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A polymorphism of serotonin 2A receptor (5-HT_{2A}R) influences delay discounting

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Abstract

The present study investigated the association between a polymorphism of the serotonin 2A receptor (5-HT_{2A}R) gene and the form of impulsive choice known as delay discounting. Using a hypothetical situation, we asked Japanese participants to choose between receiving (or paying) a different amount of money immediately or with a specified delay (one week, two weeks, one month, six months, one year, five years, or 25 years), and estimated the parameters of intertemporal choice models (exponential, hyperbolic, hyperbolic with exponent, and quasi-hyperbolic). Regardless of the genotypes, the hyperbolic with exponent model, which always indicated minimum AICc (Akaike Information Criterion with small sample correction), fitted better the observed data than the other models. Future gains were discounted more steeply than future losses. Moreover, as expected, individuals with the AA genotype of the 5-HT_{2A}R A-1438G polymorphism discounted the future more steeply than did individuals with the GG genotype, although this effect was limited to only gains. The findings implied individual differences based on the A-1438G polymorphism in the modulation of serotonin in the reward valuation underlying delay discounting (175 words).

Key words: 5-HT_{2A}R; delay discounting; impulsivity; hyperbolic with exponent model; future gains and losses

1. Introduction

Impulsivity is generally considered a dysfunctional trait and is associated with poor self-control (e.g., Baumeister, 2002), aggressive behavior (e.g., Barratt, 1994), substance dependence (e.g., Wills, Vaccaro, & McNamara, 1994), and psychiatric disorders (e.g., Moeller, Barratt, Dougherty, Schmitz, & Swann, 2001). Thus far, a wide array of studies on impulsive behavior has been conducted (see Bari & Robbins, 2013 for a review), particularly in terms of motor response inhibition (e.g., Horn, Dolan, Elliott, Deakin, & Woodruff, 2003) and impulsive choice (e.g., Winstanley, Theobald, Cardinal, & Robbins, 2006). Although impulsivity is a multidimensional construct, this study focuses on delay discounting—i.e., one's tendency to discount the value of rewards that are obtained at some later point in time. This delay discounting reveals people's preference for immediate, smaller gains over larger, delayed gains (e.g., $10 today vs. $20 after one year). Although individual differences in the delay discounting tendency have been documented, to our knowledge, the genetic underpinnings of such individual differences have not been intensively investigated. Thus, we targeted a polymorphism of the serotonin 2A receptor (5-HT_{2A}R) gene and examined its impact on delay discounting.

1.1. Delay discounting

Classical economic theory presupposes an exponential model that assumes an exponential decay of the subjective value of a reward along with the delay. The exponential discounting function is written as follows (e.g., Samuelson, 1937):

$$V(D) = \frac{V(0)}{\exp(kD)} \qquad (1)$$

where V(D) is the subjective value of a reward (or payment) at delay D, and k is a free parameter that represents the discount rate. This function predicts that individuals have time-consistent preferences. Suppose that one prefers $10 today to $11 tomorrow. If this person

has time-consistent preferences, he/she prefers \$10 earned *x* days later to \$11 earned (*x* + 1) days later.

Nevertheless, empirical evidence suggests that delay discounting often exhibits time-inconsistent patterns and that the reduction in the subjective value of an outcome is much steeper in the early phase of delay and becomes more gradual as the delay gets longer (e.g., Ainslie, 1975; Mazur, 1987). For instance, people tend to prefer to receive \$450 immediately rather than to receive \$500 after one week, whereas they prefer to receive \$500 after five years and one week rather than to receive \$450 after five years. Although the length of the delay is identical in both cases (i.e., one week), people's preferences for the two options are reversed. It has been pointed out that a hyperbolic function better describe such time-inconsistent choice behavior (e.g., Kirby, 1997).

The equation is

$$V(D) = \frac{V(0)}{1+kD} \qquad (2)$$

where D and k represent delay and discount rate, respectively.

Moreover, more general forms of the hyperbolic equation have been suggested. For example, Rodriguez and Logue (1988) proposed an equation in which an exponent is added to the delay (see also Rachlin, 2006).

$$V(D) = \frac{V(0)}{1+kD^S} \qquad (3)$$

The exponent S, which is a power-function parameter, suggests individual differences in sensitivity of V (D) / V (0) to D. When S = 1, the equation is identical to the hyperbolic equation (2). On the other hand, when S is less than 1, the decrease of V (D) / V (0) over the course of the delay diminishes faster than it does in the (simple) hyperbolic model.

Such a time-inconsistent delay discounting pattern has also been expressed by an

equation based on quasi-hyperbolic discounting (e.g., Laibson, 1997).

$$V(D) = \begin{cases} V(0) & when\ D = 0 \\ V(0)\beta\delta^{D} & when\ D > 0 \end{cases} \quad (4)$$

When β and δ are less than 1, the equation indicates that subjective value decreases more in the near term, whereas it decreases less in the long term. When $\beta = 1$, the equation is similar to the exponential equation (1). Thus, δ corresponds to an individual's discount rate, whereas β suggests the degree to which an individual values present outcomes relative to future outcomes.

1.2. Serotonin and delay discounting

Previous research, including animal studies, has suggested that the serotonergic system regulates inhibitory control, so that a reduction in serotonin function is associated with impulsivity. Lower levels of serotonin increase delay discounting rates in rats (Mobini et al., 2000) and humans (Schweighofer et al., 2008). Serotonin depletion also leads to a failure to wait for delayed but large reinforce in rats (e.g., Wogar, Bradshaw, & Szabadi, 1993). Moreover, using microdialysis, Winstanley et al. (2006) showed that an increase in 5-HT efflux was found in the medial prefrontal cortex (mPFC) during delay discounting. Furthermore, Tanaka et al. (2007) found that activity of the ventral parts of the striatum was linked to steeper delay discounting of future gains in participants with low serotonin levels, whereas activity of the dorsal parts of the striatum was linked to less delay discounting in participants with high serotonin levels. Although the specific mechanisms through which the serotonergic system interacts with the activities of neural substrates (e.g., mPFC and striatum) are still unclear, the involvement of the serotonergic system in regulating impulsive behaviors has been established (Miyazaki, Miyazaki, & Doya, 2012).

The 5-HT$_{2A}$ receptor is one type of 5-HT receptors. Although it is widely distributed in the brain, it is concentrated in the cerebral cortex (Varnas, Halldin, & Hall, 2004). Associations

between the 5-HT_{2A}R gene and substance abuse disorders have been reported (Cao et al., 2014). Moreover, 5-HT_{2A}R binding in the prefrontal cortex is associated with aggression in suicide subjects (Oquendo et al., 2006), which implies a relationship between the 5-HT_{2A}R gene and impulsivity. Polymorphisms of the 5-HT_{2A}R gene are also associated with impulsivity. For example, focusing on one of the polymorphisms on this gene, A-1438G (rs6311), Preuss, Koller, Bondy, Bahlmann, and Soyka (2001) demonstrated an association between alcohol dependence with the AA genotype and impulsivity. In addition, by administering a go/no-go task to healthy participants, Nomura et al. (2006) showed that individuals with the AA genotype found it more difficult to withhold to-be-withheld stimuli and made more commission errors than did individuals with the GG genotype. This suggests greater difficulty for individuals with the AA genotype in motor response inhibition.

1.3. The present study

Although the associations between the A-1438G polymorphism in the 5-HT_{2A}R gene and impulsive behaviors have been suggested using subtypes of impulsivity measures, such as motor response inhibition (e.g., Nomura et al., 2006), no studies have directly examined the effect of this polymorphism on delay discounting. Although delay discounting is considered a type of impulsivity, it might be more regulated by overlapping but different neural mechanisms than other types of impulsivity (Brewer & Potenza, 2008). This study thus examined whether the A-1438G polymorphism in the 5-HT_{2A}R gene influences a particular type of impulsivity, delay discounting.

In this study, we examined the extent to which Japanese participants discounted future gains and losses, as it is known that people tend to discount future gains more than future losses—the sign effect (e.g., Frederick, Loewenstein, & O'donoghue, 2002). We then estimated

parameters of exponential, hyperbolic, hyperbolic with exponent, and quasi-hyperbolic models for each group of the genotypes of A-1438G polymorphism in the 5-HT_{2A}R gene. We expected that individuals with the AA genotype would more heavily discount the future than G carriers.

2. Method

2.1. Participants

Two hundreds and twelve Japanese undergraduate students (112 females and 100 males, M_{age} = 19.25, *SD* = 0.99) at a Japanese University participated in this study. They were recruited through a psychology subject pool in the university. This study was conducted as part of a half-day experiment, which included the administration of questionnaires on a wide range of topics, such as the self, emotion, cognition, and interpersonal behaviors. In addition, the session included behavioral game experiments. Participants were paid 4,000 yen (about $40) plus some bonuses based on the results of the behavioral games.

2.2. Procedures

This study focused on a decision-making task that included hypothetical gains and losses. Participants were asked to make a series of 1,120 hypothetical binary choices under the assumption that their choices involved real money. Each choice consisted of two alternatives: (a) receiving (or paying) a certain amount of money immediately or (b) receiving (or paying) the fixed amount of 100,000 yen (about $1,000) after a certain period of delay. The immediate option (a) was always presented in the left column and the delayed option (b) was always presented in the right column. Participants were asked to choose whether they preferred option (a) or (b). In (a), the immediate options varied from 0 to 97,500 yen, with an increment of 2,500 yen (i.e., in 2.5% increments); thus, there were 40 variants. There were seven periods of delay: one week, two weeks, one month, six months, one year, five years, and 25 years. A single page

of this task included 40 choices: the 40 immediate options were compared with the fixed amount of 100,000 yen at one of the seven periods of delay. For instance, in the case of gain after a one-week delay, participants were instructed as follows: “If you had to choose one of two alternatives, whether you receive the money indicated in the left column today or the money indicated in the right column after one week, which of the alternatives would you choose? For each of the cases numbered one to 40, please circle the amount of money you prefer.” The order of the 40 immediate options (ascending vs. descending) was a within-participant factor. The domain of the choice (gain vs. loss) was also a within-participant factor. Accordingly, there were 1,120 choices (i.e., 40 immediate options × 7 delays × 2 domains × 2 orders). This task was adapted with little modification from previous studies conducted by Han and Takahashi (2012).

2.3. Data analysis

For each participant, seven indifference points associated with the seven delay conditions were computed. Following Han and Takahashi (2012), an indifference point was operationally defined as the fixed amount of gain (or loss) that is subjectively equivalent to a 100,000-yen gain (or loss) after a certain delay. When the amounts of the immediate gains were small, such as 0 and 2,500 yen, participants were naturally inclined to choose the delayed 100,000 yen. When the amounts of the immediate gains were large, at some point, participants switched their choice from the delayed 100,000 yen to the immediate gains. The indifference point was obtained by averaging the largest non-chosen immediate gain and the smallest chosen immediate gain. For example, if a participant preferred a delayed 100,000 yen to an immediate 50,000 yen, whereas he/she preferred an immediate 52,500 yen to a delayed 100,000 yen, his/her indifference point was 51,250 yen. Because the participants made the same decisions twice (in an ascending and descending order), the two indifference points associated with a

single delay were averaged. The mean indifference points in ascending and descending orders were highly correlated for both gains (r = .998) and loses (r = .997).

For the loss tasks, the procedures were the same. However, the switching pattern was reversed. Participants were inclined to choose immediate, small losses such as 0 and 2,500 yen to a delayed loss of 100,000 yen. Participants become more likely to choose the delayed 100,000 yen when the immediate losses got closer to 100,000 yen. Nevertheless, switching points were present, and they were averaged to obtain the indifference points.

By performing a nonlinear regression with R, we then fitted the exponential, hyperbolic, hyperbolic with exponent, and quasi-hyperbolic models, which correspond to the equations (1) to (4), respectively, to the mean indifference points across all the participants for each outcome type. We further fitted these models to the mean indifference points in each genotype. Akaike Information Criterion with small correction (AICc) was used to estimate the goodness of fit. We performed model selection based on AICc using the AICcmodavg package in R. A smaller AICc indicates a better model fit.

In addition, we computed an area under the curve (AUC) for the gain or loss conditions separately to estimate the extent to which participants discounted delayed gains or losses, following Ohmura, Takahashi, and Kitamura (2005). The delays and indifference points were standardized by dividing them by the maximum values so that they varied between 0 and 1. Instead of fitting a curve, we connected adjacent delay points by straight lines and computed the area under these lines. Each line made a trapezoid; thus, the total area could be computed by summing the sizes of the trapezoids: $(y_{i+1} + y_i) \times (x_{i+1} - x_i) / 2$, where x_i and x_{i+1} are successive delays (x_{i+1} is a one-unit future time compared to x_i) and y_i and y_{i+1} are the subjective values of a gain or loss with these delays (see Figure 1 for an example). A smaller AUC indicated greater

delay discounting.

2.4. Genotyping

Nail samples were collected, from which Genomic DNA was extracted by using ISOHAIR kits (NIPPON GENE CO., LTD, Tokyo, Japan). The SNP marker for rs6311 was genotyped using TaqMan® SNP Genotyping Assays (Thermo Fisher Scientific Inc., Waltham, Massachusetts), which were functionally tested by Thermo Fisher Scientific Inc. and available on demand. All polymerase chain reactions (PCR) and allelic discrimination reactions were performed on the StepOne Plus™ Real-Time PCR System (Thermo Fisher Scientific Inc.).

3. Results

3.1. Genotype distribution

The distribution of genotypes (59 AA, 104 GA, 48 GG, 1 undetermined) was not different from that predicted by the Hardy-Weinberg equilibrium, $\chi^2(1) = 0.82$, $p = .64$.

3.2. Delay discounting task

Because two participants did not follow the instructions of the delay discounting task, their data were excluded from the analyses. The AICc and parameters were estimated for each of the four models. Table 1 summarizes the results. The AICc values showed that the hyperbolic with exponent model fitted the observed data better than the other three models. Also, participants discounted future gains more steeply than future losses. Figure 2 plotted the means of subjective value for all the participants, those with GG genotype, GA genotype, and AA genotype, respectively, which were fitted with the hyperbolic with exponent model. Although the superiority of the hyperbolic with exponent model and the greater delay discounting of gains were constant across the genotype groups, the three groups differed in discount rates for gains: the estimated discount rate (k) was larger in individuals with the AA genotype than in

individuals who were G carriers. In contrast, for losses, the discount rate was not remarkably different across the three genotype groups. Moreover, the parameter S was smaller in GG-individuals than in AA- and GA-individuals for both gains and losses.

Next, the AUC was submitted to a mixed-model ANOVA with one between-subject variable (genotype: AA, GA, and GG) and one within-subject variable outcome: gain and loss). Figure 3 presents frequency histograms of the AUCs with the density distributions for each genotype. The results showed a significant main effect of outcome, $F(1, 206) = 91.04$, $p < .001$, $\eta_p^2 = .31$. The AUC was significantly smaller for gains ($M = 0.63$, $SD = 0.26$) than for losses ($M = 0.80$, $SD = 0.24$). The interaction between genotype and outcome was also significant, $F(2, 206) = 6.42$, $p = .002$, $\eta_p^2 = .06$. For gains, the main effect of genotypes was significant, $F(2, 206) = 4.16$, $p = .02$, $\eta_p^2 = .04$. Multiple comparisons were conducted with Shaffer's modified sequentially rejective Bonferroni procedure. The AUC was significantly smaller for individuals with the AA genotype ($M = 0.57$, $SD = 0.27$) than for individuals with the GG genotype ($M = 0.72$, $SD = 0.25$), $t(206) = 2.87$, adjusted $p = .01$, $d = 0.40$. The size of the AUC of the GA genotype group ($M = 0.63$, $SD = 0.26$) was in between that of the other two groups. Whereas the difference between the GA and AA genotype groups was not significant, $t(206) = 1.33$, adjusted $p = .19$, the difference between the GG and GA genotype groups was significant, $t(206) = 1.96$, adjusted $p = .05$, $d = 0.27$. In contrast, for losses, the main effect of genotypes was not significant, $F(2, 206) = 0.34$, $p = .71$ (AA: $M = 0.82$, $SD = 0.25$; GA: $M = 0.79$, $SD = 0.24$; GG: $M = 0.80$, $SD = 0.25$). Moreover, the mean AUCs for gains and losses were highly correlated in all the groups (AA: $r = .61$, GA: $r = .52$, GG: $r = .69$, ps $< .001$).[1]

4. Discussion

To our knowledge, this study offered the first evidence for the association between the

polymorphism of the 5-HT_{2A}R gene and impulsive choices in delay discounting. As predicted, we found that individuals with the AA genotype of the A-1438G polymorphism discounted future gains more steeply than did individuals with the GG genotype. This finding supported previous studies indicating a relationship between impulsivity and polymorphisms of the 5-HT_{2A}R gene. Among previous studies, Nomura et al. (2006) demonstrated greater difficulty for individuals with the AA genotype in motor response inhibition. These findings suggested that the effect of the A-1438G polymorphism might extend to a broader range of impulsivity, including delay discounting. This point was one advantage of this study.

Regardless of genotype, we found that the hyperbolic with exponent model fitted the observed data better than the other models for both gains and losses. Moreover, the participants discounted future gains more steeply than future losses. Although two-parameter models can account for time-inconsistent delay discounting compared to single-parameter models (McKerchar et al., 2009), the hyperbolic with exponent model provided a better fit than did the quasi-hyperbolic model. Interestingly, the exponent S in the hyperbolic with exponent model, which was less than 1 as a whole, was smaller in GG-individuals than in A carriers. The patterns of indifference points plotted in Figure 2 suggest that future time intervals may not be estimated precisely but perceived as shrinking logarithmically, and that this tendency may be more pronounced in GG individuals. Future research will be needed to more fully examine the genetic effect on time-inconsistency in delay discounting.

Reward valuation is one of processing stages underlying delay discounting. Value functions in particular are computed in the striatum (O'Doherty et al., 2004). An expectation of immediate rewards is associated with activation of the ventral striatum, medial orbitofrontal cortex, medial prefrontal cortex, and posterior cingulate cortex (McClure et al., 2004). It has

been suggested that serotonergic neurons, which control dopamine release in the striatum, could modulate the computation of value function (Schweighofer, Tanaka & Doya, 2007). On the other hand, animal studies examining the effects of the 5-HT_{2A}R gene on response inhibition have suggested an impulsivity-enhancing effect of 5-HT_{2A}R agonist in the medial prefrontal cortex (Hadamitzky, Feja, Becker, & Koch, 2009) and the orbitofrontal cortex (Wischhof, Hollensteiner, & Koch, 2011). Taken together, these findings may reveal individual differences based on the A-1438G polymorphism in the modulation of serotonin in reward valuation.

Although the individual differences in the tendency to discount gains and losses were highly positively correlated, this study showed a gain–loss asymmetry in delay discounting. Overall, the participants were sensitive to future losses as much as immediate losses. The asymmetric effect of the 5-HT_{2A}R genetic polymorphism was indirectly supported by Nomura et al. (2006), indicating that although individuals with the AA genotype made more commission errors than did individuals with the GG genotype when they were rewarded by withholding to-be-withheld stimuli, no genetic effect was found on commission errors when participants were punished by responding to to-be-withheld stimuli. The findings of Nomura et al. (2006) may have suggested that there is no difference in sensitivity to punishment among the three genotypes of the 5-HT_{2A}R gene. This study suggested that an association between the 5-HT_{2A}R gene and impulsive choice depends on context and that it helps to specify what kind of impulsive behaviors interact with a polymorphism of the 5-HT_{2A}R gene.

However, we may need to carefully interpret the null effect of the 5-HT_{2A}R gene on the loss delay discounting task. A previous study revealing an association between the 5-HT_{2A}R gene and risk-averse decisions (Macoveanu et al., 2013) suggested that the behavioral measure of delay discounting may be less reliable than brain measures in capturing the effect of the

5-HT_{2A}R gene. Moreover, whereas we investigated individual differences based on a specific polymorphism of the 5-HT_{2A}R gene (i.e., A-1438G), Macoveanu et al. (2013) experimentally manipulated the function of the 5-HT_{2A} receptor with ketanserin, which is a known ligand of the 5-HT_{2A} receptor, and revealed that pharmacologically blocking the 5-HT_{2A} receptor made participants more risk-averse. The direct blocking of the 5-HT_{2A} receptor may be useful for further examination of the association between the 5-HT_{2A}R gene and delay discounting, particularly in examining the asymmetric effects of gain and loss contexts.

One limitation that should be taken into account is that we used hypothetical rewards in this study. Thus, we did not address uncertainty of action, which promotes risk-taking and exploratory choices. Another limitation is that we did not consider how reward amount would influence the association between the 5-HT_{2A}R gene and delay discounting. Given that people discount less steeply as reward amount increases (Green, Myerson, Oliveira, & Chang, 2013), future work will be needed to test a possibility that the association may change as a function of reward amount. In spite of these limitations, this study went beyond previous work by providing the first empirical evidence of an association between the A-1438G polymorphism and impulsive choice, using a delay discounting task and fitting exponential and hyperbolic models to the observed data. While we believe that this study has helped to shed light on the role of genetic factors, such as a 5-HT_{2A}R polymorphism, in impulsivity, it is crucial to establish the generalizability of this study's findings in future research.

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Footnote

1. As another measurement of delay discounting at the individual level, we also computed each participant's discount rate (*k*) for gains and losses based on the hyperbolic with exponent model. The obtained individual discount rates (*k*) were log-transformed, *k*' = log (*k* + 1). A 3 (genotype) x 2 (outcome) ANOVA revealed a significant main effect of outcome, $F(1, 168) = 54.34$, $p < .001$, $\eta_p^2 = .24$. The participants discounted gains ($M = 0.52$, $SD = 0.56$) more than losses ($M = 0.24$, $SD = 0.42$). Although the interaction was not significant ($F(2, 168) = 2.13$, $p = .12$, $\eta_p^2 = .02$), GG individuals ($M = 0.65$, $SD = 0.61$) were less likely than A carriers to discount future gains (AA: $M = 0.42$, $SD = 0.65$, GA: $M = 0.54$, $SD = 0.53$). Genotypes did not influence the delay discounting for future losses either (AA: $M = 0.22$, $SD = 0.43$; GA: $M = 0.28$, $SD = 0.40$; GG: $M = 0.26$, $SD = 0.48$).

Table 1

AICc (Akaike Information Criterion with small correction) and parameters for four models

	Hyperbolic with Exponent	Exponential	Hyperbolic	Quasi-hyperbolic
Gain				
All				
AICc	-41.52	-9.29	-12.39	-8.78
Parameter	k_{he} = 1.09	k_e = 0.94	k_h = 1.60	β = 0.93
	S = 0.50			δ = 0.46
AA group				
AICc	-29.32	-5.76	-9.63	-4.95
Parameter	k_{he} = 1.91	k_e = 1.23	k_h = 2.52	β = 0.91
	S = 0.50			δ = 0.37
GA group				
AICc	-41.59	-10.13	-13.72	-8.88
Parameter	k_{he} = 1.18	k_e = 0.95	k_h = 1.64	β = 0.94
	S = 0.53			δ = 0.44
GG group				
AICc	-37.67	-12.82	-14.47	-14.75
Parameter	k_{he} = 0.38	k_e = 0.64	k_h = 0.92	β = 0.94
	S = 0.43			δ = 0.59
Loss				
All				
AICc	-59.09	-20.34	-21.65	-20.78
Parameter	k_{he} = 0.16	k_e = 0.42	k_h = 0.52	β = 0.96
	S = 0.47			δ = 0.70
AA group				
AICc	-53.02	-22.19	-23.33	-23.89
Parameter	k_{he} = 0.13	k_e = 0.38	k_h = 0.46	β = 0.96
	S = 0.47			δ = 0.72
GA group				
AICc	-53.50	-21.68	-23.51	-21.69
Parameter	k_{he} = 0.26	k_e = 0.47	k_h = 0.59	β = 0.97
	S = 0.54			δ = 0.66
GG group				
AICc	-38.13	-15.87	-16.62	-15.92
Parameter	k_{he} = 0.06	k_e = 0.37	k_h = 0.45	β = 0.95
	S = 0.37			δ = 0.75

Figure Captions

Figure 1. An example of the total area under standardized indifference points curve (i.e., AUC)

Figure 2. Hyperbolic with exponent functions with delay for all the participants (gain: a, loss: b), the GG genotype group (gain: c, loss: d), the GA genotype group (gain: e, loss: f), and the AA genotype group (gain: g, loss: h). Mean indifference points were plotted in black circle. Expected subjective values were plotted in gray circle with 95% confidence intervals.

Figure 3. Frequency histograms of the AUCs with the density distributions for (a) gains and (b) losses for the AA, GA, and GG genotype groups.

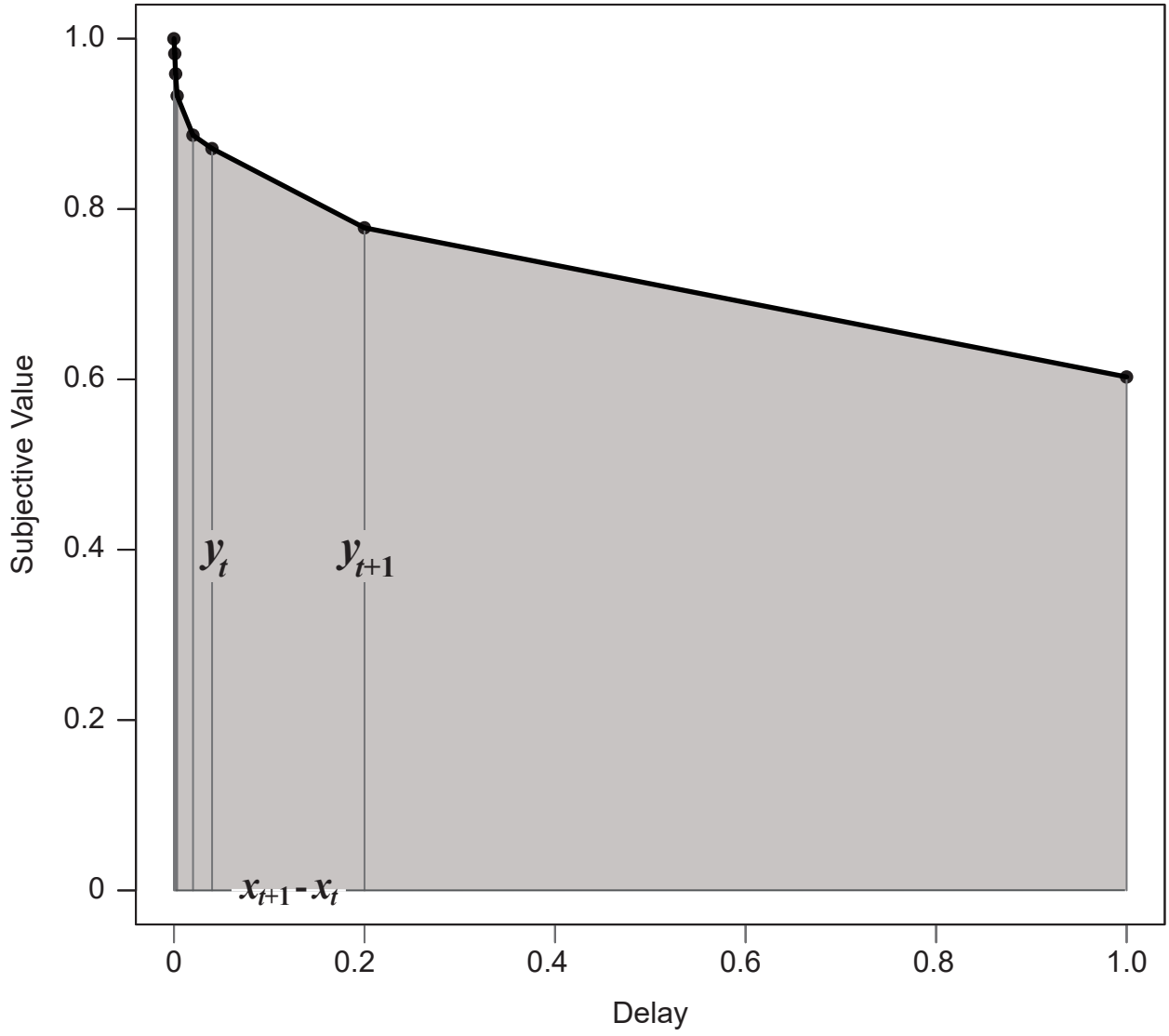
1.0
0.8
0.6
0.4
0.2
0
Subjective Value
y_t
y_{t+1}
$x_{t+1} - x_t$
0
0.2
0.4
0.6
0.8
1.0
Delay

Figure 1.

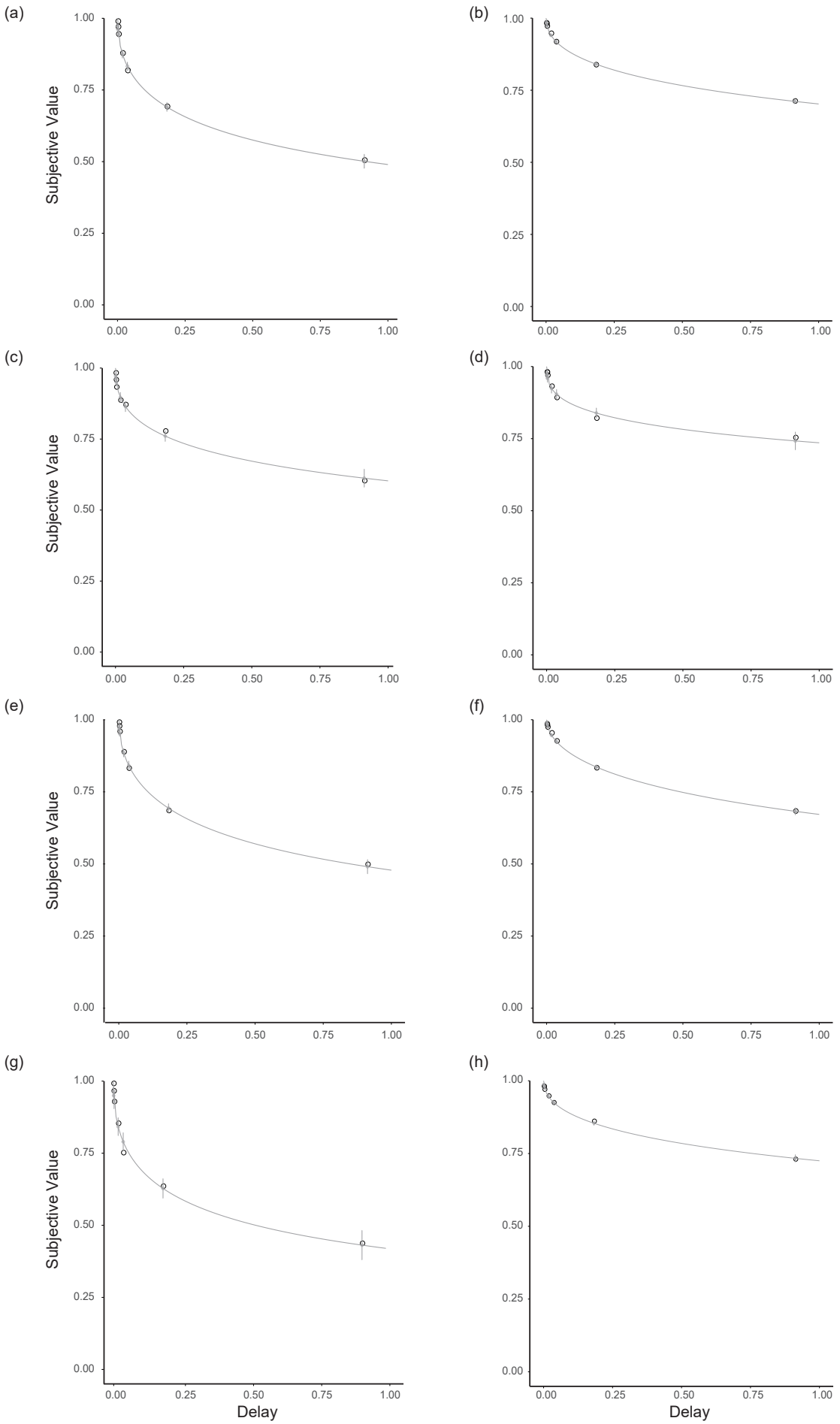

Figure 2.

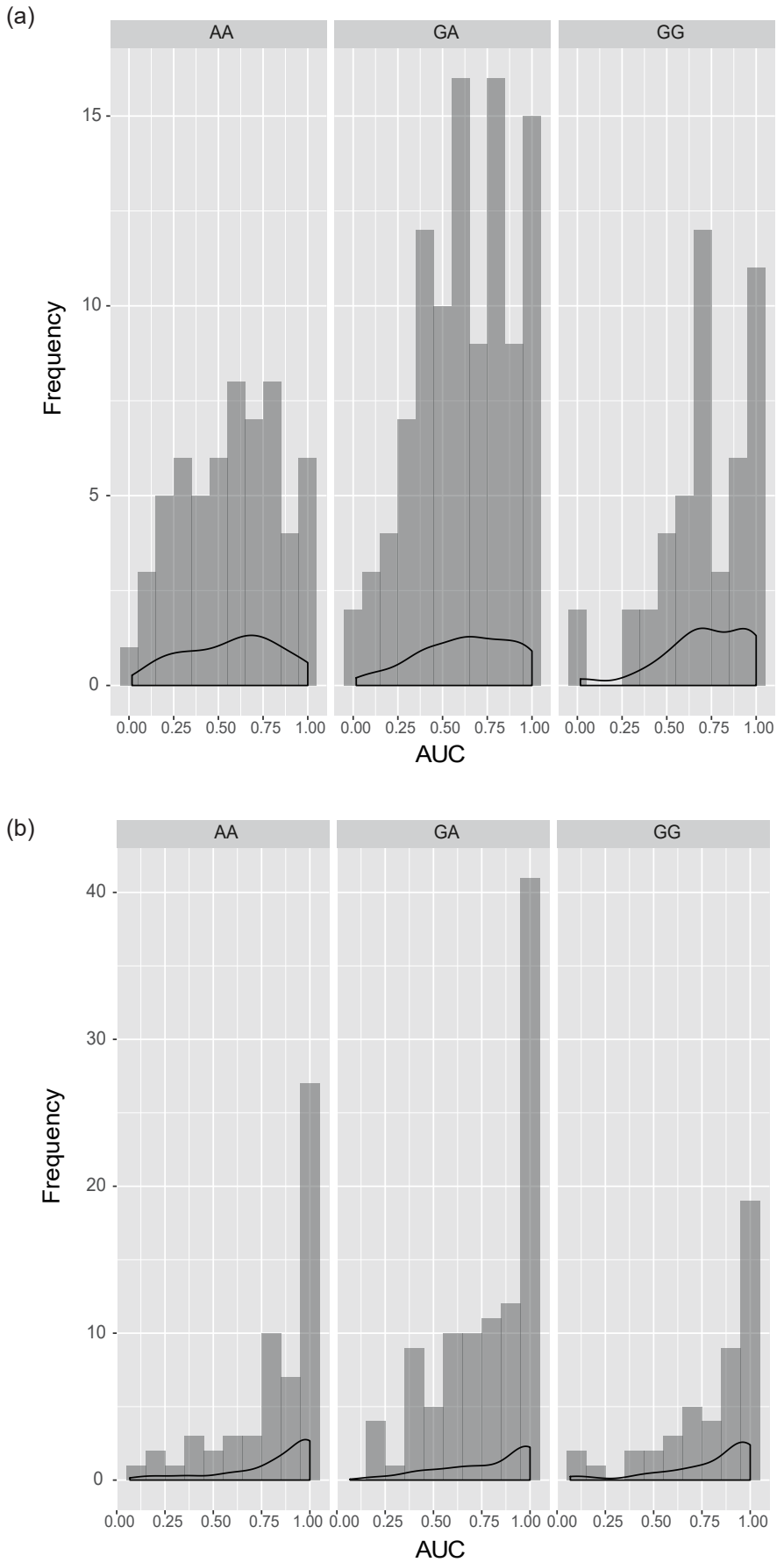
(a)
AA
GA
GG
Frequency
15
10
5
0
0.00
0.25
0.50
0.75
1.00
AUC
(b)
AA
GA
GG
Frequency
40
30
20
10
0
0.00
0.25
0.50
0.75
1.00
AUC

Figure 3.