into separate 2 × 2 (*DRD4* Status × Culture) ANOVAs. Results confirmed the PCA results for all three components. For the RewP and P3a, the difference waves were significantly greater than zero ($F(1, 68) = 44.71$, $p < .001$, $\eta_p^2 = 0.40$ and $F(1, 68) = 29.38$, $p < .001$, $\eta_p^2 = 30$, respectively), with gains showing greater positivity than losses (RewP: $M = 3.00$, $SD = 3.93$; P3a: $M = 2.40$, $SD = 4.18$), and there was a significant main effect of *DRD4* status for both components ($F(1, 68) = 5.09$, $p = .027$, $\eta_p^2 = 0.07$ and $F(1, 68) = 9.76$, $p < .01$, $\eta_p^2 = 0.13$, respectively), with the 7/2R group (RewP: $M = 4.14$, $SD = 4.10$; P3a: $M = 4.07$, $SD = 4.27$) showing greater gain-loss differences than the 4R group (RewP: $M = 2.07$, $SD = 3.60$; P3a: $M = 1.14$, $SD = 3.68$). For the P3b, the difference wave was significantly greater than zero ($F(1, 68) = 4.72$, $p = .033$, $\eta_p^2 = 0.07$), with gains showing greater positivity than losses ($M = 0.94$, $SD = 3.93$). However, there was no significant main effect of *DRD4* status for the P3b ($p > .17$). There were no other significant effects ($ps > .17$) and none of these component difference waves were related to self-construal scores ($ps > .42$). Equivalent supplementary analyses carried out with outcome probability (i.e., percentage gain of total outcomes) entered as a covariate revealed an identical pattern of significance for all Outcome × Gene interactions (see Table S2). In addition, there were no significant differences in outcome probability between gene groups (7/2R: $M = 0.49$, $SD = 0.036$; 4R: $M = 0.48$, $SD = 0.044$) ($p > .27$).

[3]The P2 difference wave was significantly greater than zero ($F(1, 68) = 6.06$, $p = .016$, $\eta_p^2 = 0.08$) where gains displayed greater positivity than losses ($M = 0.55$, $SD = 1.97$). There were no other significant effects for the P2 ($ps > .13$).

3.3 | Effects of face priming

The face priming manipulation did not qualify any of the results discussed above. Moreover, there was no effect of prime on the magnitude of the RewP PCA component. Of note, however, using a peak-to-peak measurement approach to quantify the RewP described in Hitotoko et al. (2016), there was a marginal main effect of prime ($F(1, 68) = 3.85$, $p = .054$, $\eta_p^2 = 0.05$), showing a marginally smaller gain-loss difference wave for the face ($M = -1.44$, $SD = 2.28$) than for scramble ($M = -0.93$, $SD = 2.36$) primes, consistent with the earlier report for the two cultural groups of interest (European Americans and Asian-born Asians in the U.S., Hitokoto et al., 2014).

4 | DISCUSSION

We show for the first time that *DRD4* polymorphism status modulates both bottom-up and top-down ERP components of reward processing. First, 7/2R carriers showed an elevated RewP gain-loss difference, reflecting enhanced bottom-up reward processing that involves the computation of reward prediction errors. Second, the P3a gain-loss difference was also enhanced for 7/2R carriers, suggesting increased top-down attention to reward feedback following gains over losses. These results suggest that compared to the noncarriers, the 7/2R carriers are more closely attuned to rewards in the environment. This observation sheds new light on possible mechanisms underlying Culture × *DRD4* interactions. The 7/2R carriers may acquire the modal response patterns that are positively sanctioned in their culture to a greater extent than the noncarriers do in part because of enhanced attunement to the culture's reward contingencies.

4.1 | Two components of reward processing

The current results highlight two discrete neural mechanisms of reward processing that may drive *DRD4* × Culture interactions. First, cultural learning requires the detection of action-outcome contingencies via evolutionarily conserved striatal reward networks that use the strength of reward prediction errors to update reward expectations (Frank & Claus, 2006). Our findings suggest that 7/2R carriers might "magnify" this bottom-up system through elevated reward-prediction errors, indexed by the RewP. This bottom-up component of reward processing, however, is

too crude to learn complex reward contingencies anchored in values, beliefs, and other cultural meanings. Thus, the second mechanism of top-down modeling of reward contingencies may be involved and used to guide goal-directed behavior (Fiorillo, 2013). Our results show that the P3a was increased for 7/2R carriers, suggesting enhanced top-down attentional processing of reward feedback following gains over losses.

These two components of reward processing may work in tandem (Rauss & Pourois, 2013). The relatively ancient "habit-based" striatal system may be required for abstracting probabilistic reinforcement values and exploiting prior outcome-contingency patterns (Frank, Moustafa, Haughey, Curran, & Hutchison, 2007). Conversely, more evolutionarily recent prefrontal cortical regions (Rougier et al., 2005) may be sensitive to changing environmental reward contingencies, such as rule changes or task-switching (Stefani & Moghaddam, 2006; Tunbridge, Bannerman, Sharp, & Harrison, 2004). In all likelihood, there exists extensive crosstalk between the two systems. For example, top-down reward-related representations can bias bottom-up systems to facilitate the learning of higher order contingency information, thereby reducing computational overhead (Balleine & O'Doherty, 2010; Sutton & Barto, 1998). We may, thus, hypothesize that, as compared to their noncarrier counterparts, 7/2R carriers effectively recruit more computationally demanding prefrontal systems to leverage their increased striatal responsiveness to reward in maximizing culturally relevant rewards and identifying abstract social rules and norms (Kitayama & Salvador, 2017).

4.2 | *DRD4*: is it special?

It bears emphasis that some prior neuroscience studies examined other dopaminergic system genes, most notably, monoamine oxidase A (*MAOA*) (Ma et al., 2016), catechol-O-methyltransferase (*COMT*) (Foti & Hajcak, 2012; Marco-Pallares et al., 2009; Mueller et al., 2014), and the dopamine transporter gene (DAT1) (Heitland et al., 2012). As for *COMT*, the available evidence is mixed. A variant linked to increases in neural reward processing in one study (Foti & Hajcak, 2012) is shown to be associated with decreases in reward processing in others (Marco-Pallares et al., 2009; Mueller et al., 2014). Further, an additional study failed to find any association between *COMT* and a neural marker of reward processing (Heitland et al., 2012). As for *MAOA*, one prior study shows that some variants of this gene modulate reward processing (Ma et al., 2016). Likewise, evidence for DAT1 implicated in reward processing does exist (Heitland et al., 2012). However, these findings have yet to be independently verified. Moreover, little evidence exists that any of these genes moderate cultural differences in behavioral or neural phenotypes. In short, there is no compelling evidence that dopaminergic genes other than *DRD4* play consistent roles in modulating reward processing.

It is, therefore, tempting to speculate that *DRD4 VNTR* is in some way special. Given the evidence that the 7/2R variants of *DRD4* have been incorporated into the human genome only in the last 50,000 years (Wang et al., 2004), it stands to reason that these variants contributed to biological adaptation in the context of increasingly complex cultural environments that emerged during the period. Supposedly, the 7/2R variants of *DRD4* were capable of upregulating preexisting gene networks, including those influencing striatal reward processing and prefrontal top-down cognition. They may have been selected over time for this particular function. In this view, *DRD4* is uniquely qualified as a hub of multiple gene networks that are involved in reward processing.

As important, the 7/2R allele has not shown a selective sweep in any of the populations studied to date (Chen, Burton, Greenberger, & Dmitrieva, 1999; Matthews & Butler, 2011). It is, therefore, possible that the increased reward processing associated with the 7/2R allele may carry its cost, depending on surrounding environments. In adverse environments, the 7/2R allele may be associated with impulsivity and other maladaptive behavioral traits that are instigated by immediate and tangible rewards, such as alcohol, high-calorie food, and sex, instead of responses to culture's normative reward contingencies. Evidence is consistent with this conjecture. When directly facing an opportunity to respond to tangible rewards, such as alcohol (for drinkers, Creswell et al., 2012) and cigarettes (for smokers, Le Foll, Gallo, Le Strat, Lu, & Gorwood, 2009), carries off the 7R allele respond more strongly. Moreover, also consistent is a robust association observed between the 7R allele and Attention-Deficit/Hyperactivity Disorder (ADHD) (Li, Sham, Owen, & He, 2006).

4.3 | Limitations and conclusions

Some limitations of the current work must be acknowledged. First, our results cannot speak to the directionality of these effects due to our difference wave approach. It remains unknown, for example, whether an enhanced P3a was due to elevated attentional control following gains, or rather a reduction following losses, or both. Second, ERPs cannot address the questions of neuroanatomy by themselves (Luck, 2014). Thus, although our results are consistent with a bottom-up learning component in striatal regions and a top-down control system in prefrontal areas, future research should investigate the neuroanatomical correlates of enhanced reward-related neural activity among 7/2R carriers. Third, our work is consistent with the hypothesis that the ability of *DRD4* to modulate reward processing is a key reason why this gene

moderates the degree to which individuals with differing VNTR status may acquire culturally typical behavioral and neural phenotypes. However, our work falls short of establishing this link. More work is needed to clarify the mechanisms underlying the Culture × *DRD4* interactions observed for various behavioral (e.g., Kitayama et al., 2014; Tompson et al., 2018) and neural phenotypes (Kitayama et al., 2019; Yu et al., 2018). Fourth, the observation that the effect of *DRD4* on reward processing is common across cultures provides support to the hypothesis that this effect is a mechanism for the Culture × *DRD4* interactions. Nevertheless, given the lack of sufficient statistical power for detecting the Culture × *DRD4* interaction in the current study,[1] this null finding must be kept tentative and further investigated in future work that is fully powered to detect such an interaction.

Despite these limitations, the current work establishes that *DRD4* modulates both bottom-up and top-down components of reward processing. Prior work on this gene focused exclusively on striatal (i.e., bottom-up) reward processing with fMRI. It is important that our ERP investigation enabled us to show that this bottom-up effect exists side by side with another effect on top-down reward processing. In tandem, these two effects of *DRD4* may ensure the powerful effects of this gene to regulate reinforcement-based learning. This consideration lends itself to a conjecture that *DRD4* may be serving as a functional hub that connects gene networks implicated in multiple mechanisms of reward processing. We, thus, wonder if this putative feature of *DRD4* might be crucial in understanding why this gene is capable of modulating environmental effects, including cultural effects, so robustly and consistently.

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CONFLICT OF INTEREST

Authors have no conflicts of interest to report.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the Supporting Information section.

Supplementary Material

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