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The C957T polymorphism in the dopamine receptor D_2 gene modulates domain-general category learning

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Xie Z, Maddox WT, McGeary JE, Chandrasekaran B. The C957T polymorphism in the dopamine receptor D_2 gene modulates domain-general category learning. *J Neurophysiol* 113: 3281–3290, 2015. First published March 11, 2015; doi:10.1152/jn.01005.2014.— Adaptive learning from reward and punishment is vital for human survival. Striatal and frontal dopaminergic activities are associated with adaptive learning. For example, the C957T single nucleotide polymorphism of the dopamine receptor D_2 (*DRD2*) gene alters striatal D_2 receptor availability and affects individuals' adaptive learning ability. Specifically, individuals with the T/T genotype, which is associated with higher striatal D2 availability, show enhanced learning from negative outcomes. Prior work examining *DRD2* genetic variability has focused primarily on frontally mediated reflective learning that is under effortful, conscious control. However, less is known about a more automatic, striatally mediated reflexive learning. Here we examined the extent to which this polymorphism differentially influences reflective and reflexive learning across visual and auditory modalities. We employed rule-based (RB) and information-integration (II) category learning paradigms that target reflective and reflexive learning, respectively. Results revealed an advantage in II category learning but poorer RB category learning in T/T homozygotes. The pattern of results was consistent across sensory modalities. These findings suggest that this *DRD2* polymorphism exerts opposite influences on domain-general frontally mediated reflective learning and striatally mediated reflexive learning.

single-nucleotide polymorphism; D_2 receptor availability; rule-based learning; information-integration learning

ADAPTIVE LEARNING FROM REWARD and punishment is vital for human survival and normal cognitive development. Maladaptive learning from reward and punishment has been implicated in psychopathology, including alcohol and substance dependence (Bechara et al. 2001; Bechara et al. 2002; Redish et al. 2007), depression (Eshel and Roiser 2010; Pizzagalli et al. 2009), obsessive-compulsive disorders (Gillan et al. 2011), and attention deficit hyperactivity disorder (Scheres et al. 2007). A myriad of evidence points to a critical role for the neurotransmitter dopamine (DA) in the regulation of reward and punishment learning (Bayer and Glimcher 2005; Frank 2005; Frank et al. 2009; Frank and Hutchison 2009; Frank et al. 2007; Frank et al. 2004; Gorlick et al. 2014; Satoh et al. 2003; Schultz 2002). Specifically, striatal and frontal dopaminergic activities are associated with selection of behaviors that maximize rewards and minimize punishments (Frank et al. 2009; Frank and Hutchison 2009; Frank et al. 2007; McClure et al. 2003; Robbins and Everitt 1992; Waelti et al. 2001). Dopaminergic genes modulate DA function and thereby impact individuals' ability to learn from positive and negative outcomes (Frank et al. 2009; Frank and Hutchison 2009; Frank et al. 2007). Prior research has primarily focused on learning in a reflective mode that is under effortful, conscious control. Less work has explicitly examined learning in a reflexive mode that is relatively more automatic and not under conscious control. Recent evidence suggests that dopaminergic genetic effects may differentiate depending on whether learning is predominantly reflective or reflexive (Karabanov et al. 2010). Here we examined the effects of an extensively studied polymorphism in the dopamine D_2 receptor (*DRD2*) gene on reflective and reflexive learning.

The *DRD2* gene, located at chromosome 11q23.1 (Eubanks et al. 1992), encodes the D_2 dopamine receptor. This gene is highly expressed in the striatum (Meador-Woodruff et al. 1996). The C957T single-nucleotide polymorphism (SNP) (rs6277) of the *DRD2* gene alters D_2 receptor availability in striatum, with greatest D_2 receptor availability in individuals with two copies of the T allele (T/T homozygotes), intermediate in C/T carriers, and least in C/C carriers (Hirvonen et al. 2005). The enhanced striatal *DRD2* availability with the T allele may have complex effects in the brain, since altered *DRD2* affinity (as measured by K_D value) has been reported and explained by changes in dopaminergic tone affecting competition between dopamine and [^{11}C]raclopride for binding sites (Hirvonen et al. 2009). Hence, individuals with the T allele may show increased sensitivity to reductions in dopamine that are associated with negative consequences (Frank et al. 2009; Frank and Hutchison 2009; Frank et al. 2007). Functionally, T/T homozygotes show enhanced learning from negative outcomes (Frank et al. 2009; Frank and Hutchison 2009; Frank et al. 2007). These studies show clear effects of *DRD2* variation on reward and punishment learning, but they provide less clear information regarding the neural circuitry underlying differential learning. This follows because the tasks used in these studies did not exclusively target reflective or reflexive learning processes. Thus, it remains to be determined the extent to which *DRD*2 genetic variation modulates reflective and reflexive learning.

In the category learning literature, researchers have developed optimal paradigms that selectively target reflective and reflexive learning (Ashby et al. 2011; Ashby et al. 1998; Ashby and Maddox 2005; 2011). According to the Competition be-

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tween Verbal and Implicit System (COVIS) model (Ashby et al. 2011; Ashby et al. 1998), optimal RB category learning involves developing and testing verbalizable rules about category membership, which is mediated by an explicit, reflective, hypothesis-testing system. Processing in the reflective system is available to conscious awareness and critically depends on structures including prefrontal cortex, anterior cingulate, and head of caudate nucleus (Ashby and Ell 2001; Filoteo et al. 2005a; Schnyer et al. 2009; Seger and Miller 2009). Optimal II category learning, on the other hand, involves predecisional integration across stimulus dimensions, which is mediated by a reflexive, procedural-based learning system. Learning in the reflexive system is not consciously penetrable, and is highly dependent on the striatal structures such as putamen, body, and tail of the caudate nucleus (Ashby and Ennis 2006; Filoteo et al. 2005b; Nomura et al. 2007; Seger and Cincotta 2005). The reflective optimal paradigm examines learning of rule-based (RB) category structures, where the optimal rules are verbalizable. In contrast, the reflexive optimal paradigm examines learning of information-integration (II) category structures, where the optimal rules are not verbalizable. Interestingly, learning performance in reflective- and reflexive-optimal tasks is dissociable (Maddox et al. 2003; Maddox et al. 2004; Maddox et al. 2013; Maddox et al. 2014; Maddox et al. 2005; Maddox et al. 2008; Tam et al. 2013; Zeithamova and Maddox 2007). For example, individuals with elevated depressive symptoms show a deficit in reflective-optimal learning but an advantage in reflexive-optimal learning (Maddox et al. 2014). As discussed before, *DRD*2 C957T T/T homozygotes show enhanced striatal function. Thus, we predict that T/T homozygotes will demonstrate better learning of II category structures but may exhibit worse learning of RB category structures.

This dual-learning systems (reflective vs. reflexive) theoretical framework has been presumed to be domain general but has primarily been examined in the visual domain (Ashby et al. 2011; Ashby et al. 1998; Ashby and Maddox 2005; 2011). Only recently, it has been extended to speech category learning (Chandrasekaran et al. 2014b; Maddox and Chandrasekaran 2013; Yi et al. 2014). However, these auditory studies have not employed constrained stimuli that specifically target the reflective or reflexive learning system. Hence, it remains undetermined whether this dual-learning systems framework extends to the auditory domain.

Previous studies showed that the visual and auditory domains share similarities, such as a topographical organizing principle (vision: retinotopy; audition: tonotopy), and functionally distinct dorsal and ventral cortical streams (Marois et al. 2000; Rauschecker and Scott 2009; Romanski et al. 1999). However, critical differences between the two domains are also documented (Chandrasekaran et al. 2014a). For example, significant auditory signal processing occurs well before the midbrain, whereas the visual pathway lacks functional processing centers at the level of the brain stem. In addition, the auditory system is subserved by massive efferent feedback connectivity, which yields substantial top-down control over the lower-level auditory centers, whereas the efferent connectivity of the visual system is less massive. Furthermore, of relevance to cognition and learning, human auditory short-term and recognition memory has been shown to be inferior to the visual analogs (Bigelow and Poremba 2014; Cohen et al. 2009). The existence of both commonalities as well as differences across the two domains posits the question of whether the dual-learning systems framework, developed primarily based on the visual domain, is truly domain general. Thus, we also aimed to examine reflective and reflexive learning across visual and auditory modalities to test for domain generality.

Taken together, the current study aimed to examine the association of *DRD*2 genetic variation on reflective and reflexive learning across visual and auditory domains. We employed reflective- and reflexive-optimal category learning tasks to target reflective and reflexive learning, respectively. *Experiment 1* examined RB and II visual category learning, and *experiment 2* examined RB and II auditory category learning.

MATERIALS AND METHODS

Experiment 1: Visual RB and II Category Learning

Participants. Two independent groups of healthy young adults aged 18 to 35 yr were recruited from the greater Austin Community. The first group consisted of 185 participants (mean age ± SD: 18.84 ± 3.16; 68 male, 117 female). They took part in *experiment 1a* and completed the RB learning task. The second group consisted of 169 participants (mean age ± SD: 21.02 ± 8.00; 56 male, 113 female). They took part in *experiment 1b* and completed the II learning task. All participants provided written informed consent and received monetary compensation for their participation. All materials and procedures were approved by the Institutional Review Board at the University of Texas at Austin.

Genotyping. The rs6277 polymorphism within the *DRD2* gene was genotyped using Taqman assay C_11339240_10 (Applied Biosystems) using an ABI 7900HT Real-Time PCR system.

Stimuli. Stimuli consisted of color images of houses, plants, or food on a plate. Each stimulus was four dimensional with one of the two possible values for each dimension being presented (16 stimuli total). For houses, the stimuli varied along the following four dimensions: shape of window (circle vs. rectangle), color of wall (pink vs. green), number of clouds (one vs. two), and landscape (tree vs. lawn) (see Fig. 1 for examples). For plants, the stimuli varied along these four dimensions: petal (long and thin vs. short and fat), shape of center (circular vs. square), number of leaves (three vs. six), and color of pot (blue vs. yellow). For food on a plate, the stimuli varied along these dimensions: number of strawberries (one vs. two), color of plate (blue vs. yellow), utensil (fork vs. knife), and carbohydrate (pancake vs. toast). In the experiment, one of these surface features was randomly sampled for each participant.

For the RB task in *experiment 1a*, categories were defined by arbitrarily making two stimulus dimensions relevant (e.g., shape of window and color of wall for houses) and two stimulus dimensions irrelevant (e.g., number of clouds and landscape for houses). For the two relevant dimensions, the binary properties of each dimension were arbitrarily given the values 1 or −1 (e.g., rectangle = 1 and circle = −1; green = 1 and pink = −1). Stimuli in category A were those with values of 1 on both relevant dimensions (houses with rectangle window and green walls), yielding a total of 4 A stimuli. Stimuli in category B were those with a value of −1 on at least one relevant dimension (houses with rectangle window and pink walls, houses with circle window and green walls, and houses with circle window and pink walls), yielding 12 B stimuli. Although the number of unique A and B items differed, we equated the category base rates by sampling equally from the A and B items on each trial. A schematic of one possible RB problem is displayed in Fig. 1*A*.

For the II task in *experiment 1b*, we first made one stimulus dimension irrelevant (e.g., color of wall for houses). Then, for the three remaining relevant stimulus dimensions, the possible properties of each stimulus were given a value of 1 or −1 (e.g., for shape of window in houses, rectangle = 1 and circle = −1). Next, each

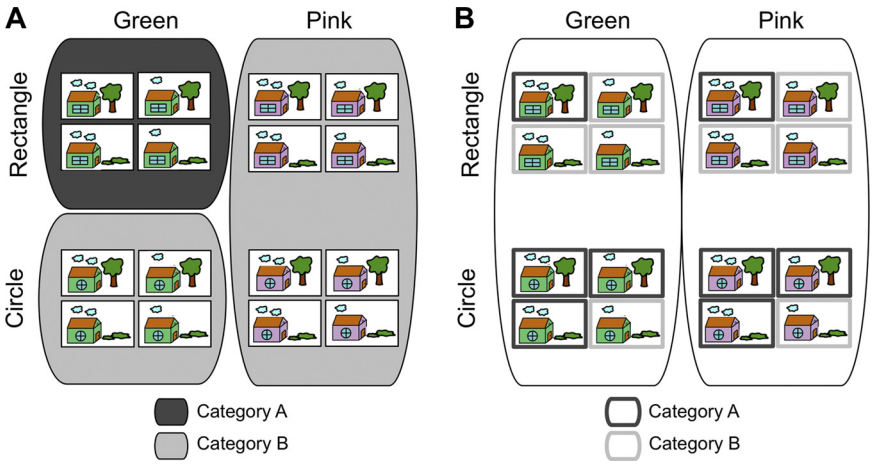

Fig. 1. *A*: a schematic of one possible rule-based (RB) problem in which the shape of window (rectangle vs. circle) and color of wall (green vs. pink) dimensions are relevant. *B*: a schematic of one possible information-integration (II) problem in which the dimension of color of wall (green or pink) is irrelevant.

category structure was created by the following mathematical formula (where the three relevant stimulus dimensions are *X*, *Y*, and *Z*):

If $X + Y + Z > 0$, then "A," else "B."

This yielded eight unique A and eight unique B items. We again equated base rates by sampling equally from the A and B items on each trial. A schematic of one possible II problem is displayed in Fig. 1*B*.

Procedure. Task procedures were identical for *experiments 1a* (RB task) and *1b* (II task). Participants performed the task on a personal computer in a testing room. Participants were informed that they would be viewing pictures that vary across trials in four dimensions. They were informed that each picture was a member of one of two categories (A or B) and that their task was to determine the category membership for each picture by using the computer key and pressing either the "z" button, which corresponded to category A, or the "m" button, which corresponded to category B. Participants were informed that they would receive feedback following each response that would state whether their response was "correct" or "incorrect." Finally, they were informed that their goal was to generate 10 correct responses in a row. Once they achieved 10 correct responses in a row, or after 200 trials, whichever came first, the task would end.

Data analysis. The primary dependent measure was the number of trials needed to reach criteria (i.e., 10 correct responses in a row). If an individual did not reach criterion after 200 trials, we assume a trials-to-criterion of 200. First, we conducted Welch Two-Sample *t*-tests to examine the *DRD2* genotype effects on trials-to-criterion in the RB and II task. We applied these analyses to all the participants. Next, because the allele frequencies in the *DRD2* C957T polymorphism differ across race/ethnicity groups (National Center for Biotechnology Information, http://www.ncbi.nlm.nih.gov/projects/SNP/snp_ref.cgi?rs=6277), to reduce the possibility that our findings might be related to population stratification (Hutchison et al. 2004), we applied similar analyses to the sample only with Caucasian participants. Furthermore, we examined the allele-dose effects on visual RB and II category learning. We calculated the number of T alleles (0, 1, or 2) for each participant and treated this factor as a continuous variable (i.e., an additive genetic effect). We then ran general linear regression to test the effect of the number of T alleles on trials-to-criterion for RB and II tasks separately. For all analyses involving multiple comparisons, we adjusted the α-level of 0.05 with the Bonferroni method.

Experiment 2: Auditory RB and II Category Learning

Participants. One hundred and nine healthy adults aged 18–35 yr (mean age ± SD: 27.73 ± 2.91; 46 male, 63 female) were recruited from the greater Austin Community. All participants were screened using the Mini International Neuropsychiatric Interview (Lecrubier et al. 1997; Sheehan et al. 1997) to ensure that they did not meet criteria for a current or past psychiatric diagnosis such as drug and alcohol addiction. None of the participants was taking psychoactive medication or in psychotherapy at the time of study. None of the participants reported a previous history of brain trauma. All participants reported no previous history of hearing problems. All participants underwent a hearing screening to ensure thresholds ≤25 dB hearing level (HL) at 500, 1,000, 2,000, and 4,000 Hz. Because recent evidence suggests that music experience influences auditory category learning performance (e.g., Elmer et al. 2012), to control for participants' music experience, we also administered a music history questionnaire, which provides a self-report measure of music ability. This questionnaire includes items about *1*) the number of instruments they played; *2*) age of onset, playing hours per week, and self-rated proficiency for each instrument they played; and *3*) whether they played an instrument at the time of study. These self-reported measures have been used widely in previous studies to classify participants' musical ability (e.g., Chandrasekaran et al. 2009). All participants provided written informed consent and received monetary compensation for their participation. All materials and procedures were approved by the Institutional Review Board at the University of Texas at Austin.

Genotyping. Genotyping methods were identical to *experiment 1*.

Stimuli. Stimuli consisted of auditory tones presented via headphones. Each stimulus was four dimensional with one of the two possible values for each dimension being presented (16 stimuli total). The stimuli varied along the following four auditory dimensions: vowel (/a/ vs. /i/), duration (long vs. short; 500 vs. 250 ms), pitch (high vs. low; 180 vs. 80 Hz), and number (one vs. two nonoverlapping tones). In the RB task, categories were defined by arbitrarily making two stimulus dimensions relevant (e.g., vowel and number) and two stimulus dimensions irrelevant (e.g., duration and pitch). For the two relevant dimensions, the binary properties of each dimension were arbitrarily given the values 1 or −1 (e.g., /a/ = 1 and /i/ = −1; one tone = 1 and two nonoverlapping tones = −1). Stimuli in category A were those with values of 1 on both relevant dimensions (one /a/) or values of −1 on both relevant dimensions (two /i/). Stimuli in category B were those with a value of 1 on one relevant dimension and a value of −1 on the other relevant dimension (two /a/ and one /i/). This yielded eight unique A items and eight unique B items. A schematic of one possible RB problem is displayed in Fig. 2*A*.

In the II task, we first made one stimulus dimension irrelevant (e.g., vowel). Then, for the three remaining relevant stimulus dimensions, the possible properties of each stimulus were given a value of 1 or −1 (e.g., for duration, long = 1 and short = −1). Next, each category structure was created by the following mathematical formula (where the three relevant stimulus dimensions are *X*, *Y*, and *Z*):

If $X + Y + Z > 0$, then A, else B.

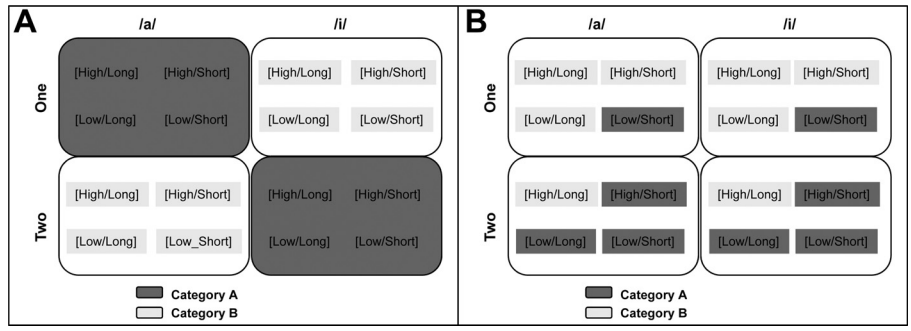

Fig. 2. *A*: a schematic of one possible RB problem in which the vowel (/a/ vs. /i/) and number (one vs. two) dimensions are relevant. *B*: a schematic of one possible II problem in which the dimension of vowel (/a/ vs. /i/) is irrelevant.

This yielded eight unique A items and eight unique B items. A schematic of one possible II problem is displayed in Fig. 2*B*.

Procedure. The procedure was identical to *experiment 1* except that *1*) participants were informed that they would be listening to sounds that vary across trials in vowel duration, pitch, and the number of tones. Their task was to determine the category membership for each sound presented via Sennheiser HD 280 Pro headphones. *2*) Each participant completed both the RB and II learning tasks. The order of these two tasks was counterbalanced across participants.

Data analysis. Identical to *experiment 1*, the primary dependent measure was the number of trials needed to reach criteria (i.e., 10 correct responses in a row). If an individual did not reach criterion after 200 trials, we assume a trials-to-criterion of 200. First, we employed a χ^2-test to examine whether, for each *DRD2* genotype, the number of participants who did not reach criterion differs between RB and II tasks. Second, we conducted a 2 (*DRD2* genotype: C carriers vs. T/T homozygotes) $\times$ 2 (task: RB vs. II) mixed-design ANOVA on the trials-to-criterion measure to examine the impact of *DRD2* C957T polymorphism on RB and II learning. Third, we examined the allele-dose effects on auditory RB and II category learning separately using the identical procedure as in *experiment 1*. We applied these analyses to the samples with all the participants. Moreover, because recent evidence suggests that music experience influences auditory category learning performance (e.g., Elmer et al. 2012), we conducted identical analyses only including participants with no or limited music experience. Specifically, we only examined participants who did not play instruments at the time of study and had none or no more than eight years of music playing at any point in their lives. These criterion have been used to define musicians in previous studies (e.g., Chandrasekaran et al. 2009). Finally, as in *experiment 1*, we also examined the samples with only Caucasian participants with the second and third analyses. For all analyses involving multiple comparisons, we adjusted the α-level of 0.05 with the Bonferroni method.

RESULTS

Experiment 1: Visual RB and II Category Learning

Participants. Six participants in *experiment 1a* and 14 participants in *experiment 1b* were excluded from analysis because of incomplete data on DNA. The final samples consisted of 179 participants (C/C, $n = 92$; C/T, $n = 73$; T/T, $n = 14$) in *experiment 1a* and 155 participants (C/C, $n = 56$; C/T, $n = 72$; T/T, $n = 27$) in *experiment 1b*. The distributions of the rs6277 genotypes did not differ from the Hardy-Weinberg equilibrium in either sample (*experiment 1a*: $\chi^2 = 0.008$, $P = 0.927$; *experiment 1b*: $\chi^2 = 0.215$, $P = 0.643$). The demographics are displayed in Table 1.

DRD2 polymorphism and visual category learning tasks. In both tasks, all participants reached trials-to-criterion before 200 trials. Figure 3 displays the average trials-to-criterion for C carriers (C/C, C/T) and T/T homozygotes in the RB and II visual category learning tasks. For the RB task in *experiment 1a*, T/T homozygotes did not significantly differ from C carriers in reaching trials-to-criterion [$t(14.95) = -0.06$, $P = 0.953$] (Fig. 3*A*). However, for the II task in *experiment 1b*, T/T homozygotes took significantly less trials to reach criterion than C carriers [$t(42.868) = -2.444$, $P = 0.019$] (Fig. 3*B*). Furthermore, we observed a similar pattern of results when the analysis was restricted to Caucasian participants (RB task: $n = 94$; II task: $n = 78$), although the effects were not significant (Table 2). Finally, there was no allele-dose effect on learning performance in the RB [$F(1,179) = 0.80$, $P = 0.372$] or II [$F(1,156) = 2.92$, $P = 0.090$] tasks. There was also no allele-dose effect when we focused on Caucasian participants [RB: $F(1,94) = 0.35$, $P = 0.553$; II: $F(1,77) = 2.01$, $P = 0.160$].

Summary. Results from *experiment 1* demonstrate that T/T homozygotes were faster to learn reflexive-optimal II visual categories relative to C carriers (i.e., C/C and C/T). We did not observe differences in learning reflective-optimal RB visual categories between T/T homozygotes and C carriers. These results partially support our hypothesis that T/T homozygotes will demonstrate better learning of II category structures but may exhibit worse learning of RB category structures. Note that the two learning tasks were administered to separate individuals in *experiment 1*. To truly test dissociable effects of *DRD2* genetic variation on reflective and reflexive learning, we need to adopt a within-subject design. Moreover, because the participants in *experiment 1* were not screened for neuropsychiatric disorders, we wanted to determine whether the findings

Table 1. *Demographics of the samples for analyses in experiments 1a and 1b*

	Experiment 1a: RB Task		Experiment 1b: II Task	
	C/T, C/C	T/T	C/T, C/C	T/T
n	165	14	128	27
Age	18.84 (1.01)	18.93 (0.83)	20.51 (4.01)	21.30 (4.73)
Education, yr	12.73 (1.01)	12.71 (0.91)	13.44 (1.72)	14.07 (2.92)
Gender, M/F	62/103	6/8	42/86	9/18
Ethnicity				
Hispanic	49	0	20	2
Nonhispanic	116	13	103	22
Decline to state	0	1	5	3
Race				
Caucasian	80	14	59	19
Asian	37	0	40	2
Other	41	0	23	3
Decline to state	7	0	6	3

SD are listed in parentheses. RB, rule based; II, information integration; M, males; F, females.

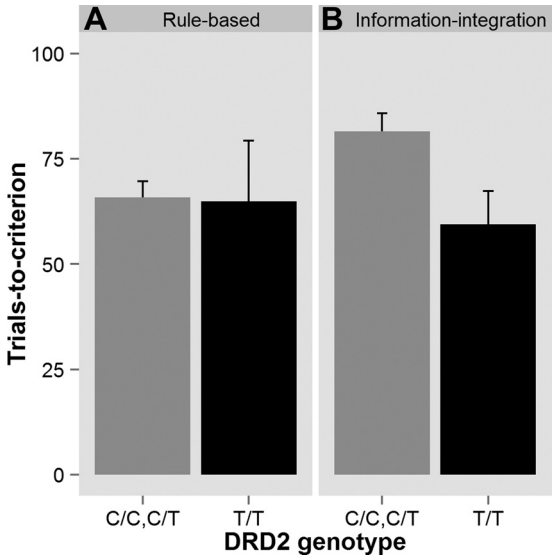

Fig. 3. Trials-to-criterion for dopamine receptor D_2 (*DRD2*) C carriers(C/C, C/T) and T/T homozygotes in *experiment 1a* RB and *experiment 1b* II visual category learning tasks. SE bars included.

still hold in a sample that was more systematically screened for these disorders. Furthermore, candidate gene studies have been criticized for poor replicability (Ioannidis et al. 2001). To increase confidence in the validity of these results, it is necessary to replicate the results in a separate study. Finally, the category sizes were unequal in the RB condition (4 category A stimuli and 12 category B stimuli), leading to the possibility that a memorization strategy was used in the category A items. Hence, in *experiment 2*, we aimed to replicate and extend the findings from *experiment 1* to test auditory RB and II category learning in a screened sample using within-subject design and equal category sizes in the RB and II conditions.

Experiment 2: Auditory RB and II Category Learning

Participants. Two participants were excluded from analysis because of incomplete data on DNA. The final sample consisted of 107 participants (C/C, $n = 38$; C/T, $n = 45$; T/T, $n = 24$). The frequency of the rs6277 alleles in this sample did not differ from the Hardy-Weinberg equilibrium ($\chi^2 = 2.23$, $P = 0.13$). The demographics are displayed in Table 3.

DRD2 polymorphism and auditory category learning tasks. The number of participants who did not reach trials-to-criterion before 200 trials were 67 (C/C, $n = 20$; C/T, $n = 29$; T/T, $n = 18$) in the RB task and 30 (C/C, $n = 11$; C/T, $n = 13$; T/T, $n = 6$) in the II task. χ^2-test showed that the effect of *DRD2* polymorphism on the number of participants who did not reach trials-to-criterion was not related to types of category learning tasks [$\chi^2(2) = 0.70$, $P = 0.706$].

Table 2. *Average trials-to-criterion for the Caucasian subset of dopamine receptor D_2 (DRD2) C carriers (C/C, C/T) and T/T homozygotes in the RB and II visual category learning tasks in experiment 1*

	C/T, C/C	T/T	*t* Value	*P*
RB	64.11 (48.46)	64.93 (53.77)	0.05	0.958
II	83.95 (46.98)	70.79 (43.69)	−1.121	0.271

SD are listed in parentheses.

Figure 4 displays the average trials-to-criterion for C carriers (C/C, C/T) and T/T homozygotes in the RB and II auditory category learning tasks. The main effect of *DRD2* genotype was not significant [$F(1,105) = 0.060$, $P = 0.807$], whereas the main effect of task was significant [$F(1,105) = 32.168$, $P < 0.001$]. Importantly, there was a significant crossover interaction between *DRD2* genotype and task [$F(1,105) = 4.191$, $P = 0.043$]. To examine the nature of this crossover interaction, we calculated simple main effects. On average, as shown in Fig. 4, T/T homozygotes took 175.54 trials to reach criterion in the RB task and 102.54 trials to reach criterion in the II task. The C carriers took 158.61 trials to reach criterion in the RB task and 124.34 trials to reach criterion in the II task. However, the statistical comparisons between T/T homozygotes and C carriers yielded no difference in trials to reach criterion for neither the RB task [$t(105) = -1.311$, $P = 0.193$] nor the II learning task [$t(105) = 1.505$, $P = 0.135$]. The pattern of results held when the analyses were restricted to Caucasian participants ($n = 77$), although the *DRD2* genotype-by-task interaction effect was not significant (Table 4).

We also examined the gene-dose effects on auditory RB and II category learning. In both the RB and II tasks, there were no allele-dose effects when including all participants [RB: $F(1,105) = 1.96$, $P = 0.165$; II: $F(1,105) = 1.07$, $P = 0.303$] or considering Caucasian participants only [RB: $F(1,75) = 3.42$, $P = 0.069$; II: $F(1,75) = 0.46$, $P = 0.499$].

We conducted additional analysis only including participants with no or limited music experience. The sample for analysis consisted of 68 participants (C/C, $n = 24$; C/T, $n = 30$; T/T, $n = 14$). The frequency of the rs6277 genotypes in this sample did not differ from the Hardy-Weinberg equilibrium ($\chi^2 = 0.655$, $P = 0.418$). The number of participants who did not reach trials-to-criterion before 200 trials were 49 (C/C, $n = 15$; C/T, $n = 22$; T/T, $n = 12$) in the RB task and 19 (C/C, $n = 8$; C/T, $n = 10$; T/T, $n = 1$) in the II task. A χ^2-test showed that the effect of *DRD2* polymorphism on the number of participants who did not reach trials-to-criterion was again not associated with the types of category learning tasks [$\chi^2(2) = 3.36$, $P = 0.187$].

Figure 5 displays the average trials-to-criterion for C carriers (C/C, C/T) and T/T homozygotes in the RB and II auditory category learning tasks for this sample. Results showed that the main effect of *DRD2* genotype was not significant [$F(1,66) = 0.633$, $P = 0.429$], whereas the main effect of task was significant [$F(1,66) = 35.73$, $P < 0.001$]. Importantly, there

Table 3. *Demographics of the sample for analysis in experiment 2*

	C/C, C/T	T/T
n	83	24
Age	27.60 (2.70)	28.33 (3.32)
Education, yr	16.29 (1.99)	16.58 (2.72)
Gender, M/F	34/49	11/13
Ethnicity		
Hispanic	22	0
Nonhispanic	60	24
Decline to state	1	0
Race		
Caucasian	55	22
Asian	8	2
Other	14	0
Decline to state	6	0

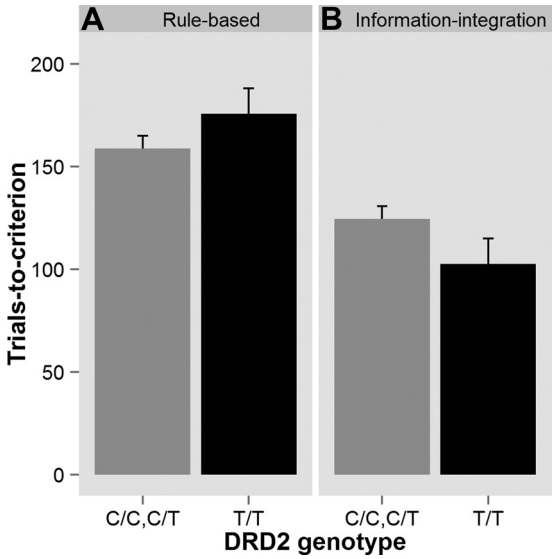

Fig. 4. Trials-to-criterion for *DRD2* C carriers (C/C, C/T) and T/T homozygotes in the RB and II auditory category learning tasks in *experiment 2*. SE bars included.

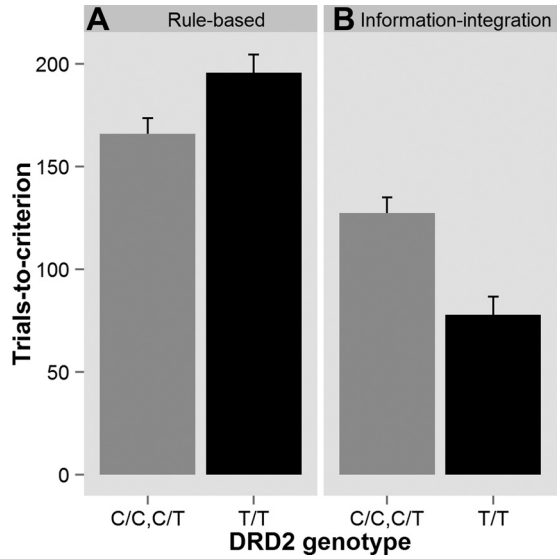

Fig. 5. Trials-to-criterion for *DRD2* C carriers (C/C, C/T) and T/T homozygotes in the RB and II auditory category learning tasks for participants with no or limited music experience (who did not play instruments at the time of study and had no more than 8 yr of music playing at any point in their lives) in *experiment 2*. SE bars included.

was a significant interaction between *DRD2* genotype and task [$F(1,66) = 12.19$, $P < 0.001$]. To examine the nature of this interaction, we calculated simple main effects. In the RB learning task, T/T homozygotes took significantly more trials to reach criterion than C carriers [$t(65.88) = 3.506$, $P < 0.001$] (Fig. 5*A*). The reverse pattern held in the II learning task, with T/T homozygotes taking significantly less trials to reach criterion than C carriers [$t(25.851) = -3.199$, $P = 0.004$] (Fig. 5*B*). These effects held when the analyses were restricted to Caucasian participants ($n = 47$) (Table 5).

Furthermore, we tested the allele-dose effect on RB and II learning. In the RB task, there was a allele-dose effect that was characterized by increasing the number of T alleles being associated with reduced RB performance [marginally significant for all participants with no or limited music experience: $F(1,66) = 4.86$, $P = 0.031$, Fig. 6; significant for Caucasian participants with no or limited music experience: $F(1,45) = 8.08$, $P = 0.007$]. However, in the II task, the pattern reversed such that increasing the number of T alleles was associated with enhanced II performance [marginally significant for all participants with no or limited music experience: $F(1,66) = 4.20$, $P = 0.044$, Fig. 6; although not significant for Caucasian participants with no or limited music experience: $F(1,45) = 2.00$, $P = 0.164$].

Table 4. *Average trials-to-criterion for the Caucasian subset of DRD2 C carriers and T/T homozygotes in the RB and II auditory category learning tasks in experiment 2*

	C/C, C/T	T/T
RB	157.95 (59.01)	173.32 (53.12)
II	120.36 (63.72)	105.36 (65.00)

SD are listed in parentheses. We conducted a 2 (*DRD2* genotype: C carriers vs. T/T homozygotes) × 2 (task: RB vs. II) mixed-design ANOVA on the trials-to-criterion measure. The main effect of *DRD2* genotype was not significant [$F(1,75) = 0.0003$, $P = 0.986$], whereas the main effect of task was significant [$F(1,75) = 23.791$, $P < 0.001$]. The interaction between *DRD2* genotype and task was not significant [$F(1,75) = 1.970$, $P = 0.165$].

DISCUSSION

Summary of Findings

The goal of the current study was to examine the impact of *DRD2* genetic variation on reflective and reflexive learning. A second goal was to assess the extent to which the impact of *DRD2* variation on the dual-learning systems is domain general. We employed category learning paradigms (i.e., RB and II category learning) that target reflective and reflexive learning. Specifically, optimal learning of RB category structures is thought to be under conscious control and is predominantly governed by the frontally mediated reflective system, whereas optimal learning of II category structures is assumed to operate outside of conscious awareness and is predominantly controlled by the striatally mediated reflexive system (Ashby et al. 1998; Maddox and Ashby 2004). We focused on the C957T SNP (rs6277) in the *DRD2* gene that has been demonstrated to

Table 5. *Average trials-to-criterion for DRD2 C carriers and T/T homozygotes in the RB and II auditory category learning tasks in experiment 2 in the Caucasian subset with no or limited music experience (who did not play instruments at the time of study and had none or less than 8 yr of music playing)*

	C/C, C/T	T/T
RB	167.54 (58.64)	199.34 (59.19)
II	118.23 (62.12)	78.83 (62.57)

SD are listed in parentheses. We conducted a 2 (*DRD2* genotype: C carriers vs. T/T homozygotes) × 2 (task: RB vs. II) mixed-design ANOVA on the trials-to-criterion measure. The main effect of *DRD2* genotype was not significant [$F(1,66) = 0.633$, $P = 0.429$], whereas the main effect of task was significant [$F(1,45) = 37.382$, $P < 0.001$]. Importantly, there was a significant interaction between *DRD2* genotype and task [$F(1,45) = 7.182$, $P = 0.01$]. Simple effects analysis showed that T/T homozygotes took significantly more trials to reach criterion than C carriers [$t(43.346) = 2.606$, $P = 0.013$] in the RB task, whereas they took marginally significantly less trials to reach criterion than C carriers [$t(23.771) = -2.12$, $P = 0.045$] in the II task.

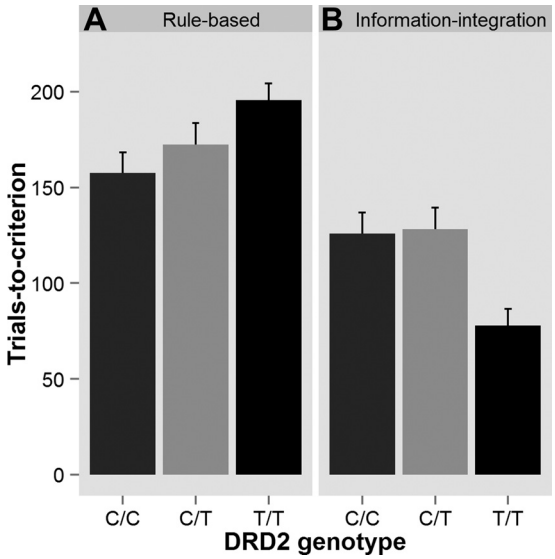

Fig. 6. Trials-to-criterion for *DRD2* C/C, C/T, and T/T genotypes in the RB and II auditory category learning tasks for participants with no or limited music experience (who did not play instruments at the time of study and had no more than 8 yr of music playing at any point in their lives) in *experiment 2*. SE bars included.

modulate striatal learning from negative outcomes (Frank et al. 2009; Frank and Hutchison 2009; Frank et al. 2007). We predicted an advantage in II category learning but a potential deficit in RB category learning in *DRD*2 T/T homozygotes relative to C carriers.

As predicted, individuals with the T/T genotype were faster to learn both visual (*experiment 1*) and auditory (*experiment 2*) II categories. In contrast, individuals with the T/T genotype did not show an advantage when learning RB categories, irrespective of sensory modality. Interestingly, T/T homozygotes even exhibited a deficit in learning auditory RB categories. This may be related to the fact that the auditory RB task was more challenging than the visual RB task. This argument is evidenced by the fact that participants took more trials to reach criterion, and a smaller proportion of participants reached criterion before 200 trials in the auditory RB task compared with the visual RB task. In summary, these findings suggest dissociable *DRD2* genetic effects on reflective and reflexive learning, and the findings that these dissociable genetic effects occurred across visual and auditory modalities provide evidence that dual-learning systems are domain general.

Dissociable DRD2 Genetic Effects on Reflective vs. Reflexive Learning

To our knowledge, the present study represents one of the first attempts to examine dopaminergic genetic effects on learning within the dual-learning system's theoretical framework. Our findings demonstrate that the C957T SNP in the *DRD2* gene is associated with learning. However, the exact influence of this polymorphism critically depends on the extent to which learning is predominantly frontally or striatally mediated. The C957T polymorphism within the *DRD2* gene affects the availability of D_2 receptors in the striatum (Hirvonen et al. 2005). Specifically, T/T homozygotes show an increased number of striatal D_2 receptors relative to C carriers (Hirvonen et al. 2005). Functionally, D_2 receptors in the striatum are hypothesized to be critical for learning during DA dips that are associated with negative outcomes (Cohen and Frank 2009; Frank 2005). Hence, this *DRD2* polymorphism is assumed to predict learning from negative outcomes but not from positive outcomes. Indeed, a series of studies show that the T/T genotype is associated with enhanced learning from negative feedback but has no effect on learning from positive feedback (Frank et al. 2009; Frank and Hutchison 2009; Frank et al. 2007). Overall, *DRD2* T/T homozygotes, associated with enhanced striatal function, may be superior in learning tasks that are predominantly mediated by the striatum. This argument is supported by the present findings that T/T homozygotes were better at learning II category structures, which are optimally learned by a reflexive system that is not consciously penetrable and is highly dependent on the striatum (Filoteo et al. 2005b; Nomura et al. 2007; Seger and Cincotta 2005).

In contrast, our results show that T/T homozygotes are no better than or are worse at learning RB category structures that are optimally learned by a reflective system that is available to conscious awareness and critically depends on prefrontal cortex (Filoteo et al. 2005a; Schnyer et al. 2009). It has been suggested that prefrontal and striatal systems compete to control reinforcement learning. The relative certainty of each system's prediction determines which one of the two systems is deployed (Ashby et al. 2011; Ashby et al. 1998; Daw et al. 2005). Those with enhanced striatal function, as in the case of T/T homozygotes, should have greater certainty in their striatal predictions. Hence, T/T homozygotes may rely relatively more on the striatum, and less on the prefrontal cortex, to learn RB category structures. As a result, T/T homozygotes may be at a disadvantage or at least show no particular advantage in RB category learning.

We speculate that anterior cingulate cortex (ACC) may be the region that is responsible for determining which system (prefrontal or striatal) to deploy during reinforcement learning (Melloni et al. 2012; Shenhav et al. 2013). Hence, it is interesting to know the extent to which genetic variation modulating ACC activity might affect reflective and reflexive learning, in addition to those influences on striatal and prefrontal function. Future studies should examine a set of genes that modulate prefrontal, ACC, and striatal activities respectively, and test their independent and cumulative effects on reflective and reflexive learning and effective deployment between the two systems.

DRD2 Genetic Effects are Domain General

Our study replicates and extends existing findings that the *DRD2* C957T polymorphism influences visual and auditory learning similarly (although there are differences in reflective learning, we will discuss later in this section). This suggests that this *DRD2* polymorphism may affect learning in a domain-general manner. We speculate that this is closely tied to that brain regions regulating reflective (e.g., prefrontal cortex) and reflexive (e.g., striatum) learning are similar across visual and auditory modalities (Chandrasekaran et al. 2014a). It should be noted that the *DRD*2 genetic effects across modalities are less consistent in the reflective RB learning task. A reason for this could be relative task difficulty differences between visual and auditory RB learning tasks (compare Figs. 3 and 4). In RB learning, memory abilities are critically important (Zeithamova

and Maddox 2006; 2007). Existing work shows that human short-term and recognition memory for audition is worse than for vision (Bigelow and Poremba 2014; Cohen et al. 2009). Hence, we speculate that, compared with the auditory RB learning task, the visual RB task may be learned more quickly. Future studies should match stimulus parameters and cognitive/memory load more carefully to allow for a direct comparison between visual and auditory reflective RB learning.

Other Plausible Explanations on the Specificity of DRD2 Genetic Effects

The present study builds upon the COVIS model (Ashby et al. 2011; Ashby et al. 1998) that hypothesizes that optimal RB learning is mediated by an explicit, reflective, hypothesis-testing system, and optimal II category learning is mediated by a reflexive, procedural-based learning system. In addition to an extensive body of support from animal, neuropsychological, and neuroimaging studies, support for the dual-learning systems framework also comes from behavioral dissociation studies. Recently some of the dissociation work has been questioned, with a common criticism being that II tasks are often higher dimensional than RB tasks (Edmunds et al. 2015; Wills et al. 2013). The crux of the argument is that higher-dimensional tasks are more "difficult" (i.e., lead to worse accuracy) and thus will be more affected by experimental manipulations of the task. This argument does not hold when applied to *experiment 1* or *experiment 2*, since the more difficult task is the RB task, even though the RB task is lower dimensional (2 dimensional) than the II task (3 dimensional) (Figs. 3, 4, 5, and 6). Thus, although dimensionality likely has some effect on category learning, the effects are complicated and are not even monotonic. Even so, future work should explore RB and II category learning with matched dimensionalities.

We also acknowledge that the neurobiological bases of the behavioral results may be more complicated than what we postulate. For example, it should be noted that the reflective and reflexive systems are highly interactive. It is possible that alterations in *DRD2* function in regions underlying the reflective system such as cingulate cortex, instead of local D_2 receptor dynamics in the striatum, lead to enhanced striatal dopaminergic function, which produces improved II category learning. Furthermore, some studies suggest that C alleles of *DRD2* C957T polymorphism, which is associated with higher dopamine D_2 receptor availability in the extrastriatal areas (Hirvonen et al. 2009), may be impaired in reflective tasks such as the Wisconsin Card Sort Task (Lumme et al. 2007) but may show advantage in some procedural tasks (Huertas et al. 2012). These results were contradictory to our findings that *DRD2* C allele was associated with enhanced RB learning but reduced II learning, particularly in the auditory paradigm. More work is needed to elucidate the complex influence of the *DRD2* C957T polymorphism on reflective and reflexive learning. The strength of our work derives from a neurobiological-based theoretical framework that has been demonstrated with numerous dissociation studies. Given our dissociable behavioral results, a next step would be to examine the neurobiological bases of these differences using functional neuroimaging.

Limitations

The association between *DRD2* polymorphism and reflective-reflexive learning should be interpreted with several limitations in mind. First, this association may be driven by another genetic variant in linkage disequilibrium with *DRD2* rs6277 or another unmeasured third variable (e.g., within-ethnicity population stratification). Second, although we tried to screen the participants, particularly in *experiment 2* with the Mini International Neuropsychiatric Interview, we may have failed to screen out various other conditions linked to the reward-processing system, such as obesity, gambling, and sex addiction. These conditions have been associated with *DRD2* polymorphisms and other dopaminergic gene polymorphisms such as *DAT1*, *COMT*, *MAOA*, and the Taq A1 allele of the *DRD2* gene (Blum et al. 2011a; Blum et al. 2011b). These other polymorphisms may modulate the impact of *DRD2* C957T polymorphisms on category learning found in the present study. Future studies should impose a more thorough screening to provide a rigorous test of polymorphisms in dopaminergic genes on dual-system learning. Third, in the present study we used well-studied category learning paradigms to target reflective and reflexive learning. Future research should determine the extent to which the observed genetic effects generalize to other types of learning. Fourth, this association may be mediated by neural mechanisms other than those posited here. Future imaging studies are required to confirm that the *DRD2* rs6277 polymorphism modulates brain activities that underlie reflective and reflexive learning. Finally, for a genetic association study, the samples in the present study are relatively small. Thus, a larger sample would be needed to further increase our confidence in the findings reported in this study.

Conclusions

In summary, the current study shows that the C957T polymorphism within the *DRD2* gene, associated with D_2 receptor function in the striatum, influences domain-general frontally mediated reflective learning and striatally mediated reflexive learning in an opposite direction. These findings validate the dual-learning system's (reflective vs. reflexive) theoretical framework. Future studies should implement the dual-learning system's framework to fully account for genetic effects on learning.

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DISCLAIMER

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

Author contributions: Z.X., W.T.M., J.E.M., and B.C. conception and design of research; Z.X., W.T.M., J.E.M., and B.C. performed experiments; Z.X., W.T.M., J.E.M., and B.C. analyzed data; Z.X., W.T.M., J.E.M., and B.C. interpreted results of experiments; Z.X. prepared figures; Z.X., W.T.M., J.E.M., and B.C. drafted manuscript; Z.X., W.T.M., J.E.M., and B.C. edited and revised manuscript; Z.X., W.T.M., J.E.M., and B.C. approved final version of manuscript.

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