DRD4 Long Allele Carriers Show Heightened Attention to High-priority Items Relative to Low-priority Items

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Abstract

■ Humans with seven or more repeats in exon III of the *DRD4* gene (long *DRD4* carriers) sometimes demonstrate impaired attention, as seen in attention-deficit hyperactivity disorder, and at other times demonstrate heightened attention, as seen in addictive behavior. Although the clinical effects of *DRD4* are the focus of much work, this gene may not necessarily serve as a "risk" gene for attentional deficits, but as a plasticity gene where attention is heightened for priority items in the environment and impaired for minor items. Here we examine the role of *DRD4* in two tasks that benefit from selective attention to high-priority information. We examine a category learning task where performance is supported by focusing on features and updating verbal rules. Here, selective attention to the most salient features is associated with good performance. In addition, we examine the Operation Span (OSPAN) task, a working memory capacity task that relies on selective attention to update and maintain items in memory while also performing a secondary task. Long *DRD4* carriers show superior performance relative to short *DRD4* homozygotes (six or less tandem repeats) in both the category learning and OSPAN tasks. These results suggest that *DRD4* may serve as a "plasticity" gene where individuals with the long allele show heightened selective attention to high-priority items in the environment, which can be beneficial in the appropriate context. ■

INTRODUCTION

The *DRD4* gene codes a postsynaptic D_4 dopamine receptor primarily transcribed in the PFC (Wells, Beevers, Knopik, & McGeary, 2012; Oak, Oldenhof, & Van Tol, 2000) where the variable number of tandem repeats in exon III are involved in modulating attention. Interestingly, the presence of an allele with seven or more repeats (long) has been associated with both disrupted and heightened attention. For example, the long allele has been associated with increased incidence of attention-deficit hyperactivity disorder (ADHD) with impaired executive attention (Gizer & Waldman, 2012; Bidwell et al., 2011; Gizer, Ficks, & Waldman, 2009; Munafò, Yalcin, Willis-Owen, & Flint, 2008; Laucht, Becker, Blomeyer, & Schmidt, 2007; Laucht, Becker, El-Faddagh, Hohm, & Schmidt, 2005; Langley et al., 2004; Hutchison et al., 2003; Kustanovich et al., 2003; Manor et al., 2001; Swanson et al., 2000). However, other work has found that long *DRD4* allele carriers demonstrated heightened executive attention for emotional stimuli (Wells et al., 2012) and smoking-related cues (Munafò et al., 2008; Laucht et al., 2005, 2007; Hutchison et al., 2003). Thus, prior work has been mixed regarding the role of the *DRD4* in modulating attention.

It has been proposed that *DRD4* behaves as a plasticity gene rather than a vulnerability gene (Wells et al., 2012; Belsky & Pluess, 2009; Oak et al., 2000). Under this view, long allele carriers are not simply more susceptible to adverse environmental stimuli, rather, their cognitions are perturbed to a greater extent by environmental factors generating greater changes in behavior. These changes could be advantageous or disadvantageous depending on the task. One possibility is that long allele carriers show heightened attention to high-priority items and impaired attention to low-priority items in the environment.

Biased competition theory suggests that frontal brain structures are critical for goal-directed biases (Gizer & Waldman, 2012; Lee, Itti, & Mather, 2012; Bidwell et al., 2011; Beck & Kastner, 2009; Gizer et al., 2009; Langley et al., 2004; Kustanovich et al., 2003; Manor et al., 2001; Swanson et al., 2000). Here, goal-relevant information is held in working memory and used to enhance attention for priority targets amid distractors. For example, when searching for a friend's face in a crowd, their high-priority facial features are stored in working memory systems where reciprocal projections to the visual cortex enhance similar features. As *DRD4* is primarily transcribed in the PFC (Wells et al., 2012; Oak et al., 2000), we hypothesize that genetic polymorphisms change the way goal-directed priorities are selected, which would influence performance across multiple cognitive domains. In line with this theory, common top–down priority maps have been

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demonstrated in the prefrontal and parietal cortices across several cognitive domains including working memory and attention (Ikkai & Curtis, 2011; Munafò et al., 2008; Laucht et al., 2005, 2007; Hutchison et al., 2003). Together with prior research on the long allele, we predict a *DRD4* long-allele advantage in tasks that require goal-directed attention to high-priority items in a complex environment.

We test this hypothesis by examining *DRD4* in nonclinical populations performing two tasks where greater plasticity for high-priority items and reduced plasticity for low-priority items improves subsequent learning and memory. First, we examine a category learning in a task where stimuli that differ along 10 binary dimensions must be classified. Previous research has found that narrow goal-directed attention to a small number of features supports learning in this task and computational models are available to determine how much attentional weight is given to each feature (Gorlick & Maddox, 2013). We predict long allele carriers will show heightened attention to salient features relative to short homozygotes and, as a result, demonstrate superior task performance. We also predict impaired attention for minor features in long allele carriers relative to short homozygotes.

Although the category learning paradigm is ideal for mapping improved and impaired attention within the same study, it does not demonstrate whether these effects are driven by bottom–up or top–down processes. *DRD4* is primarily expressed in the PFC; thus, one nuance of our hypothesis is that these effects are likely driven by top–down goal-directed processes. To evaluate whether these effects hold during a task where bottom–up attentional competition is not important for performance, we also examine whether long allele carriers show superior performance in a complex sequential task that requires sustained attention to a primary, demanding working memory task amid distraction, the Operation Span (OSPAN) task (Conway et al., 2005; Engle, Tuholski, & Conway, 1999). Here the high-priority goal is to accurately recall sequences of letters while simultaneously performing a distracting secondary task. Performance in this task is dependent on goal-directed attentional biases for the priority letter span task in the face of interference (Conway et al., 2005; Conway, Cowan, & Bunting, 2001; Kane, Bleckley, Conway, & Engle, 2001). We predict that long allele carriers will outperform short carriers because of heightened top–down attention to the letters that must be remembered on each trial.

METHODS

Participants

Replication is an important step in determining whether single-nucleotide polymorphism effects will be consistent across studies and populations. To improve our confidence in the generalizability of these effects, we have included data from two samples. One sample was an unscreened pool of participants (general sample) that completed a shorter version of the category learning task consisting of one block of training and test. The second sample was screened for clinical, neuropsychological, and personality differences described below. As the screened sample has fewer potential confounds, they completed more rigorous testing with two blocks of the category learning tasks as well as the memory span task.

General Sample

Participants aged 18–35 years were recruited from the University of Texas at Austin introductory participant pool (127 women, 60 men). Participants were not screened for clinical symptoms or neuropsychological differences during recruitment.

Screened Sample

Participants aged 18–35 years were recruited from the greater Austin community through fliers and newspaper ads (overall: 125 women, 96 men). The samples for the screened category learning and OSPAN tasks were largely overlapping (92.8%) within this group, depending on task exclusions and available data. To rule out anyone who had significant psychiatric disease, potential participants were screened via telephone using the Mini International Neuropsychiatric Interview (MINI), which screened for 17 different Axis I *Diagnostic and Statistical Manual of Mental Disorders-IV* disorders, including alcohol and drug abuse and/or dependence, and ADHD. The MINI has acceptable validity, test–retest, and interrater reliability (Sheehan, Lecrubier, & Sheehan, 1998; Lecrubier et al., 1997). Participants who met criteria for a current or past psychiatric diagnosis (determined by the MINI), currently taking psychoactive medication, currently in psychotherapy, or with a history of brain trauma were excluded from the study. Excluded participants were offered referrals to local mental health clinics.

Category Learning Task

Cartoon animals constructed from 10 binary features such as head orientation (up or forward), body color (gray or yellow), and tail (thin or thick) served as stimuli from a total of $2^{10} = 1024$ possible stimuli (Figure 1A). Because of varied contrast and characteristic differences between dimensions, some are more salient than others. For each participant, one stimulus was selected at random to represent the A prototype. The B prototype has the opposite value on each feature. Category stimuli were derived by distorting the prototypes on one to four randomly selected features. Exemplars that differ from the prototype on 5 features were not used as they are ambiguous. Thus, each of 10 features is equally relevant; however, some features are more salient than others because of bottom–up visual differences such as contrast which influences priority during learning.

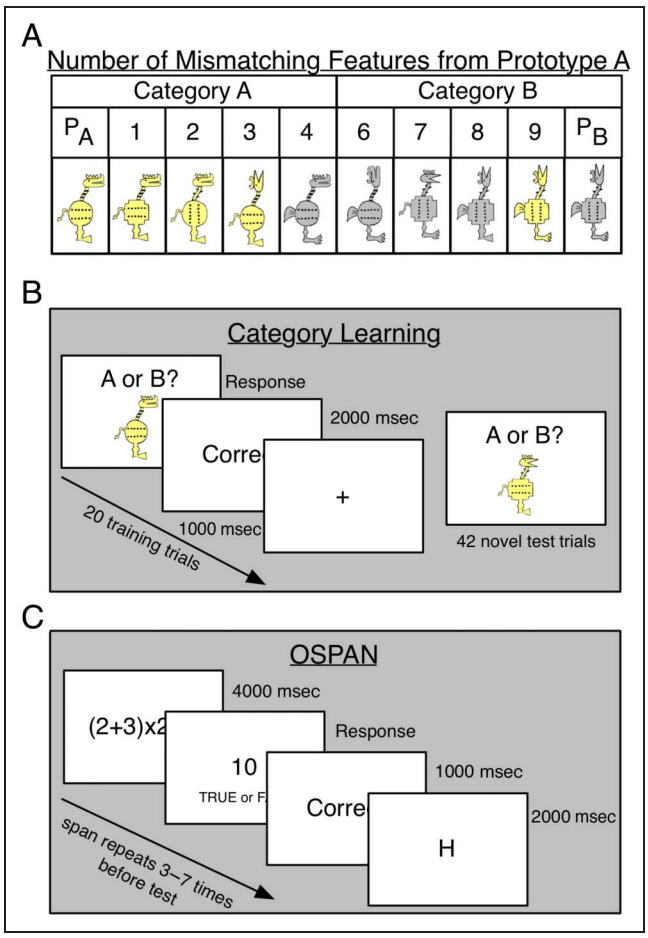

Figure 1. A schematic of the category learning and memory span tasks. (A) The category structure and (B) the task timeline for the category learning task. Participants completed one (general sample) or two (screened sample) blocks of 20 training trials with corrective feedback and 42 test trials. (C) A diagram of the OSPAN task. Participants completed 15 trials of three to seven memory spans. During each span, participants indicated whether math problems were correct while remembering an alternating sequence letters. After three to seven math-letter sequences, there was a free recall phase where participants were asked to recall the letters in order.

Screened sample participants completed two blocks of training and test, and general sample participants completed one block of training and test. Training consisted of 20 trials, followed by a test phase with 42 novel stimuli including the prototypes and equal numbers of A and B items (Figure 1B). During training, participants were shown 10 A and 10 B items in a random order, generated a response (self-paced with 1000 msec between items) by pressing the relevant key on the keyboard and were given corrective feedback for 2000 msec. Within each category, two training stimuli were randomly selected that differed from the category prototype on 1 feature, three differed on 2 features, three differed on 3 features, and two differed on 4 features.

A 42-trial test phase followed training that included each prototype and five stimuli that differed from each prototype on 1, 2, 3, and 4 features. On each test trial, after stimulus onset, the participant was prompted to give an A or B response by pressing the relevant key on the keyboard with no corrective feedback. Responses were self-paced with 1000 msec between items. For the Block 1 analysis, those that were nonlearners (less than 40% accuracy in Block 1; 6 long carriers and 12 short homozygotes) were excluded. For the Block 2 analysis, those that were nonlearners (less that 40% accuracy in Block 2; 2 long carriers and 2 short homozygotes) were excluded (Table 1). From the screened sample, 16 participants were not included because of incomplete or unsaved data.

To gain a more complete understanding of these effects across different samples, we examine early learning (Block 1) in an unscreened sample (General Sample) and replicate these effects in a sample that has been screened for mental illness and matched using neuropsychological measures (Screened Sample). Next, we take a closer look at learning with more experience (Block 2) in the screened sample. Prior work suggests that we should see larger effects in later learning because of differences in learning rates.

OSPAN Task

In the OSPAN task (Figure 1C), the participants' primary goal is to remember a sequence of letters presented on a computer screen while also performing distracting secondary modular arithmetic problems. Furthermore, letters are presented sequentially, reducing bottom–up influences on attention. Thus, recalling the letters has high goal-directed priority, and the arithmetic problems have low goal-directed priority. After each span, participants are asked to recall, in order, the sequence of letters that was just presented. The primary goal is to correctly recall each sequence of letters, but they must also maintain at least 85% accuracy on the math problems. This has been used as a domain-general measure of executive attention as well as working memory (Conway et al., 2005). The task consisted of 15 recall phases where participants were asked to recall spans of between three and seven letters. Participants were asked to recall a total of three spans of each span length (three to seven letters) for a total of 75 letters. From the overall sample, 25 participants were not included because of incomplete or unsaved data. Participants were excluded if they did not maintain an accuracy level of at least 85% on the arithmetic problems (3 short homozygotes; Table 1).

Importantly, there are no items that are more salient or "attention-grabbing" in the task, making it ideal for testing whether the effects seen during category learning are simply because of heightened attention to bottom–up salient items in the environment or because of goal-directed heightened attention to high-priority stimuli.

Genetics

The 48 bp VNTR in the *DRD4* was assayed using previously reported methods (Hutchison, LaChance, Niaura,

Table 1. Demographics and Individual Differences Information for Category Learning and Memory Span Tasks

	Long Carriers	*Short Homozygotes*
Category Learning		
General Sample		
Age, years	19.29 (2.28)	19.33 (2.66)
Years of education	12.93 (1.54)	12.94 (1.35)
Sex	F = 32; M = 17	F = 95; M = 43
BIS-11†	65.67 (8.51)	62.96 (8.45)
CESD	17.69 (10.55)	15.91 (9)
Ethnicity		
Hispanic	17	24
Non-Hispanic	32	112
Decline	0	2
Race		
White	36	79
Asian	2	40
Decline	2	1
Other	9	18
Screened Sample		
Age, years	24.77 (4.44)	24.88 (4.5)
Years of education	15.68 (2.63)	15.23 (2.27)
Sex	F = 20; M = 11	F = 93; M = 77
BIS-11**	69.33 (4.82)	72.55 (4.9)
CESD†	6.3 (5.17)	8.71 (6.54)
Ethnicity		
Hispanic	8	34
Non-Hispanic	20	132
Decline	3	4
Race		
White	22	102
Asian	1	40
Decline	3	7
Other	5	21
Memory Span		
Age, years	24.66 (4.42)	24.81 (4.44)
Years of education	15.59 (2.55)	15.33 (2.31)
Sex	F = 19; M = 13	F = 97; M = 64
BIS-11**	69.68 (4.67)	72.12 (4.76)
CESD†	6.81 (5.24)	9.03 (6.73)
Ethnicity		
Hispanic	7	31
Non-Hispanic	22	129
Decline	3	1
Race		
White	23	95
Asian	2	38
Decline	2	7
Other	5	21

Standard deviations are listed in parentheses where appropriate.

*Significant at $p < .05$.

**Significant at $p < .01$.

***Significant at $p < .001$.

†Marginally significant at $p < .10$.

Bryan, & Smolen, 2002). The primer sequences used are forward, 5′-AGGACCCTCATGGCCTTG-3′ (fluorescently labeled), and reverse, 5′-GCGACTACGTGGTCTACTCG-3′ (Lichter et al., 1993). Alleles were visualized using capillary electrophoresis. The seven-repeat allele is quite distinct from the two- to six-repeat alleles and likely originated as a rare mutational event that became more frequent as a result of positive selection (Ding et al., 2002). Participants were classified as *DRD4* long (i.e., homozygous or heterozygous for an allele of seven or more repeats) or as *DRD4* short carriers (i.e., both alleles <7 repeats). Details on specific genetic combinations can be seen in Table 2. For quality assurance purposes in the event of ambiguity in the genotyping, the assay is run in duplicate or triplicate to verify the results.

For both the screened sample and the general sample, results of an exact test for Hardy–Weinberg proportions using Markov chain–Monte Carlo implementation (Guo & Thompson, 1992) indicate that our observed genotype frequencies, when looking at both the entire sample and the White subset, differ significantly from Hardy–Weinberg equilibrium (HWE; $p < .00000$).

Data Analysis

Category Learning Measures

In addition to overall accuracy at test, we were interested in fine-grained measures of accuracy for exemplars that were more or less prototypical. To examine how similarity to the prototype affected performance for *DRD4* long and short homozygotes, we computed average accuracy for similar test items (i.e., those that differed from the prototype on one to two dimensions) and for dissimilar test items (i.e., those that differed from the prototype on three to four dimensions).

Table 2. Number of Tandem Repeats in Exon III for Each Allele of *DRD4*

Category Learning: General Sample

	1	2	3	4	5	6	7	8	9	10	11
1	0	0	0	0	0	0	0	0	0	0	0
2	0	9	0	0	0	0	0	0	0	0	0
3	0	1	2	0	0	0	0	0	0	0	0
4	0	18	3	98	0	0	0	0	0	0	0
5	0	0	0	6	0	0	0	0	0	0	0
6	0	0	0	0	0	1	0	0	0	0	0
7	0	4	1	30	2	3	3	0	0	0	0
8	0	2	0	2	0	0	0	1	0	0	0
9	0	0	0	1	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0

138 = *N* short homozygote (73.8%); 49 = *N* long allele carrier (26.2%)

Category Learning: Screened Sample

	1	2	3	4	5	6	7	8	9	10	11
1	0	0	0	0	0	0	0	0	0	0	0
2	0	22	0	0	0	0	0	0	0	0	0
3	0	4	1	0	0	0	0	0	0	0	0
4	0	29	5	99	0	0	0	0	0	0	0
5	0	0	1	3	1	0	0	0	0	0	0
6	0	1	1	3	0	0	0	0	0	0	0
7	0	3	1	17	0	1	6	0	0	0	0
8	0	1	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0
10	0	1	0	1	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0

170 = *N* short homozygote (84.6%); 31 = *N* long allele carrier (15.4%)

We examine measures of overall accuracy for Block 1 using 2 Sample (general, screened) × 2 *DRD4* status (long carrier, short homozygote) ANOVA. We examine the effects of similarity on accuracy using a 2 Sample (general, screened) × 2 *DRD4* status (long carrier, short homozygote) × 2 Similarity to the prototype (similar, dissimilar) repeated-measures ANOVA. For Block 2, which includes only the screened sample, we conduct independent samples *t* tests to examine overall accuracy and a 2 *DRD4* status (long carrier, short homozygote) × 2 Similarity to the prototype (similar, dissimilar) repeated-measures ANOVA to examine similarity.

Table 2. (*continued*)

Memory Span

	1	2	3	4	5	6	7	8	9	10	11
1	0	0	0	0	0	0	0	0	0	0	0
2	0	22	0	0	0	0	0	0	0	0	0
3	0	5	0	0	0	0	0	0	0	0	0
4	0	26	4	95	0	0	0	0	0	0	0
5	0	0	1	2	1	0	0	0	0	0	0
6	0	1	1	3	0	0	0	0	0	0	0
7	0	3	1	17	0	1	6	0	0	0	0
8	0	1	0	1	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0
10	0	1	0	1	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0

161 = *N* short homozygote (83.4%); 32 = *N* long allele carrier (16.6%)

Gray cells are short homozygotes (fewer than six tandem repeats for both alleles), and white cells are long allele carriers (at least one allele with seven or more tandem repeats).

Computational Models

The attentional processes underlying category learning can be better understood using computational models (Gorlick & Maddox, 2013; Glass, Chotibut, Pacheco, Schnyer, & Maddox, 2012). These prototype models incorporate attention-weighted, summed similarity between each item and the A and B prototypes to generate predicted response probabilities on a trial-by-trial basis. Thus, it is possible to estimate the amount of selective attention that was paid to each of the 10 binary features during learning. Formally, the psychological distance between the test stimulus i and the prototype P is given by Equation 1. Here k denotes the dimension (1–10) and w_k denotes the attention weight for the kth dimension ($1 > w_k > 0$; sum to 1). Distances are converted to similarities using the well-established exponential decay similarity function as seen in Equation 2 (Shepard, 1987). Here c denotes the sensitivity ($0 < c < 10$). The predicted probability of responding "A" for test stimulus i is calculated by Equation 3.

$$d_i P = \sum w_k(|x_{ik} - P_{ik}|) \tag{1}$$

$$\eta_i P = e^{-cd_i P} \tag{2}$$

$$P(A|S_i) = \frac{\eta_i P_A}{\eta_i P_A + \eta_i P_B} \tag{3}$$

Differences in salience, such as contrast differences, can elevate a subset of features to a higher priority creating

biased attentional competition (Lee et al., 2012). Although all 10 features are equally relevant to each exemplar's category membership, some features are more salient than others and tend to be selectively attended to across participants. Importantly, salience differences in conjunction with computational models that describe attention to each feature make the prototype learning task an ideal paradigm to test our hypothesis as we are able to examine both impaired and improved attention across salient and minor features within the same study.

Thus, to explore whether long allele carriers would demonstrate heightened attention for the most salient high-priority features at the expense of the least salient low-priority features, attention weights were examined. The most salient feature (most frequent dimension with maximum attention weight across participants) and least salient feature (least frequent dimension with maximum attention weight across participants) of the 10 binary dimensions were computed, and the group means were compared using 2 Sample (general, screened) × 2 *DRD4* status (long carrier, short homozygote) × 2 Feature (minor, salient) ANOVA for Block 1 and a 2 *DRD4* status (long carrier, short homozygote) × 2 Feature (minor, salient) ANOVA samples *t* tests within the screened sample for Block 2.

Memory Span Measures

The traditional method of obtaining an individual's operation span is to add the length of each span that was correctly recalled to the individual's score (Unsworth & Engle, 2005). Thus, correctly recalling a span of seven letters adds 7 points to one's score while incorrectly recalling even one letter in the span results in zero points being added to one's score. A second way of scoring the OSPAN is to simply compute the proportion of correctly recalled letters. We explore both measures of performance in the results using independent samples *t* tests.

Potential Confounds

It is important to carefully examine potential confounding factors such as the distribution of racial and ethnic groups within the sample, differences in fluid cognitive abilities, and personality differences that are associated with the behavior of interest when exploring the relationship between genetic polymorphisms and behavior. To measure these confounds, all participants completed a demographic form indicating their race and ethnicity. They also responded to a series of computer-based questionnaires that included the Center for Epidemiological Studies Depression Scale (CESD) to assess dysphoric mood, which may bias the salience of rewards and punishment (Radloff, 1977), and the Barrett Impulsiveness Scale (BIS-11) to assess novelty seeking, which has been demonstrated to moderate the effects of *DRD4* on attention in some studies (Stanford et al., 2009).

A series of neuropsychological tests was also completed by the screened sample only to assess differences in fluid cognitive abilities. The neuropsychological battery includes the Wechsler Adult Intelligence Scale-Fourth Edition's Digit Span (WAIS-IV) as a measure of working memory without interference from a secondary task and vocabulary as a measure of intelligence (Wechsler, 1981), the Stroop test as a measure response inhibition (Stroop, 1935), and the Wechsler Memory Scale (WMS-IV) as a measure of episodic memory.

Neuropsychological results were collected for the screened sample only and normalized for age and gender using standardized procedures and converted to *Z* scores. After each primary analysis, neuropsychological and personality factors that showed significant differences between *DRD4* long allele carriers and short homozygotes were included in an ANCOVA model to determine whether these effects are robust to these factors. Only those factors that demonstrated significant differences at $p < .05$ were included to avoid overparameterization. Results were also replicated within a White subgroup to ensure that models were not significantly affected by possible population stratification.

RESULTS

Category Learning Results

Block 1: Screened Sample with General Sample Replication

Accuracy. To examine *DRD4*'s influence across screened and unscreened samples, we conducted a 2 Sample (screened, general) × 2 *DRD4* (long carrier, short homozygote) ANOVA on overall accuracy (Figure 2A). There was a main effect of *DRD4* status where long allele carriers ($M = .73$, $SD = 11$) demonstrated better overall Block 1 accuracy than short homozygotes ($M = .70$, $SD = .12$), $F(1, 381) = 4.06$, $p = .045$, $\eta^2 = .01$. However, independent samples *t* tests within the general and screened sample were nonsignificant ($p < .2$). There was no effect of Sample nor interactions.

To examine *DRD4*'s influence across screened and unscreened samples, we conducted a 2 Sample (screened, general) × 2 *DRD4* (long carrier, short homozygote) × 2 Similarity (similar, dissimilar) repeated-measures ANOVA (Figure 2B, C). There is a main effect of *DRD4* status, $F(1, 381) = 4.26$, $p = .04$, $\eta^2 = .01$, where long allele carriers are more accurate ($M = .73$, $SD = .1$) than short homozygotes ($M = .70$, $SD = .12$). In addition, there was a main effect of Similarity, $F(1, 381) = 3.73$, $p < .001$, $\eta^2 = .24$, where accuracy is higher for similar ($M = .78$, $SD = .15$) than dissimilar exemplars ($M = .62$, $SD = .12$). There were no effects of Sample or any other significant effects. The main effect of Similarity held when decomposed in 2 *DRD4* × 2 Similarity ANOVAs within the general, $F(1, 185) = 191.45$, $p < .001$, $\eta^2 = .25$, and screened, $F(1, 196) = 191.3$, $p < .001$, $\eta^2 = .24$,

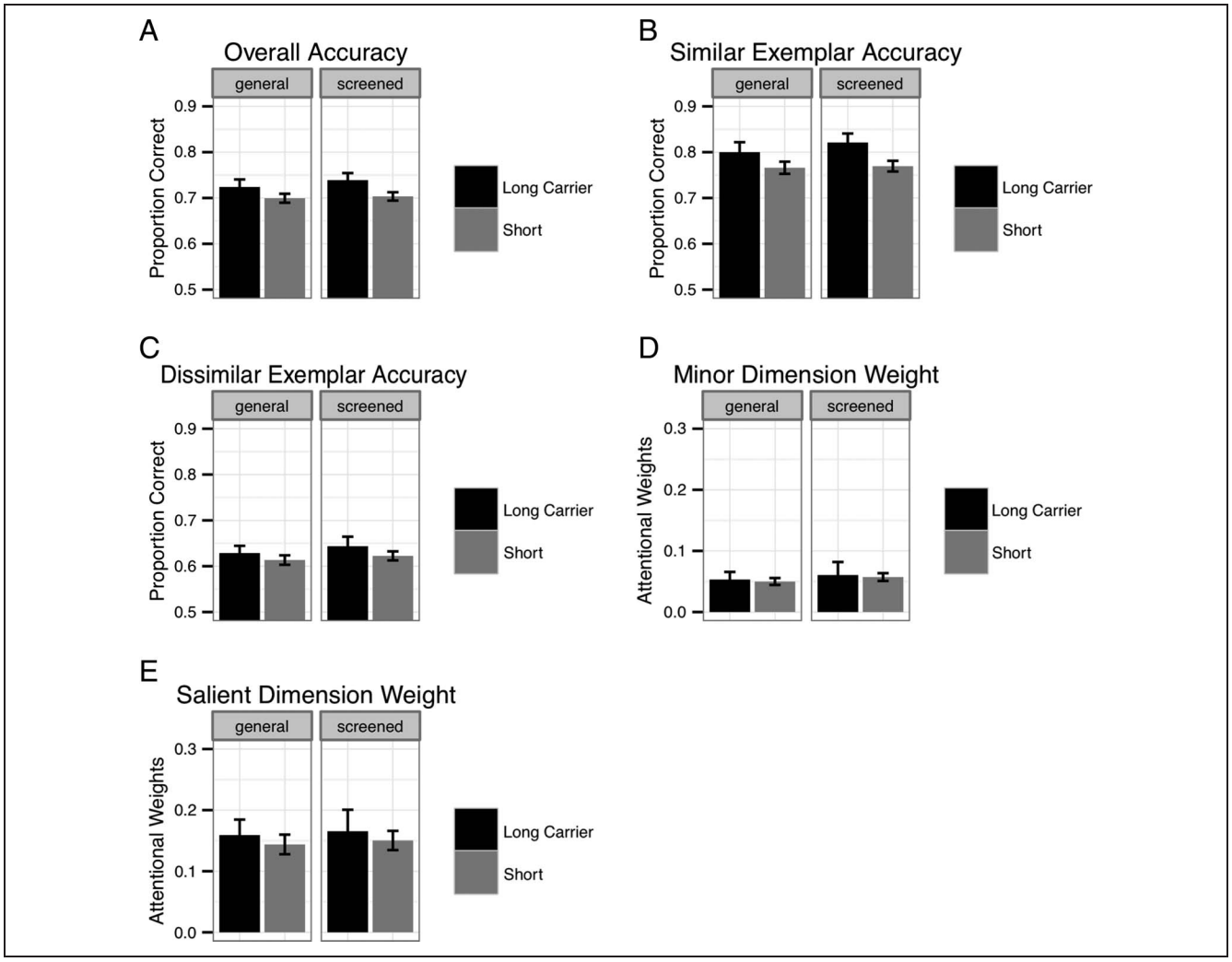

Figure 2. Plots of the results from Block 1 of the category learning task ($N_{screened}$ = 198; $N_{general}$ = 187). (A) Category learning overall accuracy by *DRD4* status, (B) similar exemplar accuracy, and (C) dissimilar exemplar accuracy by *DRD4* status, as well as the mean attention weight for (D) the most minor and (E) the most salient category dimension. Standard error bars included.

samples; however, the main effect of *DRD4* was non-significant within each sample.

Computational modeling: Salience and attention. To determine whether attentional focus for salient and minor features depends on *DRD4* allele status across screened and general samples during early learning, we conducted a 2 *DRD4* (long carrier, short homozygote) × 2 Sample (screened, general) × 2 Feature (salient, minor) mixed effects ANOVA. There was a main effect of Feature, $F(1, 381) = 7.55, p < .001, \eta^2 = .1$, where salient features have higher attentional weight than minor features ($M_{Salient}$ = .15, $SD_{Salient}$ = .19; M_{Minor} = .05, SD_{Minor} = .08) and no other significant effects. The main effect of Feature held in 2 *DRD4* × 2 Similarity ANOVAs within the general, $F(1, 185) = 44.92, p < .001, \eta^2 = .11$, and screened, $F(1, 196) = 32.94, p < .001, \eta^2 = .09$, samples.

Potential confounds. In the general sample, analysis of individual differences revealed no significant differences between *DRD4* groups at the $p < .05$ level; however, there was a marginal difference in impulsivity as measured by the BIS-11 ($p = .06$), which was significant in the screened group (Tables 1 and 3). To ensure our learning effects were not driven by impulsivity, ANCOVA was conducted (with an interaction term between BIS-11 and *DRD4* status) on performance measures and model parameters. Results replicated for overall accuracy, (p = .058) and accuracy for similar exemplars close to the prototypes, ($p = .04$). This pattern of effects held both when including race as a covariate as well as within a subset of White participants ($N_{General}$ = 115, $N_{Selected}$ = 122) for all significant analyses (Table 4).

Block 2: Screened Sample Only

Accuracy. *DRD4* long allele carriers ($M = .75, SD = .09$) were significantly more accurate overall at categorizing exemplars than short homozygotes ($M = .71$, SD = .12), $t(199) = 2.05, p = .04, \eta^2 = .02$ (Figure 3A). To

Table 3. DRD4 Long Carriers and Short Homozygotes Neuropsychological Tests for Category Learning and Memory Span Tasks

	Long Carriers	*Short Homozygotes*
Category Learning: Screened Sample		
Digit Span	0.48 (0.92)	0.27 (0.9)
WAIS Vocabulary†	1.09 (0.63)	0.77 (0.88)
Stroop Interference	0.83 (0.81)	0.63 (0.7)
WMSIII Delayed Recall	0.59 (0.85)	0.42 (0.99)
WMSIII Immediate Recall	0.63 (0.54)	0.45 (0.53)
Composite Memory	0.36 (0.78)	0.2 (0.64)
Memory Span		
Digit Span†	0.92 (0.11)	0.88 (0.18)
WAIS Vocabulary†	0.5 (0.9)	0.21 (0.84)
Stroop Interference†	1.08 (0.62)	0.76 (0.88)
WMSIII Delayed Recall	0.84 (0.8)	0.59 (0.69)
WMSIII Immediate Recall	0.57 (0.84)	0.33 (0.9)
Composite Memory†	0.35 (0.78)	0.14 (6)

Note that the general sample did not undergo neuropsychological testing.

Composite memory is the average z scores across the three memory tests: Digit Span, WMSIII Delayed Recall, and WMSIII Immediate Recall. Standard deviations are listed in parentheses. Independent samples t tests.

*Significant at $p < .05$.

**Significant at $p < .01$.

***Significant at $p < .001$.

†Marginally significant at $p < .10$.

assess whether accuracy effects differed as a function of similarity to the prototype, we conducted a 2 *DRD4* (long carrier, short homozygote) × 2 Similarity to prototype (similar, dissimilar) repeated-measures ANOVA (Figure 3B, C). There was a significant main effect of *DRD4*, $F(1, 199) = 3.96, p = .05, \eta^2 = .01$, where long carriers were more accurate than short homozygotes, and a significant main effect of Similarity, $F(1, 199) = 249.84$, $p < .001$, $\eta^2 = .28$, where accuracy was higher for exemplars that were more similar to the prototype (M = .8, $SD = .15$) than those that were dissimilar (M = .63, $SD = .12$).

Computational modeling: Salience and attention. To determine whether attentional focus for salient and minor features depends on *DRD4* allele status after experience, we conducted a 2 *DRD4* (long carrier, short homozygote) × 2 Feature (salient, minor) mixed effects ANOVA for Block 2. There was a significant main effect of Feature, $F(1, 199) = 40.20, p < .001, \eta^2 = .11$, qualified by a significant interaction between feature and *DRD4* status where long carriers have more polarized attention than short homozygotes, $F(1, 199) = 4.23, p = .04, \eta^2 = .01$. To decompose the effects, we conducted independent samples t tests within each feature type between genetic groups. Although nonsignificant, long allele carriers demonstrated some evidence of heightened attention for salient features ($M_{\text{Long Carrier}} = .22$, $SD = .23$, $M_{\text{Short}} = .16$, $SD = .20$; Figure 3E), $t(199) = 2.51, p = .13, \eta^2 = .01$,

Table 4. Average Dependent Measures for the White Subset of *DRD4* Long Carriers and Short Homozygotes for the Category Learning and Memory Span Tasks

	Long Carriers	*Short Homozygotes*
Category Learning: Block 1		
General Sample		
Overall accuracy	0.7 (0.13)	0.68 (0.17)
Similar exemplar accuracy	0.77 (0.18)	0.74 (0.21)
Dissimilar exemplar accuracy	0.61 (0.11)	0.61 (0.15)
Salient feature weight	0.04 (0.06)	0.06 (0.07)
Minor feature weight	0.19 (0.4)	0.18 (0.38)
Screened Sample		
Overall accuracy	0.71 (0.16)	0.7 (0.13)
Similar exemplar accuracy	0.77 (0.2)	0.76 (0.17)
Dissimilar exemplar accuracy	0.63 (0.15)	0.63 (0.13)
Salient feature weight	0.05 (0.1)	0.05 (0.07)
Minor feature weight	0.13 (0.34)	0.19 (0.4)
Category Learning: Block 2		
Screened Sample		
Overall accuracy*	0.78 (0.1)	0.71 (0.12)
Similar exemplar accuracy*	0.86 (0.13)	0.79 (0.15)
Dissimilar exemplar accuracy	0.67 (0.12)	0.62 (0.13)
Salient feature weight	0.19 (0.2)	0.15 (0.19)
Minor feature weight*	0.03 (0.04)	0.07 (0.09)
Memory Span		
Score**	50 (12.98)	41.94 (16.31)
Proportion correct*	0.85 (0.09)	0.8 (0.15)

Standard deviations are listed in parentheses. Independent samples t tests.

*Significant at $p < .05$.

**Significant at $p < .01$.

***Significant at $p < .001$.

†Marginally significant at $p < .10$.

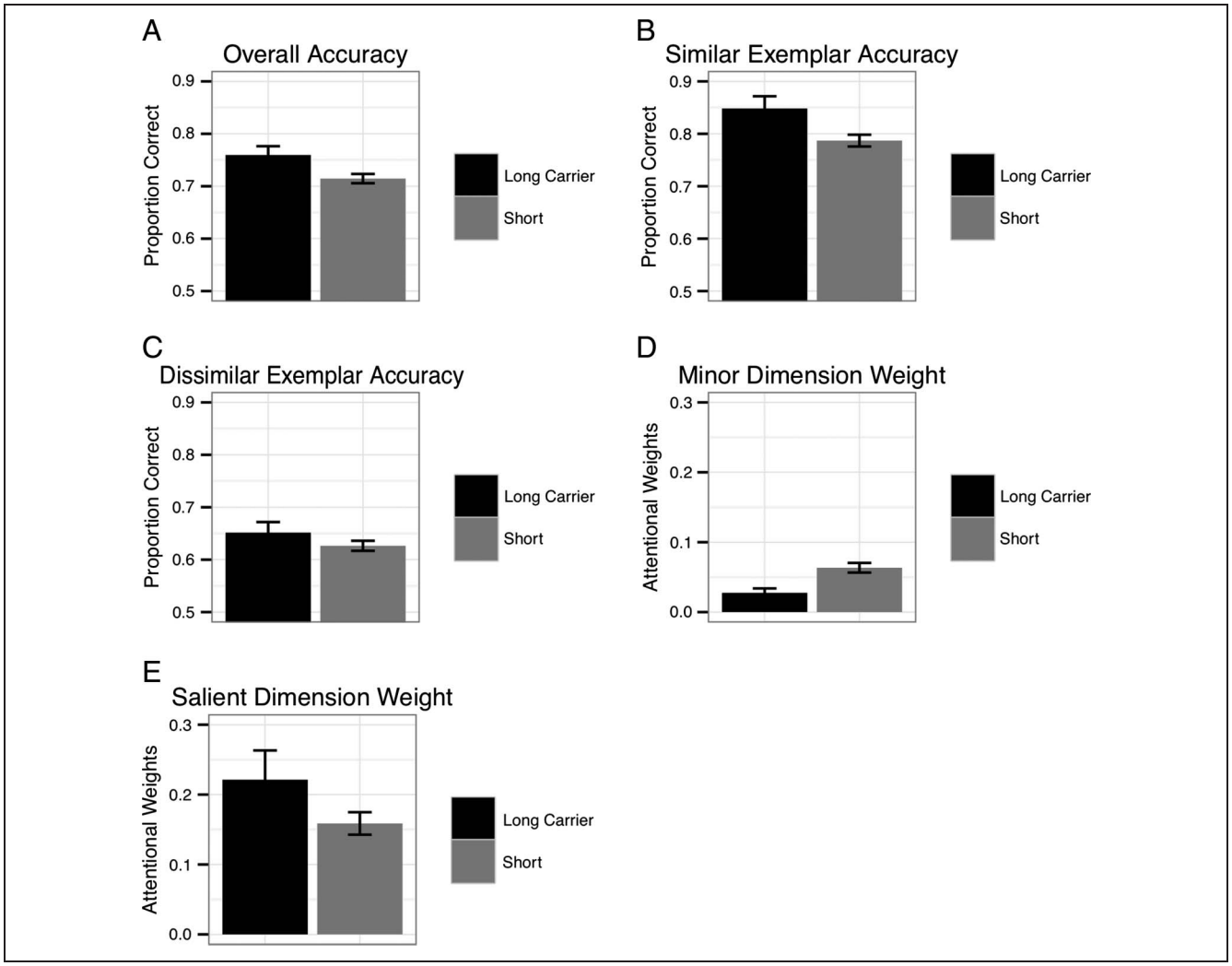

Figure 3. Plots of the results from Block 2 of the category learning task (n = 201). (A) Category learning overall accuracy, (B) similar exemplar accuracy, and (C) dissimilar exemplar accuracy by *DRD4* status, as well as the mean attention weight for (D) the most minor and (E) the most salient category dimension are shown by *DRD4* status. Standard error bars included.

and significantly impaired attention for minor features, $t(199) = 2.18, p = .03, \eta^2 = .02$, relative to short homozygotes ($M_{\text{Long Carrier}} = .03, SD = .03, M_{\text{Short}} = .06, SD = .09$; Figure 3D). To verify that narrow attentional weight is important during reflective category learning, maximum attention weight was correlated with prototype accuracy across groups. Narrow attention was positively correlated with accuracy, $r(199) = .21, p = .002$.

Potential confounds. Analysis of individual differences in impulsivity as measured by the BIS-11 was significantly greater for long allele carriers relative to short homozygotes,

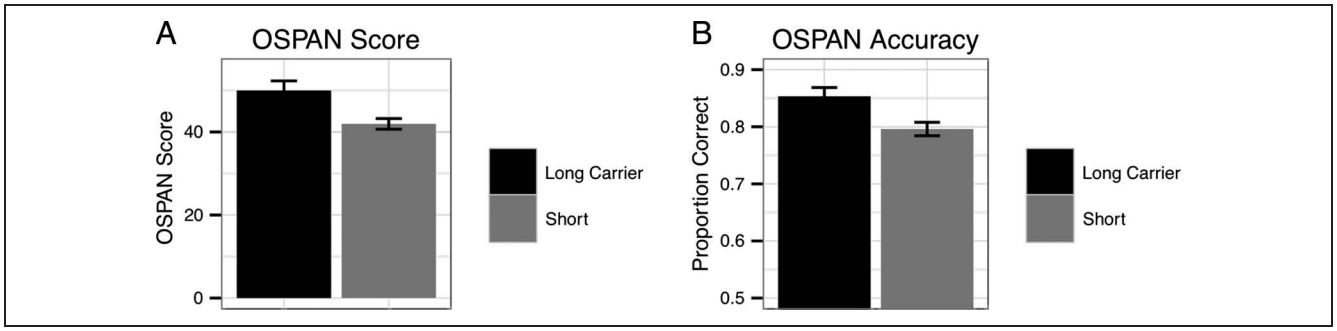

Figure 4. Behavioral results from the memory span task (OSPAN; n = 193). (A) OSPAN scores and (B) OSPAN overall accuracy are shown by *DRD4* status. Standard error bars included.

$t(190) = 3.31$, $p = .001$, with no other significant differences in personality or neuropsychological variables at the $p < .05$ level (Table 1, Table 3). To ensure our learning effects were not driven by impulsivity, ANCOVA was conducted (with an interaction term between BIS-11 and *DRD4* status) on performance measures and model parameters. *DRD4*'s effect on overall accuracy ($p = .04$), similar exemplars ($p = .03$), and minor weight ($p = .04$) remained significant. These effects held both when including race as a covariate as well as within a subset of White participants ($n = 124$) for all analyses (Table 4).

Memory Span Task

Examining scores for the traditional OSPAN measure where errors result in a span score of 0, long allele carriers scored significantly higher ($M = 50.00$, $SD = 12.97$) than short homozygotes ($M = 41.94$, $SD = 16.31$), $t(191) = 2.63$, $p = .009$, $\eta^2 = .04$ (Figure 4A). The proportion of correctly recalled letters was also significantly higher for long allele carriers ($M = .85$, $SD = .15$) than for short homozygotes ($M = .80$, $SD = .08$), $t(191) = 2.09$, $p = .04$, $\eta^2 = .02$ (Figure 4B).

Potential confounds. Other studies that have examined the OSPAN task have found that performance is dependent on two dissociable processes—the interplay of executive attention and working memory during updating and STM capacity (Conway et al., 2005). An examination of Table 3 indicates that there are no significant differences in multiple measures of memory between *DRD4* polymorphisms (working memory, STM, episodic memory). This indicates that memory differences alone are not driving these effects. Furthermore, during the digit span task participants are asked to remember sequences of three to nine numbers without interference from a secondary task. The *DRD4* long allele advantage is absent in the absence of primary and secondary priorities as seen in the OSPAN task.

Analysis of individual differences in impulsivity as measured by the BIS-11 was significantly greater for long allele carriers relative to short homozygotes, $t(190) = 3.31$, $p = .008$, with no other significant differences in personality or neuropsychological variables at the $p < .05$ level (Table 1, Table 3). To ensure our learning effects were not driven by impulsivity, ANCOVA was conducted (with an interaction term between BIS-11 and *DRD4* status) on performance measures and model parameters. *DRD4*'s effect on OSPAN score ($p = .008$), and overall accuracy ($p = .03$) remained significant. These effects held both when including race as a covariate as well as within a subset of White participants ($n = 118$) for all analyses (Table 4).

DISCUSSION

Prior findings on the role of *DRD4* in modulating attention have been mixed, with some work finding a link between the long allele and deficits in attention and other work finding a link between the long allele and heightened attention to contextually relevant information such as addictive cues. We tested a recently developed theory that suggests that *DRD4* serves as a "plasticity" gene, rather than a "risk" gene, where the long allele is associated with heightened attention to goal-directed high-priority items and impaired attention to low-priority items in the environment. Under this hypothesis, heightened attention to high-priority items biases cognitive resources resulting in greater plasticity in learning and memory for high-priority items and reduced plasticity for low-priority items. Thus, although the long allele is generally characterized as a deleterious polymorphism, if high-priority items are critical for performance we expect long allele carriers to outperform short homozygotes. Given the predominant transcription of *DRD4* in prefrontal areas (Oak et al., 2000), we propose that differences will be driven by goal directed processes.

In this study, we examined two domains of cognition where task performance was supported by greater attention to either goal-related salient features in a category learning task or goal-related primary items in a sequential memory task. Long allele carriers were better able to attend to these high-priority stimuli and, as a result, outperformed short allele homozygotes in both tasks. Long allele carriers also demonstrated impaired attention for minor features, which was not related to performance in these tasks. Importantly, this advantage generalized in two cognitive domains—learning and memory.

In addition, these studies examine both immediate (exemplar categorization) and long-run (sequential memory) goal-directed processes. During category learning, each exemplar was processed alone without secondary distraction; however, each stimulus was complex and had many perceptual features that were more or less salient. Immediate focus on a small number of features was critical to create verbal rules that described the category structure. The benefits of carrying the long allele are apparent during early learning where accuracy is greater across a screened sample and a more general replication sample. Interestingly, genetic differences in attention become apparent with experience. In line with our plasticity hypothesis, computational models indicated that screened long allele carriers had biased attention to high-priority salient features at the expense of low-priority minor features relative to short homozygotes in the second block of learning. Thus, long allele carriers' greater plasticity during learning was due to exaggerated biased competition for priority items. Interestingly, impaired attention to minor features may help explain attentional deficits that are sometimes seen in long allele carriers, particularly those with ADHD (Kegel & Bus, 2012; Bidwell et al., 2011).

During the OSPAN memory task, on the other hand, priority items must be maintained across three to seven trials in the face of interference from a distracting secondary

task. The OSPAN task has been extensively used to measure working memory capacity, which has been strongly linked with executive attention (Engle, 2002). A distinction has often been made in the literature between working memory capacity or executive attention and short-term working memory (STM) span. Working memory and executive attention require maintenance of high-priority items in memory in the face of interference, whereas short-term working memory refers to basic memory processes like simply recalling a span of digits in order in the Digit Span task. We observed a strong effect of *DRD4* in the OSPAN task, a task that measures working memory capacity and executive attention, but not in the Digit Span task, which measures only STM ability. This suggests that our findings were due to differences in executive attention, rather than differences in STM. Future work should extend these findings into other cognitive domains such as decision-making and other category learning tasks to further examine the role of *DRD4* in attention, learning, and memory-related processes.

It is important to note that heightened attention to high-priority items in the environment may explain findings from several studies that have found heightened cravings for addictive substances in *DRD4* long allele carriers (reviewed in McGeary, 2009). Such cravings may result from heightened attention toward fulfilling the goal of using the desired substances. Additionally, our findings may be relevant to work that has shown an association between ADHD and prolonged video game and internet use (Chan & Rabinowitz, 2006). Children with ADHD may have trouble focusing on stimuli that do not seem contextually relevant or interesting (i.e., "boring") or that are not tied to goal-related processes but may show heightened attention to stimuli that are interesting or engaging like video games.

It is also interesting to note that long allele carriers have significantly higher impulsivity than short homozygotes as measured by the BIS-11. This might suggest that the impulsivity personality trait heightens attention to dominant items and reduces attention to minor items and is driving our effects. However, in our analysis, advantages in both category learning and memory spans in long allele carriers were robust when controlling for impulsivity. Under our hypothesis, we speculate that differences in impulsive behavior might emerge when long allele carriers are drawn more strongly to novel items, which have been demonstrated to have higher-priority than mundane items (Itti & Baldi, 2006; Ranganath & Rainer, 2003). Together, these findings lend support to prior literature that has linked *DRD4* with increased impulsivity or novelty seeking but does not support the relationship with behavior (Gizer & Waldman, 2012; Ray et al., 2009; Munafò et al., 2008; Laucht et al., 2005). However, the literature is still mixed and more work needs to be done to determine whether effects of impulsivity and novelty seeking mediate behavioral outcomes in long allele carriers and how clinical symptoms interact with these effects.

As with all genetic association studies, the associations reported here may be driven by an unmeasured third variable (including but not limited to; another genetic variant in linkage disequilibrium with *DRD4* exon III, population stratification, or environmental influences). The inclusion of ancestry informative markers could help reduce this threat (Kosoy et al., 2009). Future directions that manipulate the dopaminergic system through pharmacology or dietary depletion may provide supporting evidence for these findings (e.g., use of a medication with D4 properties such as olanzapine to lend credence to initial association findings; Hutchison et al., 2003). Similarly, more comprehensive molecular characterization of the *DRD4* and other genes within the candidate biological system may increase confidence in and understanding of these relationships. Finally, given the departure from HWE, the sample recruited for this study may not represent a random sample of the population, and therefore, the results should be considered with caution. There are a number of situations that may lead to departures from HWE (e.g., genotyping error, nonrandom mating, selected samples, etc.) and it is not clear which factor may be responsible. Genotyping error is highly unlikely given the quality control checks in place and numerous other samples genotyped by this lab that have not deviated from HWE (genotyped for this same polymorphism). Furthermore, the sample for this study was recruited from the community and was not selected on any phenotype that would drive such results; thus, it is unlikely that the deviation from HWE is because of sample selection.

Although we do demonstrate attentional impairments for minor items in long allele carriers, another limitation of the current study is that it does not demonstrate impaired performance during a task where attention to high-priority items is detrimental. Future research would do well to examine whether long allele carriers demonstrate heightened attention to priority features and impaired attention to minor features when in tasks that are both supported and impaired by this kind of attention to priority features. Finally, despite theoretically consistent findings across two studies that are based on biologically supported hypotheses, replication of these relationships in separate larger samples is warranted.

Conclusions

The *DRD4* long allele has been positively selected, which suggests that it likely confers some type of adaptive advantage (Ding et al., 2002; Oak et al., 2000). Although the long allele has been associated with attentional disorders in prior work (Gizer & Waldman, 2012; Bidwell et al., 2011; Gizer et al., 2009; Munafò et al., 2008; Laucht et al., 2005, 2007; Langley et al., 2004; Hutchison et al., 2003; Kustanovich et al., 2003; Manor et al., 2001; Swanson et al., 2000), our results add to a growing body of research that suggests that the presence of this allele may confer advantages in certain situations and may interact

with the environment and other contextual and goal-related factors to modulate goal-directed attention. Future work should continue to examine whether this gene does indeed serve as a plasticity gene, rather than one that simply confers risk, by considering the important interplay between genetics and environment in modulating attention.

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