The Dopamine D4 Receptor Gene and Moderation of the Association Between Externalizing Behavior and IQ

*Colin G. DeYoung, PhD; Jordan B. Peterson, PhD; Jean R. Séguin, PhD; Jose Maria Mejia, MD;
Robert O. Pihl, PhD; Joseph H. Beitchman, MD; Umesh Jain, MD, PhD; Richard E. Tremblay, PhD;
James L. Kennedy, MD, MSc; Roberta M. Palmour, PhD*

Background: Dopaminergic neurotransmission is implicated in externalizing behavior problems, such as aggression and hyperactivity. Externalizing behavior is known to be negatively associated with cognitive ability. Activation of dopamine D4 receptors appears to inhibit the functioning of the prefrontal cortex, a brain region implicated in cognitive ability. The 7-repeat allele of the dopamine D4 receptor gene produces less efficient receptors, relative to other alleles, and this may alter the effects of dopamine on cognitive function.

Objective: To examine the influence of a polymorphism in the third exon of the dopamine D4 receptor gene on the association between externalizing behavior and IQ.

Design: In 1 community sample and 2 clinical samples, the presence or absence of the 7-repeat allele was examined as a moderator of the association between externalizing behavior and IQ; the strength of this effect across samples was estimated meta-analytically.

Patients: Eighty-seven boys from a longitudinal community study, 48 boys referred clinically for aggression, and 42 adult males diagnosed with attention-deficit/hyperactivity disorder.

Main Outcome Measures: IQ scores and observer ratings of externalizing behavior were taken from existing data sets.

Results: Among individuals lacking the 7-repeat allele, externalizing behavior was negatively correlated with IQ (mean $r=-0.43$; $P<.001$). Among individuals having at least 1 copy of the 7-repeat allele, externalizing behavior and IQ were uncorrelated (mean $r=0.02$; $P=.45$). The difference between these correlations was significant ($z=-2.99$; $P<.01$).

Conclusions: Allelic variation of the dopamine D4 receptor gene appears to be a genetic factor moderating the association between externalizing behavior and cognitive ability. This finding may help to elucidate the adaptive value of the 7-repeat allele.

Arch Gen Psychiatry. 2006;63:1410-1416

Author Affiliations: Department of Psychology (Drs DeYoung and Peterson) and Centre for Addiction and Mental Health and Department of Psychiatry (Drs Beitchman, Jain, and Kennedy), University of Toronto, Toronto, Ontario; Department of Psychiatry (Dr Séguin) and Departments of Pediatrics, Psychology, and Psychiatry (Dr Tremblay), Université de Montreal, Montreal, Quebec; University of Alberta, Alberta Hospital Edmonton (Dr Mejia); and Departments of Psychology and Psychiatry (Dr Pihl) and Departments of Biology, Psychiatry, and Human Genetics (Dr Palmour), McGill University, Montreal.

EXTERNALIZING BEHAVIOR REfers to a broad category of behaviors involving disinhibition and approach, including aggression, antisocial behavior, hyperactivity, and impulsivity.[1,2] Externalizing behavior problems are typically associated with cognitive impairment, and the negative association between externalizing behavior and IQ is particularly well established.[3-7] In attention-deficit/hyperactivity disorder (ADHD), this negative association appears to be primarily genetically based.[5] The neuromodulator dopamine has been implicated in various forms of externalizing behavior[8-11] and is known to affect cognitive function.[12] Localization of the dopamine D4 receptor in the prefrontal cortex[13-15] and findings that specific blockade of D4 receptors improves some cognitive impairments[16-18] prompted our investigation of the possibility that allelic variation in the dopamine D4 receptor gene (*DRD4*) might moderate the negative association between externalizing behavior and IQ.

DRD4 contains a functional polymorphism consisting of a variable number of tandem repeats of a 48–base pair sequence in the third exon of the gene.[19] The 7-repeat allele (*DRD4-7*), which is present in about 20% of the population worldwide but varies widely in frequency geographically,[20] has been associated with ADHD,[21] novelty seeking,[22,23] and alcohol and drug abuse.[24,25] However, findings regarding these phenotypic associations with *DRD4-7* have not been consistently replicated.[26-28] The best-established finding to date is the association between *DRD4-7* and

ADHD.[29] *DRD4-7* is approximately twice as prevalent in ADHD probands and appears to be associated with 25% to 50% of the genetic risk for ADHD.[29,30] Inconsistencies in past findings may reflect, in part, a complex relation between *DRD4* variation and externalizing behavior problems. A review of recent research on the properties and functions of the dopamine D4 receptor may allow the generation of more sophisticated hypotheses regarding likely phenotypic associations with *DRD4-7*.

The D4 receptor is heavily expressed in the prefrontal cortex,[13-15] where it appears to modulate excitatory signaling.[16] This suggests that D4 receptors may be involved in the dopaminergic modulation of the cognitive functions of the dorsolateral prefrontal cortex, which include working memory and have been linked to general cognitive ability and IQ.[12,31-33] Dopamine has a generally salutary effect on these cognitive functions, but the effect exhibits an inverted U–shaped function, with impairments evident at high, as well as low, levels of dopamine.[12] Some of the negative effects of excess dopamine on cognition may be produced by the action of D4 receptors.[12] Clozapine, an atypical antipsychotic with a much stronger affinity for D4 than for other dopamine receptors, appears to improve the cognitive symptoms of schizophrenia, a disorder that involves irregularities of dopaminergic transmission.[16] In contrast, traditional antipsychotics, which do not preferentially target D4 receptors, do not improve these cognitive symptoms.[16] Additionally, selective D4 receptor antagonists appear capable of reversing pharmacologically induced cognitive deficits in monkeys.[17,18] Further, it appears that D4 blockade is only effective in producing cognitive benefits when other dopamine receptors are not blocked, suggesting a unique role for D4 among dopamine receptors in inhibiting cognitive processes.[16,18]

Relative to the 2 other most common *DRD4* alleles (2- and 4-repeat) and to the 10-repeat allele, *DRD4-7* produces less efficient receptors, with decreased potency for coupling with adenylate cyclase, part of the receptor's second messenger system.[34,35] *DRD4-7* also appears to decrease gene expression, which would further diminish the effects of D4 receptors in the brain.[36] Because of these reductions in D4 function and expression, *DRD4-7* may act as an endogenous D4 suppressor; carriers of this allele seem likely to exhibit lower levels of the processes associated with D4 receptors. One might expect some similarity, therefore, between the effects of D4 antagonists and the *DRD4-7* phenotype. Because D4 antagonists appear to alleviate some cognitive impairments, *DRD4-7* could conceivably attenuate negative associations between cognitive ability and behaviors associated with increased dopaminergic activity, such as externalizing behavior.[8-11] (Although dopamine agonists, such as methylphenidate, are used in relatively low doses to reduce externalizing behavior, they appear to produce this effect by decreasing net dopaminergic activity through activation of presynaptic inhibitory autoreceptors.[11]) Consistent with this possibility, Swanson and colleagues[37] found that among children diagnosed with ADHD, those who had *DRD4-7* did not show deficits relative to controls on 3 neuropsychological tests of the attentional network involving dorsolateral prefrontal cortex, whereas those who did not have *DRD4-7* did show deficits.

We tested the hypothesis that *DRD4* variation might moderate the commonly reported negative association between externalizing behavior and IQ,[3-6] using 3 male samples with high mean levels of externalizing behavior. We then employed meta-analysis to obtain an estimate of effect size across all 3 samples.

METHODS

GENOTYPING

For all 3 samples, DNA was isolated from peripheral leukocytes using standard procedures and genotyped following amplification of the region in the third exon of the *DRD4* gene containing the 48–base pair variable number of tandem repeats, using a modification of the methods of Lichter and colleagues.[38] The forward and backward primers were D4-3 (5′-GCGACTACGTGGTCTACTCG-3′) and D4-42 (5′-AGGACCCTCATGGCCTTG-3′). The polymerase chain reaction was performed in 25 µL (final volume) of Taq polymerase buffer (50 mmol/L potassium chloride, 10 mmol/L Tris-chloride, pH=9, 1 mmol/L magnesium chloride, and 1% Triton X-100), containing 10% dimethyl sulfoxide; 200 µm each of deoxyadenosine, deoxycytidine, and deoxythymidine triphosphates; 100 µm deoxycyguanosine triphosphate; 100 µmol/L deaza-deoxyguanosine triphosphate; 500 ng of each primer; and 1 ng of DNA. Conditions for amplification were 40 cycles of 20 seconds at 95°C, 20 seconds at 54°C, and 40 seconds at 72°C, followed by a final extension of 4 minutes at 72°C, using an MJ Research Inc PT-100 thermocycler (Waltham, Mass). Polymerase chain reaction products were analyzed after electrophoresis (10% nondenaturing polyacrylamide or 3.5% agarose) and ethidium bromide staining. Participants were considered *DRD4-7* positive if they had at least 1 copy of *DRD4-7* and *DRD4-7* negative if they did not.

PARTICIPANTS

Sample 1

Genotypes were available for 50 male children who were referred clinically to participate in a study of aggression at the Centre for Addiction and Mental Health in Toronto, Canada. They ranged in age from 5 to 15 years (mean, 9.89±2.53 years). Forty were white (80%), 8 were African American (16%), 1 was East Asian (2%), and 1 was Native American (2%). The Asian and Native American participants were excluded from analysis because of population stratification; *DRD4-7* frequencies are very different in East Asian and Native American populations than in white and African American populations.[20] Because the frequency of *DRD4* alleles is very similar in white and African American populations, inclusion of African Americans does not present a significant risk of population stratification. Nonetheless, we note how our results would have changed if African American participants had been excluded. Twenty-eight boys were *DRD4-7* negative (58%) and 20 were *DRD4-7* positive (42%). Twelve of these boys were being treated with a psychostimulant (eg, methylphenidate) at the time of assessment, but treatment status was not significantly related to *DRD4-7* status ($\chi^2_1=1.87$; $P=.17$).

Sample 2

Genotypes were available for 67 male adults diagnosed with ADHD in adulthood who participated in a study of pharmacological treatments for ADHD at the Centre for Addiction and Mental Health. Of these, 42 had observer ratings from which

Table 1. Instruments Used to Assess Externalizing Behavior (EB) and IQ

Sample	Instrument
Sample 1	EB: Parent and teacher ratings of aggressive and delinquent behaviors on the Child Behavior Checklist and Teacher Report Form.[41] Parent ratings of child and adolescent indicators of psychopathy.[42]
	IQ: WISC-III or WPPSI-R[43,44]; information and similarities subtests (24 participants); vocabulary and picture completion subtests (16); vocabulary (4); full-scale IQ from prior clinical testing (6).
Sample 2	EB: Spouse or mother ratings on 3 items: anger control, speech control, and impulsivity level ($\alpha = .79$).
	IQ: Full-scale WAIS-III.[45]
Sample 3	EB: Teacher ratings on aggression, opposition, and hyperactivity scales at age 6 y and yearly from age 10 to 14 y.[1,7,39,40]
	IQ: WISC-R Vocabulary and Block Design subtests[46]; yearly from age 9 to 12 y and at age 15 y; mean number of IQ assessments, 2.47 (SD = 1.67).[40,47]

Abbreviations: WAIS-III, Wechsler Adult Intelligence Scale, Third Edition; WISC-III, Wechsler Intelligence Scale for Children, Third Edition; WISC-R, Wechsler Intelligence Scale for Children–Revised; WPPSI-R, Wechsler Preschool and Primary Scale of Intelligence–Revised.

an index of externalizing behavior could be calculated. They ranged in age from 18 to 56 years (mean, 35.17±10.22 years). Forty-one (98%) were white and 1 (2%) was African American. Twenty-nine (69%) were *DRD4-7* negative and 13 (31%) were *DRD4-7* positive. Externalizing behavior and IQ were assessed prior to all pharmacological treatment.

Sample 3

Genotypes were available for 87 boys participating in a longitudinal study of French-speaking white boys who started kindergarten in 1983 in the 53 lowest socioeconomic status schools of the Catholic School Commission of Montreal, Montreal, Canada.[39] Genotyping was done at age 17 years, recruiting from a sample of 203 boys who had been selected from the longitudinal cohort, primarily on the basis of teacher ratings of physical aggression at ages 6, 10, 11, and 12 years, to participate in laboratory studies at 15 years.[40] Nonaggressive boys had teacher-rated aggression scores below the 70th percentile at all assessment points and constituted 35% of the complete longitudinal sample. Unstable-aggressive boys exceeded the 70th percentile for aggression at 1 or 2 assessment points and constituted 46% of the complete longitudinal sample. Stable-aggressive boys had aggression scores above the 70th percentile at age 6 years and at least twice more from ages 10 to 12 years and constituted 19% of the complete longitudinal sample. In the genotyped sample, 29 boys (33%) were nonaggressive, 29 were unstable aggressive, and 29 were stable aggressive. Fifty-seven boys (66%) were *DRD4-7* negative and 30 (34%) were *DRD4-7* positive. *DRD4-7* status was unrelated to physical aggression category ($\chi^2_2=1.22$; $P=.53$). Six boys were being treated with a psychostimulant at 1 or more assessment points (an additional 6 did not have treatment status reported). Treatment status was unrelated to *DRD4-7* status ($\chi^2_1=0.00$; $P=.95$). Not surprisingly, treatment status was significantly linearly related to aggression category; 2 of the 6 boys undergoing treatment were unstable aggressive and 4 were stable aggressive ($\chi^2_1=4.11$; $P<.05$).

BEHAVIORAL AND COGNITIVE ASSESSMENT

Assessments of externalizing behavior and IQ were made using the instruments described in **Table 1**. Assessments took place at time of entry to the studies, unless otherwise noted. In all cases where multiple assessments of either construct were available, they were standardized and averaged to yield a single score. Full-scale IQ scores in samples 1 and 3 were estimated based on scores from the administered subtests. IQ estimates of this sort typically correlate at approximately $r=0.90$ with full-scale IQ, even when based on a single administration; this is a common method for assessing cognitive ability while conserving time and resources.[5,48] IQ is highly heritable and stable over time, so minor differences in time of administration relative to assessments of externalizing behavior should not reduce the sensitivity of our analyses.[5,49]

RESULTS

Figure 1 shows the main finding of interest, confirming in all 3 samples our hypothesis that possession of the *DRD4-7* allele attenuates the association between externalizing behavior and IQ. Only in the *DRD4-7*–negative groups was there a significant negative correlation between these 2 variables. Because different instruments and assessment techniques were used in the 3 samples, the Schmidt-Hunter method of meta-analysis was used to calculate pooled effect sizes.[50] Correlations between externalizing behavior and IQ were weighted by sample size and combined for each genotype group. The mean n-weighted (population-weighted) r for the *DRD4-7*–negative group ($n=114$) was -0.43 ($P<.001$), while for the *DRD4-7*–positive group ($n=63$) it was 0.02 ($P=.45$). These effect sizes differed significantly between the genotype groups ($z=-2.99$; $P<.01$). (All P values are 2 tailed, unless noted otherwise.)

SAMPLE 1

The mean estimated IQ across both genotype groups was 99.29 (SD=12.97; range, 70-127). Boys who were being treated with psychostimulants did not differ significantly in IQ or externalizing behavior from those who were not: IQ, $t_{48}=-0.17$, $P<.86$; externalizing behavior, $t_{48}=-0.35$, $P=.73$. The genotype groups did not differ significantly in IQ or externalizing behavior (**Table 2**), and the correlation between IQ and externalizing behavior when both genotype groups were combined was not significant ($r=-0.20$; $P=.18$). If the 8 African American participants were excluded from the primary analysis, the correlation in the *DRD4-7*–positive group remained the same as that reported in Figure 1A; in the *DRD4-7*–negative group, it changed only slightly, from −0.38 to −0.34.

SAMPLE 2

The mean full-scale IQ across both genotype groups was 113.48 (SD=14.00; range, 79-143). The genotype groups did not differ significantly in IQ or externalizing behavior (Table 2). The correlation between IQ and externalizing behavior in the full sample was significant ($r=-0.32$; $P<.05$), but weaker than the correlation in the *DRD4-*

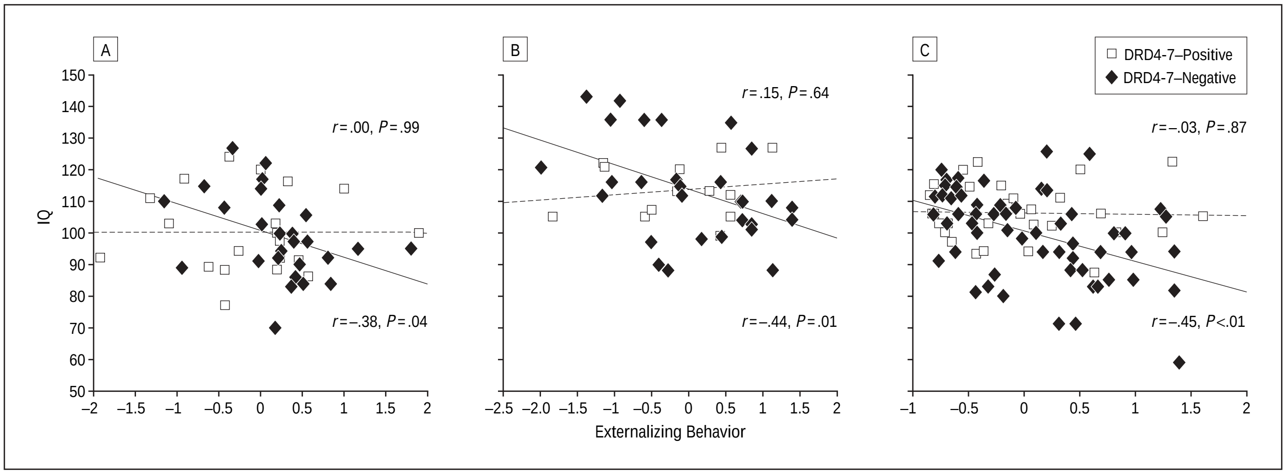

Figure 1. Association between externalizing behavior (standardized within each sample) and IQ in 3 male samples, as a function of dopamine D4 receptor 7-repeat allele (*DRD4-7*) status. A, Sample 1: aggressive children (n=48). B, Sample 2: adult attention-deficit/hyperactivity disorder (n=42). C, Sample 3: low economic status community child sample (n=87). All *P* values are 2-tailed.

Table 2. Means (SDs) of IQ and Externalizing Behavior as a Function of *DRD4-7* Status

	***DRD4-7*–Negative**		***DRD4-7*–Positive**			
Sample	**No.**	**Mean (SD)**	**No.**	**Mean (SD)**	***df***	**t**
Sample 1	28		20			
IQ		98.71 (13.10)		100.10 (13.07)	46	−0.36
EB		0.22 (0.59)		−0.09 (0.85)	46	1.51
Sample 2	29		13			
IQ		113.45 (15.94)		113.54 (9.16)	40	−0.02
EB		0.02 (0.90)		−0.15 (0.85)	40	0.64
Sample 3	57		30			
IQ		99.60 (14.04)		106.24 (8.90)	81.92*	−2.69†
EB		0.08 (0.65)		−0.05 (0.69)	85	0.82

Abbreviations: *DRD4-7*, dopamine D4 receptor 7-repeat allele; EB, externalizing behavior.
*Corrected for unequal variances according to the Leven test of equality of variances (F = 6.99; $P<.05$).
†$P<.01$.

7–negative group alone, which is reported in Figure 1B. If the 1 African American participant was excluded, the only change was in the *DRD4-7*–negative group, in which the correlation rose from −0.44 to −0.45.

SAMPLE 3

The mean estimated IQ across both genotype groups was 101.89 (SD=12.85; range, 59-126). The 6 physically aggressive boys who were treated with psychostimulants did not differ significantly in IQ from the physically aggressive boys who were not treated ($t_{51}=1.26$; $P=.21$). The genotype groups differed significantly in IQ but did not differ in externalizing behavior (Table 2). The correlation between IQ and externalizing behavior when both genotype groups were combined was significant ($r=-0.34$; $P<.05$) but was weaker than the correlation in the *DRD4-7*–negative group alone, which is reported in Figure 1C.

The physical aggression, opposition, and hyperactivity scales, which were combined to yield a single externalizing behavior score for sample 3, were also examined separately to determine whether the moderating effect of *DRD4-7* was similar for different types of externalizing behavior. All 3 scales showed the same pattern as the composite score: significant negative correlations with IQ in the *DRD4-7*–negative group ($r=-0.42$, −0.44, and −0.37, respectively; $P<.01$) and no correlations with IQ in the *DRD4-7*–positive group ($r=-0.04$, 0.04, and −0.09, respectively; $P>.60$).

To examine more closely the significant difference in IQ between genotypes in this sample, boys were grouped according to the physical aggression categories by which they were originally selected for laboratory studies. (As these categories were based on the stability of aggression longitudinally, they were not applicable in samples 1 and 2.) The regression lines in Figure 1C suggest that the 2 genotype groups are more likely to differ significantly in IQ among boys higher in externalizing behavior, and this hypothesis is supported in **Figure 2**, which shows mean IQ for each of the 3 aggression categories, broken down by genotype group. An analysis of variance comparing 3 aggression categories with 2 *DRD4-7* status categories revealed significant main effects of genotype and aggression category on IQ: genotype, $F_1=5.42$, $P<.05$; aggression category, $F_2=5.06$, $P<.01$. The effect of the interaction between aggression category and

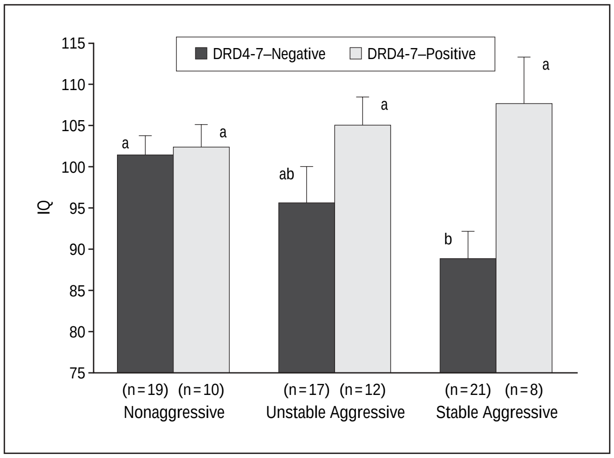

Figure 2. Sample 3. Mean estimated IQ as a function of physical aggression category and dopamine D4 receptor 7-repeat allele (*DRD4-7*) status. Groups not sharing a superscript differ significantly ($P<.05$).

DRD4-7 status neared 1-tailed significance: $F_2=2.16$, $P=.06$ (a 1-tailed test is appropriate because we could predict this effect based on the results in Figure 1C). Planned comparisons revealed that the significant difference in IQ between *DRD4-7*–negative and *DRD4-7*–positive groups was found only in the stable-aggressive group (Figure 2).

COMMENT

In 3 male samples, the association between externalizing behavior and IQ was moderated by the presence or absence of the *DRD4-7* allele. Specifically, the negative association between externalizing behavior and IQ was completely attenuated by *DRD4-7*. Although the samples were fairly small, they were independent replications, and meta-analysis provided strong evidence that this finding is likely to be robust and reliable. Variation in the *DRD4* gene thus appears to differentiate 2 distinct male phenotypes. In males without *DRD4-7*, externalizing behavior is negatively associated with IQ. In males with *DRD4-7*, however, there is no association between externalizing behavior and IQ. This effect was evident in both adults and children and it remained similar in magnitude across various types of externalizing behavior, suggesting that it may be related to a common feature of externalizing behaviors, such as increased dopaminergic neurotransmission.[8-11]

The attenuation seen in the *DRD4-7*–positive group seems likely to be the result of the fewer, less efficient D4 receptors produced by the *DRD4-7* allele.[34-36] Decreased D4 receptor function should produce a *DRD4-7* phenotype in which the cognitive disruption associated with D4 receptor activation is diminished. Males with the *DRD4-7* allele thus appear to be protected from the decrement in cognitive ability associated with externalizing behavior. Further research is necessary to determine whether this finding holds true for measures of cognitive ability other than IQ.

DRD4-7 status does not appear to affect IQ directly, despite the significant difference in IQ between genotype groups in sample 3, but rather to moderate its association with externalizing behavior. Comparisons of the 3 physical aggression groups in sample 3 revealed that significant differences in IQ between *DRD4-7*–positive and *DRD4-7*–negative groups emerged only in the most consistently aggressive group (a group that was intentionally overrepresented in this sample, relative to the general population). The pattern of increasing differences in IQ between genotype groups (Figure 2), as severity of physical aggression increases, is paralleled by the increasing gap between the 2 regression lines in Figure 1C as a function of increasing levels of externalizing behavior. Group differences in the strength of association between 2 variables can lead to differences in group means in the extremes of the distributions of those variables. The significant main effect of genotype on IQ in sample 3 seems likely to be an anomaly resulting from the selection process for that sample, rather than a genuine indicator of any direct effect of *DRD4* variation on IQ. In keeping with this hypothesis, a study by Ball and colleagues,[49] which compared individuals of high IQ with others of average IQ, failed to find any difference in the frequency of *DRD4* alleles.

Many theoretical models view intelligence as an important element in behavioral self-regulation, and both low IQ and deficits in working memory have been described as risk factors for externalizing behavior.[6,7,51] Researchers interested in antisocial behavior and delinquency have usually argued that low IQ contributes causally to externalizing behavior, rather than the reverse.[6] However, the possibility that a causal pathway in the opposite direction (from externalizing behavior to IQ) might be mediated by neurophysiological processes, such as D4 receptor activation, has not previously been considered. In this case, D4 receptor activation resulting from the increased dopaminergic activity associated with externalizing behavior might lead (both immediately and developmentally) to decreased cognitive ability. It is also possible that externalizing behavior and cognitive ability are not directly causally linked, but that they vary together because both are affected by high levels of dopamine resulting from some other genetic or environmental factor. Whatever the causal pathway, our results indicate that it is likely to involve D4 receptors, as the negative association between externalizing behavior and IQ is completely attenuated by the presence of the *DRD4-7* allele. The causal possibilities discussed here, therefore, apply only to the *DRD4-7*–negative group. Externalizing behavior may be associated with dopaminergic activity in both genotype groups, but *DRD4-7* appears to prevent this dopaminergic activity from affecting cognitive ability.

Given the meta-analysis by Faraone and colleagues,[29] which indicates that *DRD4-7* is associated with a minor increase in risk for ADHD, it is important to consider how *DRD4-7* could lead both to the decoupling of cognitive ability from externalizing behavior and to increased risk for a disorder that involves externalizing behavior. One possible explanation may be developed based on findings that *DRD4-7* is associated with faster reaction times,[30,37,52] which might lead to certain specific forms of impulsive or inattentive behavior without an associated impairment of general cognitive ability. The fact that the present study did not show an association between *DRD4-7* and externalizing behavior is not incompatible with the evidence for an association of *DRD4-7* with ADHD, because we were not testing for association with ADHD specifically. Additionally, our results in sample 2, which was composed entirely of adults diagnosed with ADHD, indicate that *DRD4* variation can moderate the association of externalizing behavior and cognitive ability even within an ADHD population.

Recent studies indicating that *DRD4-7* is a relatively new allele that has increased in frequency because of positive selection support the argument that *DRD4-7* must have some adaptive value.[30,53] Our results suggest a novel hypothesis for what that value might be. *DRD4-7* appears to produce a phenotype in which cognitive ability is decoupled from behaviors like hyperactivity, impulsivity, and aggression (at least in some male populations). Some environments may favor or even demand such externalizing behaviors, and in these environments, the ability to manifest these behaviors without associated decrement in cognitive ability could be highly advantageous to individuals with *DRD4-7*, outweighing any associated drawbacks. Externalizing behavior, especially aggression, must have been important in human evolution, given the probability that intraspecies conflict between human groups has constituted a strong selection pressure.[54,55] Externalizing behavior may have been particularly advantageous in the unstable or resource-depleted environments that are hypothesized to have driven selection for *DRD4-7*.[30,53] The other *DRD4* alleles, in contrast, may be more adaptive in stable environments, in which externalizing behavior is less likely to be advantageous.

Accepted for Publication: July 28, 2005.

Correspondence: Jordan B. Peterson, PhD, Department of Psychology, University of Toronto, Toronto, ON M5S 3G3, Canada (jordanbpeterson@yahoo.com), or Colin G. DeYoung, PhD (cdeyoung@post.harvard.edu).

Financial Disclosure: None reported.

Funding/Support: This work has been supported by grants from the Fonds de Recherche en Santé du Québec (Drs Tremblay and Palmour); grants from Québec's Conseil Québécois de la Recherche Sociale and Canada's Social Sciences and Human Research Council (Dr Tremblay); grants from the Alva Foundation (Drs Beitchman and Kennedy); and fellowships to Dr Séguin from the Canadian Institutes for Health Research and the National Science and Engineering Research Council.

Acknowledgment: We thank Chawki Benkelfat for helpful discussions and review of a previous version of the manuscript. Drs Tremblay, Kennedy, and Palmour share senior authorship of this work.

REFERENCES

1. Nagin D, Tremblay RE. Trajectories of boys' physical aggression, opposition, and hyperactivity on the path to physically violent and nonviolent juvenile delinquency. *Child Dev*. 1999;70:1181-1196.
2. Krueger RF, Hicks BM, Patrick CJ, Carlson SR, Iacono WG, McGue M. Etiologic connections among substance dependence, antisocial behavior, and personality: modeling the externalizing spectrum. *J Abnorm Psychol*. 2002;111:411-424.
3. Andersson HW, Sommerfelt K. The relationship between cognitive abilities and maternal ratings of externalizing behaviors in preschool children. *Scand J Psychol*. 2001;42:437-444.
4. Elkins IJ, Iacono WG, Doyle AE, McGue M. Characteristics associated with the persistence of antisocial behavior: results from recent longitudinal research. *Aggress Violent Behav*. 1997;2:101-124.
5. Kuntsi J, Eley TC, Taylor A, Hughes C, Asherson P, Caspi A, Moffitt TE. Co-occurrence of ADHD and low IQ has genetic origins. *Am J Med Genet B Neuropsychiatr Genet*. 2004;124:41-47.
6. Lynam D, Moffitt TE, Stouthamer-Loeber M. Explaining the relation between IQ and delinquency: class, race, test motivation, school failure, or self-control? *J Abnorm Psychol*. 1993;102:187-196.
7. Séguin JR, Nagin DS, Assaad J-M, Tremblay RE. Cognitive-neuropsychological function in chronic physical aggression and hyperactivity. *J Abnorm Psychol*. 2004;113:603-613.
8. Chambers RA, Potenza MN. Neurodevelopment, impulsivity, and adolescent gambling. *J Gambl Stud*. 2003;19:53-84.
9. Pihl RO, Peterson JB. Alcoholism: the role of different motivational systems. *J Psychiatry Neurosci*. 1995;20:372-396.
10. Soderstrom H, Blennow K, Manhem A, Forsman A. CSF studies in violent offenders, I: 5-HIAA as a negative and HVA as a positive predictor of psychopathy. *J Neural Transm*. 2001;108:869-878.
11. Solanto MV. Neuropsychopharmacological mechanisms of stimulant drug action in attention deficit/hyperactivity disorder: a review and integration. *Behav Brain Res*. 1998;94:127.
12. Arnsten AFT, Robbins TW. Neurochemical modulation of prefrontal cortical functions in humans and animals. In: Stuss DT, Knight R, eds. *Principles of Frontal Lobe Function*. New York, NY: Oxford University Press; 2002.
13. De La Garza R, Madras BK. [(3)H]PNU-101958, a D(4) dopamine receptor probe, accumulates in prefrontal cortex and hippocampus of non-human primate brain. *Synapse*. 2000;37:232-244.
14. Mrzljak L, Bergson C, Pappy M, Huff R, Levenson R, Goldman-Rakic PS. Localization of dopamine D4 receptors in GABAergic neurons of the primate brain. *Nature*. 1996;381:245-248.
15. Primus RJ, Thurkauf A, Xu J, Yevich E, McInerney S, Shaw K, Tallman JF, Gallagher DW. Localization and characterization of dopamine D4 binding sites in rat and human brain by use of the novel, D4 receptor selective ligand [3H]NGD 94-1. *J Pharmacol Exp Ther*. 1997;282:1020-1027.
16. Wong AH, Van Tol HH. The dopamine D4 receptors and mechanisms of antipsychotic atypicality. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003;27:1091-1099.
17. Arnsten AFT, Murphy BL, Merchant K. The selective dopamine D4 receptor antagonist, PNU-101387G, prevents stress-induced cognitive deficits in monkeys. *Neuropsychopharmacology*. 2000;23:405-410.
18. Jentsch JD, Taylor JR, Redmond DE Jr, Elsworth JD, Youngren KD, Roth RH. Dopamine D4 receptor antagonist reversal of subchronic phencyclidine-induced object retrieval/detour deficits in monkeys. *Psychopharmacology (Berl)*. 1999;142:78-84.
19. Van Tol HH, Wu CM, Guan HC, Ohara K, Bunzow JR, Civelli O, Kennedy J, Seeman P, Niznik HB, Jovanovic V. Multiple dopamine D4 receptor variants in the human population. *Nature*. 1992;358:149-152.
20. Chang F-M, Kidd JR, Livak KJ, Pakstis AJ, Kidd KK. The world-wide distribution of allele frequencies at the human dopamine D4 receptor locus. *Hum Genet*. 1996;98:91-101.
21. LaHoste GJ, Swanson JM, Wigal SB, Glabe C, Wigal T, King N, Kennedy JL. Dopamine D4 receptor gene polymorphism is associated with attention-deficit/hyperactivity disorder. *Mol Psychiatry*. 1996;1:121-124.
22. Benjamin J, Li L, Patterson C, Greenberg BD, Murphy DL, Hamer DH. Population and familial association between the D4 dopamine receptor gene and measures of novelty seeking. *Nat Genet*. 1996;12:81-84.
23. Ebstein RP, Novick O, Umansky R, Priel B, Osher Y, Blaine D, Bennett ER, Nemanov L, Katz M, Belmaker RH. Dopamine D4 receptor (D4DR) exon III polymorphism associated with the human personality trait of novelty seeking. *Nat Genet*. 1996;12:78-80.
24. George SR, Cheng R, Nguyen T, Israel Y, O'Dowd BF. Polymorphisms of the D4 dopamine receptor alleles in chronic alcoholism. *Biochem Biophys Res Commun*. 1993;196:107-114.
25. Kotler M, Cohen H, Segman R, Gritsenko I, Nemanov L, Lerer B, Kramer I, Zer-Zion M, Kletz I, Ebstein RP. Excess dopamine D4 receptor (D4DR) exon III seven repeat allele in opioid-dependent subjects. *Mol Psychiatry*. 1997;2:251-254.
26. Kluger AN, Siegfried Z, Ebstein RP. A meta-analysis of the association between *DRD4* polymorphism and novelty seeking. *Mol Psychiatry*. 2002;7:712-717.
27. Luciano M, Zhu G, Kirk KM, Whitfield JB, Butler R, Heath AC, Madden PA, Martin NG. Effects of dopamine receptor D4 variation on alcohol and tobacco use and on novelty seeking: multivariate linkage and association analysis. *Am J Med Genet B Neuropsychiatr Genet*. 2004;124:113-123.
28. Paterson AD, Sunohara GA, Kennedy JL. Dopamine D4 receptor gene: novelty or nonsense? *Neuropsychopharmacology*. 1999;21:3-16.

29. Faraone SV, Doyle AE, Mick E, Biederman J. Meta-analysis of the association between the 7-repeat allele of the dopamine D4 receptor gene and attention deficit hyperactivity disorder. *Am J Psychiatry*. 2001;158:1052-1057.
30. Wang E, Ding Y-C, Flodman P, Kidd JR, Kidd KK, Grady DL, Ryder OA, Spence MA, Swanson JM, Moyzis RK. The genetic architecture of selection at the human dopamine receptor D4 (*DRD4*) gene locus. *Am J Hum Genet*. 2004;74:931-944.
31. Duncan J. Attention, intelligence, and the frontal lobes. In: Gazzaniga MS, ed. *The Cognitive Neurosciences*. Cambridge, Mass: MIT Press; 1995.
32. Duncan J, Seitz RJ, Kolodny J, Bor D, Herzog H, Ahmed A, Newell FN, Emslie H. A neural basis for general intelligence. *Science*. 2000;289:457-460.
33. Gray JR, Chabris CF, Braver TS. Neural mechanisms of general fluid intelligence. *Nat Neurosci*. 2003;6:316-322.
34. Asghari V, Sanyal S, Buchwaldt S, Paterson A, Jovanovic V, Van Tol HH. Modulation of intracellular cyclic AMP levels by different human dopamine D4 receptor variants. *J Neurochem*. 1995;65:1157-1165.
35. Jovanovic V, Guan HC, Van Tol HH. Comparative pharmacological and functional analysis of the human dopamine D4.2 and D4.10 receptor variants. *Pharmacogenetics*. 1999;9:561-568.
36. Schoots O, Van Tol HH. The human dopamine receptor repeat sequences modulate expression. *Pharmacogenomics J*. 2003;3:343-348.
37. Swanson J, Oosterlaan J, Murias M, Schuck S, Flodman P, Spence MA, Wasdell M, Ding Y, Chi HC, Smith M, Mann M, Carlson C, Kennedy JL, Sergeant JA, Leung P, Zhang YP, Sadeh A, Chen C, Whalen CK, Babb KA, Moyzis R, Posner MI. Attention deficit/hyperactivity disorder children with a 7-repeat allele of the dopamine receptor D4 gene have extreme behavior but normal performance on critical neuropsychological tests of attention. *Proc Natl Acad Sci U S A*. 2000;97:4754-4759.
38. Lichter JB, Barr CL, Kennedy JL, Van Tol HHM, Kidd KK, Livak KJ. A hypervariable segment in the human dopamine receptor D4 (*DRD4*) gene. *Hum Mol Genet*. 1993;2:767-773.
39. Tremblay RE, Pihl RO, Vitaro F, Dobkin PL. Predicting early onset of male antisocial behavior from preschool behavior. *Arch Gen Psychiatry*. 1994;51:732-739.
40. Séguin JR, Pihl RO, Harden PW, Tremblay RE, Boulerice B. Cognitive and neuropsychological characteristics of physically aggressive boys. *J Abnorm Psychol*. 1995;104:614-624.
41. Achenbach TM. *Child Behavior Checklist for Ages 6 to 18*. Burlington, VT: University of Vermont, Research Center for Children, Youth, and Families; 2001.
42. Harris GT, Rice ME, Quinsey VL. Psychopathy as a taxon: evidence that psychopaths are a discrete class. *J Consult Clin Psychol*. 1994;62:387-397.
43. Wechsler D. *Wechsler Intelligence Scale for Children*. 3rd ed. Toronto, Can: Psychological Corp; 1991.
44. Wechsler D. *The Wechsler Preschool and Primary Scale of Intelligence–Revised*. San Antonio, Tex: Psychological Corp; 1989.
45. Wechsler D. *Wechsler Adult Intelligence Scale*. 3rd ed. Toronto, Can: Psychological Corp; 1997.
46. Wechsler D. *Manual for the Wechsler Intelligence Scale for Children–Revised*. San Antonio, Tex: Psychological Corp; 1974.
47. Séguin JR, Boulerice B, Harden P, Tremblay RE, Pihl RO. Executive functions and physical aggression after controlling for attention deficit hyperactivity disorder, general memory, and IQ. *J Child Psychol Psychiatry*. 1999;40:1197-1208.
48. Sattler JM. *Assessment of Children: WISC-III and WPPSI-R Supplement*. San Diego, Calif: Author; 1992.
49. Ball D, Hill L, Eley TC, Chorney MJ, Chorney K, Thompson LA, Detterman DK, Benbow C, Lubinski D, Owen M, McGuffin P, Plomin R. Dopamine markers and general cognitive ability. *Neuroreport*. 1998;9:347-349.
50. Hunter JE, Schmidt FL, Jackson GB. *Meta-analysis: Cumulating Research Findings Across Studies*. Beverly Hills, Calif: Sage; 1982.
51. Sergeant JA, Geurts H, Oosterlaan J. How specific is a deficit of executive functioning for attention-deficit/hyperactivity disorder? *Behav Brain Res*. 2002;130:3-28.
52. Langley K, Marshall L, van den Bree M, Thomas H, Owen M, O'Donovan M, Thapar A. Association of the dopamine D4 receptor gene 7-repeat allele with neuropsychological test performance of children with ADHD. *Am J Psychiatry*. 2004;161:133-138.
53. Ding Y-C, Chi H-C, Grady DL, Morishima A, Kidd JR, Kidd KK, Flodman P, Spence MA, Schuck S, Swanson JM, Zhang YP, Moyzis RK. Evidence of positive receptor selection acting at the human dopamine receptor D4 gene locus. *Proc Natl Acad Sci U S A*. 2002;99:309-314.
54. Alexander RD. Evolution of the human psyche. In: Mellars P, Stringer C, eds. *The Human Revolution*. Edinburgh, Scotland: Edinburgh University Press; 1989.
55. Diamond J. *The Third Chimpanzee: The Evolution and Future of the Human Animal*. New York, NY: Harper-Collins; 1992.