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Dopaminergic Genetic Polymorphisms Predict Rule-Based Category Learning

Kaileigh A. Byrne[1], **Tyler Davis**[2], and **Darrell A. Worthy**[1]

[1]Texas A&M University

[2]Texas Tech University

Abstract

Dopaminergic genes play an important role in cognitive function. *DRD2* and *DARPP-32* dopamine receptor gene polymorphisms affect striatal dopamine binding potential, while the Val158Met single nucleotide polymorphism of the *COMT* gene moderates dopamine availability in the prefrontal cortex. Our study assesses the role of these gene polymorphisms on performance in two rule-based category learning tasks. Participants completed unidimensional and conjunctive rule-based tasks. In the unidimensional task, a rule along a single stimulus dimension can be used to distinguish category members. In contrast, a conjunctive rule utilizes a combination of two dimensions to distinguish category members. *DRD2* C957T TT homozygotes outperformed C allele carriers on both tasks, and *DARPP-32* AA homozygotes outperformed G allele carriers on both tasks. However, we found an interaction between *COMT* and task-type where Met allele carriers outperformed Val homozygotes in the conjunctive rule task, but both groups performed equally well in the unidimensional task. Thus, striatal dopamine binding may play a critical role in both types of rule-based tasks, while prefrontal dopamine binding is important for learning more complex conjunctive rule tasks. Modeling results suggest that striatal dopaminergic genes influence selective attention processes while cortical genes mediate the ability to update complex rule-representations.

Keywords

category learning; genetics; dopamine

Friend or foe? Rain or sun? Categorization plays a central role in allowing us to use information from our past experiences to predict future events. Previous research has shown that category learning performance is affected by disorders of the dopaminergic system (e.g., Ashby et al., 1998; Ashby et al., 2003; Heindel et al., 1989; Knopman & Nissen, 1991) and covaries with individual differences in cognitive capacities, like working memory (WM; Lewandowsky, 2011), that are known to be impacted by dopamine (e.g., Colzato et al., 2011; Dumontheil et al., 2011; Goldman-Rakic, 1998; Meyer-Lindenberg et al., 2007). However, currently, little is known about how category learning is impacted by common dopaminergic gene polymorphisms in normal adults.

Please address all correspondence to: Darrell A. Worthy, PhD., worthyda@tamu.edu, Department of Psychology, Texas A&M University, 4235 TAMU, College Station, TX 77843-4235.

Although the role of dopaminergic gene polymorphisms in category learning has not been elucidated, extensive research shows that the neurotransmitter dopamine plays an important role in other types of cognitive tasks, especially reinforcement learning (e.g., Frank, Seeberger, & O'Reilly, 2004; Frank et al., 2007; Glimcher, 2011; Montague, Dayan, & Sejnowski, 1996) and working memory tasks (e.g., Bäckman & Nyberg, 2013; Jacobsen et al., 2006; Malhorta et al., 2002; Goldman-Rakic, 1998). Both D1 and D2 dopaminergic receptors have been shown to affect reinforcement learning (Frank et al., 2007; Goldman-Rakic et al., 2001; Rinaldi et al., 2007) and modulate individual differences in working memory ability (e.g., Colzato et al., 2011; Malhorta et al., 2006; Meyer-Lindenberg et al., 2007). Based on the role of dopaminergic genes in reinforcement learning and working memory, we expect dopaminergic polymorphisms to impact rule-based category learning. This type of learning requires learning a rule in response to trial-by-trial feedback and is thought to be mediated by an explicit, verbalizeable system that requires executive function and working memory (e.g., Filoteo et al., 2005; Maddox et al., 2013; Nomura & Reber, 2008).

In the present study, we examine two types of rule-based category learning tasks, unidimensional and conjunctive, which involve learning categorization rules with variable demands that may differentially recruit cognitive processes impacted by dopaminergic polymorphisms. Unidimensional tasks require individuals to attend to a single stimulus dimension to learn the correct rule and use it to categorize each stimulus. In contrast, in a conjunctive rule task, two dimensions are required to correctly categorize a stimulus, and the individual must learn the criterion that differentiates each dimension as part of the category and update that criterion on every trial (Maddox, Bohil, & Ing, 2004). Thus, unidimensional tasks entail categorization based on a criterion of a single dimension, and conjunctive tasks involve maintaining information about two criteria in working memory (Filoteo, Maddox, Ing, & Song, 2007). As a result, conjunctive tasks place greater demands on criterion learning than unidimensional tasks by requiring participants to learn criteria along two dimensions rather than one.

In both types of rule-based category learning tasks, selective attention and perceptual discriminability are required to focus on the task-relevant features of each stimulus (Ashby et al., 1998; Smith, Patalano, & Jonides, 1998; Smith & Sloman, 1994). In unidimensional tasks, individuals must selectively attend to a single relevant dimension, whereas in conjunctive tasks, rule application occurs in serial; individuals must differentially weight the dimension that is most relevant to distinguishing the categorization criteria on a given trial (Smith et al., 1998). To do this, individuals need to consider the dimensions independently by attending to the distance between a stimulus and the boundary between categories on each dimension. For example, in a task in which the categorization rule depends on both the length and orientation of a stimulus, one might first attend to the length dimension and consider how far an item is from the decision boundary. Because the category rule is defined by both dimensions, one will then also need to attend to the second dimension (orientation) in order to make a decision.

Both unidimensional and conjunctive rule tasks also rely on working memory in order to maintain rules and incorporate feedback (Ashby & O'Brien, 2005; Filoteo et al., 2007;

Waldron & Ashby, 2001). However, unidimensional tasks emphasize dimensional selective attention by encouraging learners to determine the dimension that designates the rule and focus on that dimension while ignoring the other on every trial. Conjunctive rule tasks, on the other hand, often require more extensive hypothesis testing (Nosofsky, Palmeri, & McKinley, 1994) and updating of a rule with greater Boolean complexity[1] (e.g., Feldman, 2000) in working memory (Ashby et al., 1998; Filoteo et al., 2007; Zeithamova & Maddox, 2006). Thus, in addition to correct rule specification, conjunctive tasks also entail integrating feedback to adjust the two perceptual boundaries in working memory and updating the rule criterion based on this feedback. The difference in cognitive demands between unidimensional and conjunctive tasks suggests that performance in these two tasks may interact with dopaminergic gene polymorphisms differently.

Category learning has been shown to depend on visual, motor, and executive corticostriatal loops (Seger, 2008; Seger & Miller, 2010); therefore we examine both striatal and cortical dopaminergic genes. We expect that three important modulators of dopamine availability, the *DRD2, DARPP-32*, and catechol O-methyltransferase (*COMT*) genes, may differentially impact performance in unidimensional and conjunctive rule learning tasks. The C957T polymorphism of the *DRD2* gene has previously been associated with D2 receptor binding potential in the striatum in which TT homozygotes have increased binding potential relative to C allele carriers (Duan et al., 2003; Hirvonen et al., 2004). The *DRD2* 957T polymorphism has been associated with superior working memory capacity and cognitive control (Colzato et al, 2011; Jacobsen, 2006; Rodriguez-Jimenez et al., 2007). The *DARPP-32* gene is also expressed in the striatum, but modulates D1 receptor functioning (Hämmerer et al., 2013; Nishi, Snyder, & Greengard, 1997). Prior research has shown that *DARPP-32* AA homozygotes have higher D1 dopamine receptor efficacy and increased WM capacity and cognitive flexibility (Frank et al., 2007; Houlihan et al., 2009; Meyer-Lindenberg et al., 2007). In contrast to the striatal dopaminergic genes, the *COMT* gene is important in the metabolic degradation of dopamine in the prefrontal cortex (PFC), and the Val158Met polymorphism plays a role in dopamine availability in this neural region (Frank et al, 2007; Frank et al., 2009; Malholtra et al., 2002; Matsumoto et al., 2003; Meyer-Lindenberg et al., 2005). *COMT* Met allele carriers have lower *COMT* enzyme activity and thus, higher dopamine levels in the PFC (Meyer-Lindenberg et al., 2005; Tunbridge et al, 2004). This increased dopamine can be beneficial in working memory dependent tasks by enhancing the updating and maintenance of encoded WM representations (Durstewitz & Seamans, 2008). In contrast, Val homozygotes have greater *COMT* activity which leads to faster degradation of dopamine in the PFC. As a result, Val homozygotes may have less efficient processing for WM and executive functioning, and require greater activation for a given level of performance (Egan et al, 2001; Goldberg et al., 2003; Tunbridge, Harrison, & Weinberger, 2006).

Critical to the present investigation, the effect of *DRD2, DARPP-32,* and *COMT* polymorphisms has been examined in the context of reinforcement learning. Although polymorphisms in other dopaminergic genes, such as *DRD1* and *DAT1,* which encode for

[1]Boolean complexity is the length of the shortest logically equivalent propositional formula (Feldman, 2000). In the current context this simply means the length of the most parsimonious statement describing the rule that governs categorization.

D1 receptors and the dopamine transporter, respectively, are associated with altered striatal dopamine availability, there is little evidence to demonstrate their involvement in reinforcement learning. We therefore selected dopaminergic genes based on previous work showing their association with specific aspects of reinforcement learning (Collins & Frank, 2012; Doll et al., 2011; Frank et al., 2007). Specifically, *COMT* has been shown to significantly influence the WM component of reinforcement learning in which the Met allele is associated with greater WM capacity than the Val allele (Collins & Frank, 2012). However, in this previous study, no effect of *DARPP-32* or *DRD2* on reinforcement learning or WM was observed. The authors concluded that genes involved in PFC, namely *COMT*, and basal ganglia have distinct influences on the WM and reinforcement learning aspects of learning behavior (Collins & Frank, 2012). One key distinction between the procedure utilized in this previous study and the category learning tasks in the present study is that our procedure relies on unfamiliar stimuli that involve feature discriminability in order to achieve maximum accuracy, while the task in the Collins and Frank study entailed categorizing images into familiar categories, such as fruits or sports (2012). Categorizing novel stimuli may rely on functionally different learning skills compared to categorizing familiar stimuli. Additionally, in contrast to their results, previous work has shown that *DRD2* and *DARPP-32* are involved in reinforcement learning (Doll et al., 2011; Frank et al., 2007). Similar to the stimuli used in the present study, the probabilistic selection tasks used in the studies that found an effect of *DRD2* and *DARPP-32* entailed learning novel, unfamiliar categories and identifying subtle differences in stimulus features that specify category membership. Based on these findings, it seems that the familiar categorization studies (Collins & Frank, 2012) require updating value relationships without needing to differentiate new categories. Categorizing novel stimuli, however, entails both category rule updating and specifying new categories, which may rely on different dopaminergic processes. Given these distinctions between familiar and novel categorization, it is reasonable to predict that *DRD2* and *DARPP-32* may influence different aspects of reinforcement learning than *COMT*. One theory that draws together these different observations and effects of dopaminergic genes on learning and WM is the Prefrontal, Basal Ganglia, Working Memory Model (PBWM model) (Frank, Loughry, & O'Reilly, 2001; Hazy, Frank, & O'Reilly, 2007; O'Reilly & Frank, 2006; O'Reilly, 2006). This model proposes that WM maintenance and updating is regulated by a dopaminergic gating mechanism in which only task representations that are reinforced with positive reinforcement gain access to WM through dopaminergic signaling to the PFC. When shown negative feedback, however, task representations are destabilized in WM so the representation can be updated. Thus, the PBWM model suggests that the PFC maintains information in WM, while the basal ganglia selectively triggers the updating of these memory representations by learning which category features are task relevant (Braver & Cohen, 2000; Frank, Loughry, & O'Reilly, 2001; Hazy, Frank, O'Reilly, 2007; O'Reilly & Frank, 2006; O'Reilly, 2006; Price, Filoteo, & Maddox, 2009). Therefore, if the PBWM is applied to category learning, it is reasonable to predict that striatal genes might affect learning that depends on selective attention to the stimulus dimensions that define the category rule (rule specification), while genes involved in PFC functions may influence WM-dependent rule updating.

While the unidimensional task in the current investigation may depend on correctly specifying the dimension that defines the rule and attending to that stimulus feature, performance on the conjunctive rule task may rely not only upon rule specification but also place greater demands upon WM-dependent rule updating in order to specify and update the optimal decision criteria for the conjunctive rule. Consequently, it is reasonable to predict that striatal dopaminergic genes may be involved in rule specification, while the PFC gene *COMT* may be critical for optimally updating complex rules. Therefore, relating the previous behavioral differences between dopaminergic gene polymorphisms and the PBWM model to the different reinforcement learning demands of unidimensional and conjunctive rule learning tasks, we expect both task types to be impacted by striatal dopaminergic gene polymorphisms (*DRD2* and *DARPP-32*), and the PFC dopaminergic gene *COMT* to have a stronger impact on conjunctive rule tasks. Specifically, we predict that *DRD2* TT and *DARPP-32* AA homozygotes will perform better than individuals possessing other genotypes for those genes in both tasks since both rely on rule specification and selective attention. Furthermore, *COMT* Met allele carriers should perform better than Val/Val homozygotes in the conjunctive rule task that depends on updating the appropriate rule, but not in the unidimensional task. We also investigated the possibility of interactions between *DARPP-32, DRD2*, and *COMT* on category learning performance. For example, it is possible that *COMT* Met allele carriers who are also *DRD2* TT homozygotes or *DARPP-32* AA homozygotes may excel on the conjunctive rule task. Because the conjunctive task relies on both rule specification and rule updating, performance effects alone cannot distinguish the precise mechanism that may account for genotype differences in the conjunctive task. We therefore apply computational models to the data for the conjunctive task to determine the precise genetic effects on rule specification and updating. This modeling approach will allow us to pinpoint whether poorer categorization performance on the conjunctive task is due to deficits in updating complex rules or specifying the optimal rule.

Method

Participants

One hundred and four participants (75 females, 29 males; M_{age}=21.4) were recruited from the Texas A&M University and College Station, Texas community and were compensated $24 for participating in the experiment. Two participants did not complete either category learning experiments and four participants did not complete the conjunctive rule task due to computer issues and were excluded from those analyses. In our within-subject design, participants provided saliva samples and then completed both conditions of a rule-based category learning task that consisted of a unidimensional rule task and a conjunctive rule task. The order that participants completed the tasks was counterbalanced, and participants performed each task in separate sessions at least one week apart.

The majority of the participants in our sample (n=60) were Caucasian, twenty were Asian, eighteen were Hispanic, and six were African-American. To control for population stratification in the genetic effects and assess for admixture in our sample, we included ethnicity as a factor in our statistical analyses. The ratio for *DRD2* C957T genotypes was 36:39:29 (C/C:C/T:T/T). The ratio distribution of *COMT* genotypes was 30:53:21 (Val/

Val:Val/Met:Met/Met), and the ratios for *DARPP-32* genotypes were 5:48:51 (G/G:G/A:A/A). The frequency of gene combinations for *COMT, DRD2,* and *DARPP-32* respectively was: Met/C/G: 24.3%, Met/C/AA: 30.1%, Met/TT/G: 7.8%, Met/TT/AA: 8.7%, ValVal/C/AA: 5.8%, ValVal/TT/G: 6.8%, and ValVal/TT/AA:4.9%.

Genotyping Method

DNA was collected using 2ml Oragene self-collection kits. Samples for the rs6277 (C957T), rs4680 (Val158Met), and (rs3764352) *DARPP-32* single nucleotide polymorphisms (SNPs) were genotyped using Taqman primer and probe pairs. Samples were amplified in accordance with Taqman Universal Thermal Cycling Protocol using Applied Biosystems 7900HT Real Time PCR System. Allelic discrimination was then performed.

Stimuli

Participants were presented with Gabor patches that varied in the frequency of the bars and their orientation relative to the computer screen. Figure 1 shows the frequency (bar width) and orientation of all the Gabor patterns in each block of trials as well as the boundaries that maximize accuracy for each block. Optimal performance in the unidimensional rule-based task required using the frequency dimension alone while ignoring orientation. In contrast, optimal performance in the conjunctive rule-based task entailed utilizing a conjunctive rule based on both the frequency and orientation dimensions. The unidimensional rule stimuli had a category discriminability (d') of 4.5, whereas the conjunctive stimuli had a d' equal to 10.4. In line with previous work on unidimensional and conjunctive rule category learning, these separate stimulus space d' values were selected to match the stimuli in each task in terms of psychological d', which approximately equates the tasks in accuracy rate (Zeithamova & Maddox, 2006). While the rule was more complex for the conjunctive rule task because it involved a conjunction along two dimensions, the two categories in the unidimensional task had lower perceptual discriminability, thus making the conditions similar in level of difficulty.

Procedure

Participants completed five blocks of 80 trials. They were instructed to categorize each stimulus as a member of either Category 1 by pressing the ‘Z’ key on the keyboard or Category 2 by pressing the ‘C’ key on the keyboard. No time constraint was imposed on response time. Participants were given feedback 500ms after their response selection about whether they were correct (“Correct”) or incorrect (“No, the answer is 1 (or 2)”). They were informed that at first they would need to guess a category, but as the task continued, they would learn the categorization strategy. Participants learned to categorize the Gabor patches through the feedback provided. For each block of trials, a meter located to the right of the stimulus was shown, and as participants correctly categorized the stimuli, the meter filled. Each correct response earned 2 points, and a total of 160 points was needed to fill the meter. This allowed participants to track their progress on each block of trials. The meter was reset at the beginning of each block of trials. Participants were informed that there were an equal number of stimuli that belonged to Category 1 and Category 2 over the course of the task.

Results

Category Learning Accuracy

We employed linear mixed effects models to test the effects of genetic influences on task performance while controlling for individual differences in overall accuracy and the effect of task manipulation. We measured overall accuracy, or average accuracy across all five blocks, to fully capture the selective attention aspect of the task and assess long-term learning[2]. In contrast to repeated measures ANOVA, a linear mixed effects regression is a more flexible model that can handle missing data, which allowed for a better representation of the data for the subjects who completed the unidimensional task, but not the conjunctive rule task. Additionally, the regression approach controls for the effects of other genes. Therefore, the mixed effects model is better suited for testing gene-gene interactions because it increases experimental power. Participants were included in the model as the random factor. For the fixed factors, each of the gene single nucleotide polymorphisms was coded as either 0 or 1. We tested the SNPs to determine whether they were in Hardy-Weinberg equilibrium (HWE). *COMT* and *DARPP-32* did not deviate from HWE, but *DRD2* did, (X^2 = 6.32, $p < .05$). The dichotomization of the genes should correct for the *DRD2* deviation from HWE in the results, however. The *DRD2* C957T SNP was dichotomized as TT homozygotes (coded as 0) and C allele carriers (coded as 1), and the *DARPP-32* (rs3764352) SNP was dichotomized as G allele carriers (coded as 0) and AA homozygotes (coded as 1). For *COMT* Val158Met, Met carriers (coded as 0) were compared to Val homozygotes (coded as 1). The first model we considered contained all possible interactions between genes and task type. In this first model, we observed a significant *COMT* by task type interaction whereby overall accuracy was significantly lower in the conjunctive task relative to the unidimensional task for Val homozygotes, $\beta = -0.14$, $SE = 0.06$, $t(89) = -2.27$, $p < .05$. There were no other significant gene X gene or gene X task type interactions. However, there was a significant main effect of *DARPP-32* in which AA homozygotes outperformed G allele carriers, $t(95) = 3.04$, $p < .01$. For the *DRD2* gene, although TT homozygotes performed numerically better overall on the category learning tasks compared to C allele carriers, this difference did not reach significance, $t(95) = 1.59$, $p = .11$. No main effect was observed for the *COMT* gene, $t(95) = .87$, $p = .38$. Ethnicity did not interact with *DRD2* ($t(87) = -1.32$, $p = .19$), *DARPP-32* ($t(87) = .08$, $p = .94$), *COMT* ($t(87) = -.62$, $p = .53$), or task type ($t(81) = -.08$, $p = .94$).

Because the full regression model tested several interaction effects, power to detect main effects was somewhat diminished. To have increased power for examining the main effects of genes, we ran a reduced model that only included the *COMT* X task interaction and the main effects of *DARPP-32* and *DRD2*. According to the AIC values, this reduced model fit the data better than the full model with all interactions ($AIC_{full} = -134.58$; $AIC_{reduced} = -182.79$). In this reduced model, there was a significant main effect of task type in which the conjunctive task was performed more accurately than the unidimensional task, $\beta = 0.09$, $SE = 0.02$, $t(95) = 4.33$, $p < 0.01$. Additionally, there was a main effect of *DRD2* in which TT homozygotes performed better than C allele carriers ($\beta = 0.07$, $SE = 0.03$, $t(99) = 2.74$, $p < .$

[2]We also conducted all analyses described in the Results section with final block accuracy as the outcome measure. All observed effects for average accuracy were also significant ($p<.05$) or marginally significant ($p<.10$) for final block accuracy.

01), and a main effect of *DARPP-32* whereby AA homozygotes performed better than G carriers, β = 0.06, *SE* = 0.02, *t*(99) = 2.70, *p* < .01. There was no main effect of *COMT* overall, *t*(99) = 0.06, *p* = 0.95. However, the interaction identified in the full model remained robust, though slightly weaker, in the reduced model, suggesting that Val homozygotes perform poorly compared to Met carriers only in the conjunctive task, β = -0.07, *SE* = 0.04, *t*(95) = -1.88, *p* = 0.06. Indeed, post hoc comparisons showed no difference between Met carriers and Val homozygotes in the unidimensional task (*t*(95) = -.05, *p* = .96), but a significant difference in the conjunctive rule task, β = -0.07, *SE* = .03, *t*(95) = -2.14, *p* = .03. As with the full model, ethnicity did not interact with any of the genes in the reduced model (*p*>.10). Learning curves for each genotype in the unidimensional and conjunctive rule tasks are shown in Figure 2. Mixed model ANOVAs conducted separately for each genotype in both task types indicated that learning was not significantly different by genotype in either task, *p* > .10. Thus, the observed differences in learning performance can be attributed to consistent accuracy differences in each trial block on both the unidimensional and conjunctive rule tasks. Task order, completing either the unidimensional or conjunctive rule task first, did not affect performance in either the unidimensional (*t*(101) = -.73, *p* = .47) or conjunctive (*t*(96) = -.33, *p* = .74) rule task.

Gene-Dose Effects

We also tested for linear gene-dose effects for each of the single nucleotide polymorphisms. Figure 3 shows the linear effects of each genotype in both the unidimensional and conjunctive rule tasks. The *DRD2* C957T polymorphism showed a significant linear gene-dose effect in which each copy of the T allele increased category learning performance (averaged across both the unidimensional and conjunctive tasks), *F*(2, 94)= 5.87, *p* < .01. Similarly, *DARPP*-32 also indicated a significant linear gene-dose effect whereby each copy of the A allele was associated with increased task performance, *F*(2, 94) = 4.85, *p* = .01. However, it is important to note that because there were only five *DARPP-32* GG carriers in our sample for this gene, the linear gene-dose effect analysis may not be the most valid method to represent the data for this particular gene. There were no linear effects of the minor allele frequency for *COMT* on combined (average for unidimensional and conjunctive) category learning performance, *F*(2, 102) = 1.35, *p* = .27. Given the distinctive effects of *COMT* on the unidimensional and conjunctive rule tasks, we also performed separate analyses for each task condition. While there was no gene-dose effect of *COMT* observed in the unidimensional task, *F*(2, 102) = .17, *p* = .84, there was a marginally significant gene-dose effect of *COMT* in the conjunctive rule task, *F*(2,97) = 2.46, *p* = .09, in which each copy of the Met allele corresponded to increased accuracy on the conjunctive rule task.

Decision-Bound Modeling Analysis

To examine whether *DRD2* and *DARPP-32* affected different aspects of learning within the conjunctive rule task, we fit a series of decision-bound models individually to each participant's data. These analyses were performed in the conjunctive rule task to assess whether the genes we examined had specific roles in a.) attending to both stimulus dimensions instead of a single dimension (selective attention), and b.) specifying the optimal decision-bound for the conjunctive rule (rule-updating). We predicted that the striatal genes

would be relevant for selective attention to the relevant dimensions, while *COMT* would be implicated in updating the conjunctive rule-representation so that it is closest to the optimal rule-bound. Decision-bound models have been used extensively in prior category-learning work, and the basic process involves fitting models that assume specific strategies or rules to the data to infer what types of strategies participants used to solve the task (Maddox & Ashby, 1993; Maddox, 1999; Worthy, Markman, & Maddox, 2013). We fit a total of four models to the data: two unidimensional rule models that assumed a linear decision-bound aligned with either the spatial frequency or spatial orientation dimension, a conjunctive rule model that assumed a conjunctive rule bound in the form of the optimal strategy, and a random responder model. The unidimensional rule models each had two free parameters, one representing the location of the bound along the relevant dimension and the other representing perceptual and criterial noise. The conjunctive rule model had three free parameters, two representing the location of the frequency and orientation bounds, and the third representing perceptual and criterial noise. This model is an independent-decisions classifier model that assumes that both the frequency and orientation dimensions are considered independently. The random responder model had only one free parameter that represented the probability of selecting Category 1 on any given trial.

We fit each participant's data individually over all trials and in the final block with each of the four models. Overall, the conjunctive rule model provided a much better fit (*Mean AIC* = 382.14) to the data in the conjunctive rule task for the majority of participants compared to the frequency (*Mean AIC* = 560.36), orientation (*Mean AIC* = 693.31), or random responder models (*Mean AIC* = 549.79). To examine the extent to which participants learned to selectively attend to both dimensions instead of a single dimension we computed the improvement in the conjunctive rule model's fit over the best-fitting unidimensional rule model ($AIC_{Best\ Unidimensional} - AIC_{Conjunctive}$). Figure 4a shows a typical individual data set that illustrates the improvement in the conjunctive rule model's fit in terms of decision bounds compared to the unidimensional model. Because the conjunctive rule is the optimal categorization strategy in the conjunctive task, a better model fit suggests enhanced categorization performance. We then simultaneously entered each gene polymorphism into a regression to predict the improvement in fit for the model that assumed a conjunctive rule bound over a unidimensional rule bound. There were significant effects for *DRD2,* $\beta = -.32$, $p < .01$, and *DARPP-32,* $\beta = -.22$, $p < .05$, but there was no effect for *COMT,* $\beta = -.08$, $p = .45$. A regression analysis for each gene predicting improvement in model fit in the final trial block showed similar results in which the *DRD2* gene was a significant predictor, $\beta = -.26$, $p < .05$. Although the main effect of *DARPP-32* did not reach significance for the final block, the trend was in the same direction as the analysis for all trials, $\beta = -.15$, $p = .14$. Figure 5 shows the improvement in conjunctive rule model's fit for *DRD2* and *DARPP-32* by trial block. The improvement in model fit for the conjunctive rule model over the best-fitting unidimensional model was greater for *DRD2* TT homozygotes than for C carriers, and for *DARPP-32* AA homozygotes than for G carriers. Consistent with the behavioral results showing that *DRD2* TT homozygotes and *DARPP-32* AA homozygotes performed better on both category learning tasks, these results indicate that individuals with these genotypes demonstrated enhanced selective attention to the stimulus features in both tasks.

Furthermore, the null modeling findings for *COMT* parallel the behavioral results and suggest that *COMT* is not involved in selective attention to specific stimulus features.

We also examined the best-fitting bounds for the conjunctive rule model in relation to the optimal bound location by computing the distance from the best-fitting frequency and orientation bounds to the optimal bounds. Figure 4b shows the best-fitting conjunctive rule bounds compared to the optimal model bounds for a single participant. Smaller distances from the optimal bound indicate greater precision in updating and maintaining the correct rule. Thus, as rule information from feedback is updated in working memory, accuracy in categorizing the stimuli should improve. We entered each gene polymorphism into a simultaneous regression to predict the distance between each participant's best-fitting conjunctive bounds to the optimal bounds. There was no effect for *DRD2* ($\beta = .15$, $p = .15$) or *DARPP-32* ($\beta = -10$, $p = .33$), however, we did observe a significant effect for *COMT* ($\beta = .21$, $p < .05$) where Val homozygotes' best-fitting conjunctive rule bounds were significantly further away from the optimal bound compared to Met allele carriers. Regression results for each gene predicting best- fitting bounds in the final block revealed similar results; *COMT* Val homozygotes' best-fitting bounds were closer to the optimal bound in the final block compared to Met carriers ($\beta = .25$, $p < .05$), while *DRD2* ($\beta = .12$, $p = .26$) and *DARPP-32* ($\beta = .02$, $p = .84$) were not significant predictors. figure 6 depicts the best-fitting conjunctive rule bounds for *COMT* by trial block. Based on these results, it appears that *COMT* Met allele carriers were more adept at updating and maintaining the appropriate rule in the conjunctive rule task as compared to Val homozygotes. This ability to better update and maintain the correct rule is also consistent with the behavioral results showing that Met allele carriers exhibited enhanced performance on the conjunctive rule task.

Discussion

The results of this study demonstrate that polymorphisms in striatal and PFC dopaminergic genes differentially impact performance in category learning, depending on the task demands. Striatal dopaminergic genes, *DRD2* and *DARPP-32*, influenced performance in both unidimensional and conjunctive rule-based category learning tasks in which *DRD2* TT homozygotes outperformed C allele carriers and *DARPP-32* AA homozygotes outperformed G allele carriers on both tasks. However, *COMT*, primarily expressed in the PFC, impacted performance in the conjunctive rule task alone, indicating that *COMT* may be selectively involved in learning that depends on effectively updating complex WM representations. The *COMT* Met allele predicted superior performance on the conjunctive rule task that involves both selective attention to the correct stimulus dimensions (rule specification) and appropriate rule updating of the decision bounds, but no difference in performance from Val homozygotes in the unidimensional task that relies primarily on rule specification.

Furthermore, our modeling results suggest that *COMT* Met allele carriers were able to more precisely specify the decision-bound representing the optimal rule. Increased dopamine in the PFC may lead to enhanced higher order executive function capabilities, which may account for *COMT* Met allele carriers' enhanced performance on the more demanding conjunctive task but not the unidimensional task. These results are consistent with previous

work by Goldberg and colleagues that found a relationship between *COMT* and performance on the *N*-back task that suggested that *COMT* is sensitive to PFC processes involved in information updating (2003). It appears that Val/Val homozygotes have lower dopamine levels available in the PFC and are less capable of simultaneously updating rule criteria along both stimulus dimensions as the modeling results indicated. While Val/Val homozygotes may be able to specify that the rule entails two dimensions, the additional demand of effectively learning the precise boundaries of two dimensions in the conjunctive task may compromise category learning performance. In contrast, while the unidimensional task required filtering out the orientation dimension in constructing category rules, it entailed less rule updating demands than the conjunctive rule task, and Val/Val homozygotes were able to perform at a similar level to that of Met allele carriers. Thus, the contribution of *COMT* to category learning appears to be optimally updating and applying complex rules, rather than selective attention or rule specification.

In contrast to the null findings in Collins & Frank (2012) but in line with previous work with the probabilistic selection task (Doll et al., 2011; Frank et al., 2007), we show that both *DRD2* and *DARPP-32* influence learning that entails selective attention to novel stimulus features. Furthermore, recent research examining the effect of *DRD2* on conjunctive rule-based and procedural learning showed that *DRD2* C carriers are faster to reach a learning criterion (10 trials in a row correct) than TT homozygotes (Xie, Maddox, McGeary, & Chandrasekaran, 2015). Like the task used in the Collins and Frank study, however, this task also entailed categorizing familiar items (houses, plants, and food on plates). Differences in task demands, stimulus features, stimuli familiarity, or outcome measures may account for the disparity in results. Our results suggest that *DRD2* and *DARPP-32* specifically modulate selective attention to novel stimulus features. Moreover, the modeling results from the conjunctive rule task support this assertion in that these genes were associated with improved model fit for the conjunctive rule model over the best-fitting unidimensional model, which suggests superior selective attention to the task-relevant features of the stimuli. Based on these findings, it appears that striatal dopaminergic genes affect tasks that rely on selective attention, while *COMT* is specifically involved in updating information in complex tasks that are more taxing on WM processes.

Our results are also relevant to the Competition between Verbal and Implicit Systems (COVIS) theory of rule-based learning and specify the distinctive function of dopamine on different type of verbal learning (Ashby et al., 1998). COVIS predicts that response criterion learning in rule-based tasks occurs in the striatum, while the PFC helps update the criteria and select the categorization rule that defines each stimulus. Furthermore, COVIS also predicts that increased dopamine should enhance rule-based learning (Ashby et al., 1998; Ashby & Isen, 1999). Our findings demonstrate that genes that encode for enhanced D1 and D2 dopamine receptor availability in the striatum, specifically, enhance unidimensional and conjunctive rule learning. Moreover, the *COMT* Met allele, associated with elevated PFC dopamine, enhances conjunctive rule learning, but not unidimensional rule learning. Consistent with COVIS, we find that striatal dopamine does indeed enhance rule-based learning. Our results add a novel contribution to the COVIS theory by demonstrating the specificity of D1 and D2 receptors to the selective attention and rule specification aspect of rule-based category learning, and also demonstrating the role of PFC dopamine for complex

rule-learning in particular. Future work could further examine how COVIS' proposed frontostriatal rule-based system learns different types of rule-based category structures.

Rule-based categories are learned through rule specification and updating and rely on intact executive function and adequate cognitive resources. Our results suggest that rule updating may be mediated by PFC regions, while attention to novel stimulus features may be mediated more by striatal regions. Consistent with this notion, computational models on the basal ganglia-frontal system propose that dopamine in the basal ganglia serves as a gate that selectively regulates updating of information to be maintained in the PFC and inhibition of information to the PFC (Frank et al., 2001; Middleton & Strick, 2002; Moustafa, Sherman & Frank, 2008; O'Reilly & Frank, 2006). Excitation of Go neurons via D1 receptors in the basal ganglia direct pathway disinhibit the thalamus, which allows information to pass through the basal ganglia “gate” to be updated in the PFC. In contrast, dopamine in the indirect pathway inhibits NoGo neurons via D2 receptors and prevents information from being updated in the PFC. This model suggests a mechanism for the function of dopamine in unidimensional and conjunctive rule tasks. Striatal dopamine enhances Go activity through D1 receptors, which enhances selective attention to the relevant stimulus dimensions, while dopamine inhibits NoGo activity through D2 receptors, which enables one to ignore irrelevant dimensions. Thus, only information about relevant features of a stimulus pass through the basal ganglia gate to the PFC where information about the features characterizing the categorization rule are updated and maintained. PFC dopamine thus facilitates the updating and maintenance of the appropriate rule because only rule-relevant information passed through the gate.

Thus, this process is both consistent with the results that show an effect of *COMT* only in the conjunctive rule task as well as prior work showing that the basal ganglia exerts attentional control in working memory tasks, selectively permitting only task-relevant information access to working memory resources (McNab & Klingberg, 2008). Furthermore, these results fit within the context of the PBWM model. Prior work shows that striatal D1 and D2 receptors are responsible for gating dopamine signaling to the PFC by controlling whether task representations are maintained (D1 state) or updated (D2 state), and the PFC is responsible for higher order executive functioning processes (Frank, Loughry, & O'Reilly, 2001; Hazy, Frank, & O'Reilly, 2007; O'Reilly & Frank, 2006; O'Reilly, 2006). Thus, WM-dependent learning tasks that rely on selective attention to novel stimulus features may be directly influenced by allelic variation in striatal D1 and D2 receptor genes. Our results suggest that *DRD2* TT homozygotes and *DARPP-32* AA homozygotes have enhanced attention to task-relevant stimulus features, which extends to both unidimensional and conjunctive rule-based category-learning tasks. We note that despite limited work on other dopaminergic genes, including *DRD1* and *DAT1*, impacting reinforcement and category learning, future research on possible relationships between these genes and different types of learning would be beneficial. It is possible that other dopaminergic genes specifically influence category learning; however, that analysis was outside the scope of the present study. Thus, the conclusions from this study indicate that D1 and D2 striatal genes lead to broad cognitive advantages for *DRD2* TT homozygotes and *DARPP-32* AA homozygotes in rule-based category learning tasks, and a specific contribution of *COMT* in learning tasks that require updating complex WM representations.

Taken together, we conclude that dopaminergic binding in both the striatum and prefrontal cortex influence category learning performance. These results show that individual differences in striatal and cortical dopaminergic genes are important not only in WM activity, but also in tasks that depend on rule specification (unidimensional rule) and complex rule updating (conjunctive rule) strategies necessary for task success. To our knowledge, this is the first study to associate polymorphisms in *DRD2*, *DARPP-32*, and *COMT* genes with novel category learning performance. Future work should consider whether these effects extend to other category learning tasks like information-integration tasks which are thought to be learned procedurally, but that also recruit striatal regions (Ashby et al., 1998). Learning and categorization are integral aspects of human functioning and adaptation, and the results of this study demonstrate that individual differences in dopaminergic genes may predict differences in learning performance and cognitive strategies.

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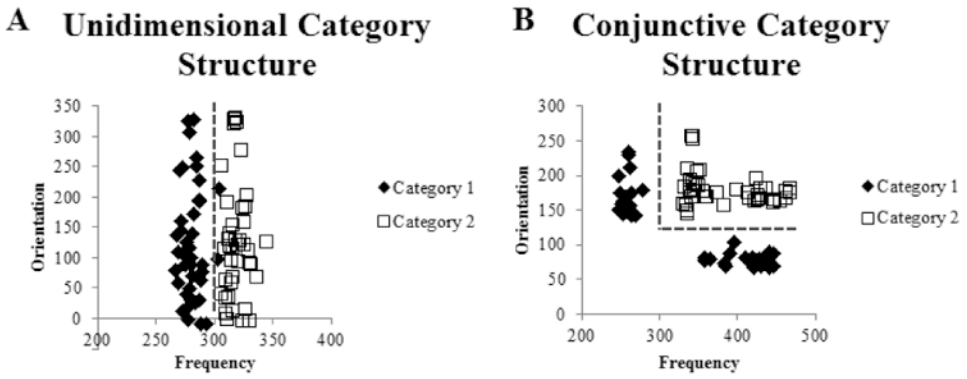

Figure 1.

(a) Plot of stimuli from unidimensional rule category structure. (b) Plot of stimuli from the conjunctive rule category structure. The dotted lines represent boundaries that maximize accuracy in each condition.

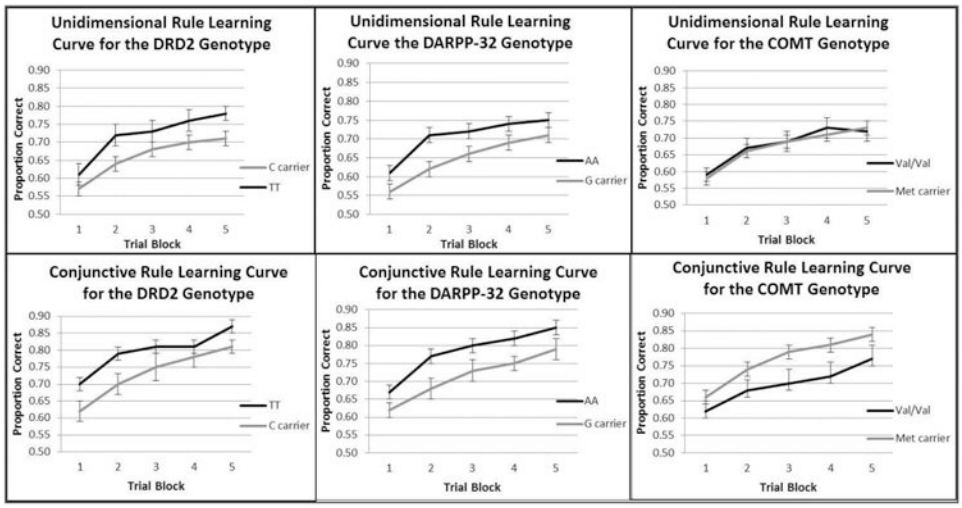

Figure 2.

Learning curves for each 80-trial block for each genotype in the unidimensional (top row) and conjunctive (bottom row) rule category learning tasks. Error bars represent standard error of the mean from the linear mixed effects reduced models.

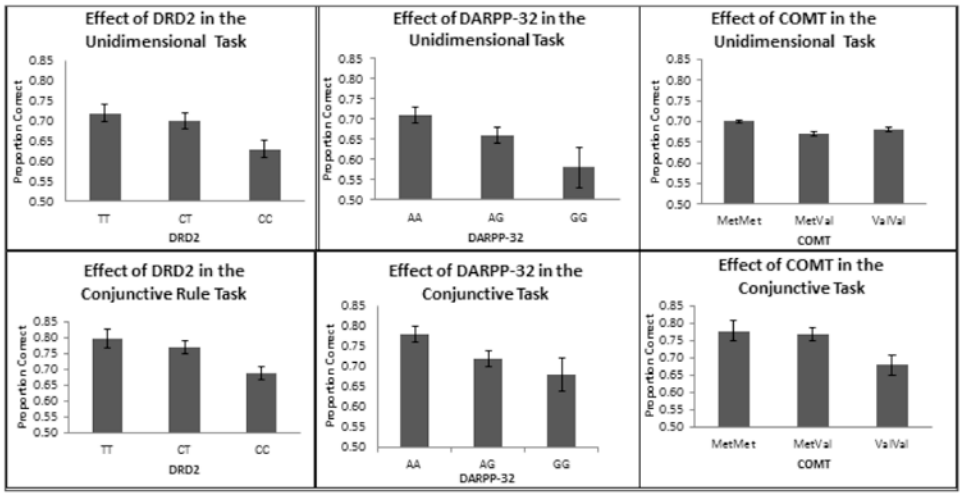

Figure 3.

Gene-dose effects of *DRD2*, *DARPP-32*, and *COMT* for the unidimensional (top row) and conjunctive (bottom row) rule tasks. *DRD2* and *DARPP-32* genotypes had a significant linear gene-dose effect on learning performance. Error bars represent standard error of the mean.

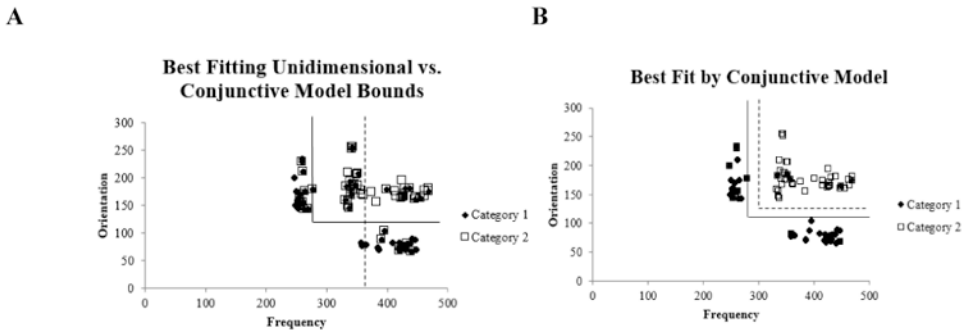

Figure 4.

Response patterns of participants who are best fit by a conjunctive rule model. (a) Responses of a participant showing the best-fitting conjunctive (solid line) and unidimensional (dashed line) rule bounds. Note that the actual difference measure was between the AICs, rather than the average decision bounds. (b) Responses of a participant showing the best-fitting conjunctive rule bounds (solid line) and the optimal bounds (dashed line).

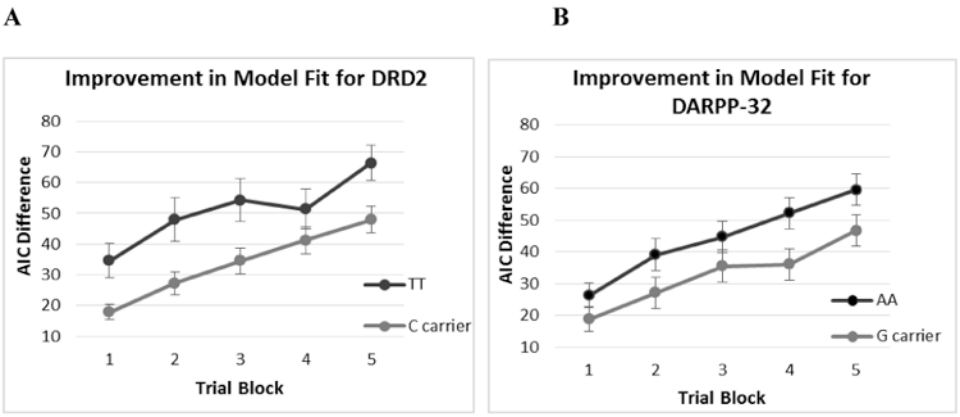

Figure 5.

Improvement in the conjunctive rule model's fit over the best-fitting unidimensional rule model for the *DRD2* (a) and *DARPP-32* (b) genes for each 80-trial block. Error bars represent standard error of the mean. Larger values indicate enhanced reliance on the optimal conjunctive rule strategy compared to a unidimensional strategy.

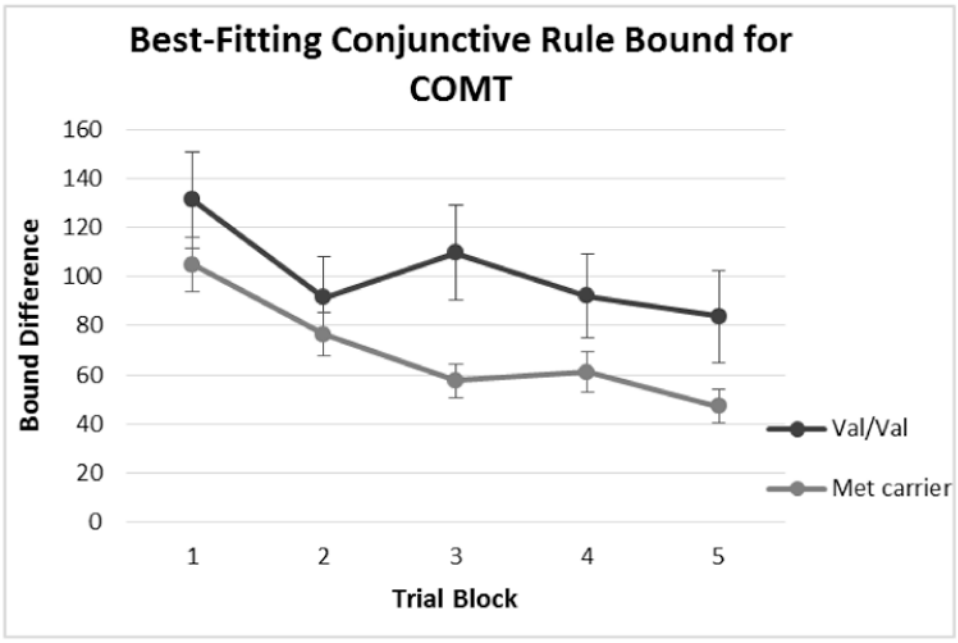

Figure 6.

Distance between the best-fitting conjunctive rule bounds and the optimal bound for *COMT* for each 80-trial block. Error bars represent standard error of the mean. Smaller values indicate best-fitting bounds closer to the optimal bounds.