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Sources of Cognitive Exploration: Genetic Variation in the Prefrontal Dopamine System Predicts Openness/Intellect

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Abstract

The personality trait Openness/Intellect reflects the tendency to be imaginative, curious, perceptive, artistic, and intellectual—all characteristics that involve cognitive exploration. Little is known about the biological basis of Openness/Intellect, but the trait has been linked to cognitive functions of prefrontal cortex, and the neurotransmitter dopamine plays a key role in motivation to explore. The hypothesis that dopamine is involved in Openness/Intellect was supported by examining its association with two genes that are central components of the prefrontal dopaminergic system. In two demographically different samples (children: $N = 608$; adults: $N = 214$), variation in the dopamine D4 receptor gene (*DRD4*) and the catechol-*O*-methyltransferase gene (*COMT*) predicted Openness/Intellect, as main effects in the child sample and in interaction in adults.

Keywords

Openness to Experience; Intellect; Personality; Dopamine; Genetics; *DRD4*; *COMT*

Openness/Intellect is one of the Big Five personality traits, and it describes the general tendency to be imaginative, curious, perceptive, artistic, and intellectual. Its compound label stems from an old debate about how best to name the trait, with some researchers favoring “Openness to Experience” and others “Intellect” (e.g., Costa & McCrae, 1992; Goldberg, 1990). Research has demonstrated that these two labels capture distinct but equally central

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aspects of the trait, with Intellect reflecting engagement with abstract information and Openness reflecting engagement with perceptual information (DeYoung, Quilty, & Peterson, 2007; Johnson, 1994; Saucier, 1994). What is core to both aspects of the trait is cognitive exploration of the structure of experience (DeYoung, Peterson, & Higgins, 2005; Saucier, 1994; Van Egeren, 2009). The present study addressed the question of what biological forces might drive this exploratory tendency.

DeYoung, Peterson, and Higgins (2002, 2005) hypothesized that the neurotransmitter dopamine is crucially involved in the biological substrate of Openness/Intellect. Four lines of evidence inspired this hypothesis. First, dopamine is well established as a driver of exploratory behavior (Depue & Collins, 1999; Panksepp, 1998). Its release in the brain is triggered both by novelty and by cues of potential reward, and once released it potentiates approach behavior, produces desire or “wanting” (Berridge & Robinson, 1998), and facilitates learning about rewards (Schultz, 2006). Importantly, the motivation to explore cognitively likewise appears to involve the reward system: discovering the answer to a trivia question about which one is curious triggers the brain’s reward system in much the same way that monetary, social, or food rewards do (Kang et al., 2009). Wanting to know or to understand, therefore, may involve dopamine just as much as wanting a tangible reward (Panksepp, 1998).

Second, dopamine is involved in the mechanisms necessary for cognitive as well as behavioral exploration. An adequate tonic level of dopamine in the prefrontal cortex (PFC) facilitates the maintenance of representations in working memory, and release of dopamine in PFC and anterior cingulate cortex triggers updating of representations in working memory, allowing for flexible direction of attention and manipulation of information (Arnsten & Robbins, 2002; Braver & Cohen, 2000). Openness/Intellect is the only Big Five trait associated positively with working memory performance and intelligence, and its Intellect aspect has been empirically linked to the brain systems in PFC that support working memory and intelligence (DeYoung et al., 2005, 2009; Schretlen, van der Hulst, Pearlson, & Gordon, 2010). Variations in dopaminergic function in PFC might, therefore, contribute to the association of cognitive processes with Openness/Intellect.

Third, Openness/Intellect is correlated with another Big Five trait, Extraversion. Although the Big Five were originally conceived as orthogonal (e.g., Costa & McCrae, 1992; Goldberg, 1990), they are in fact regularly correlated and possess a higher-order factor structure in which Extraversion and Openness load on one factor and Conscientiousness, Agreeableness, and low Neuroticism load on another (Digman, 1997; DeYoung, 2006; DeYoung et al., 2002). The influence of dopamine might account for the covariation of Extraversion and Openness/Intellect (DeYoung et al., 2002, 2005). Extraversion reflects a behavioral tendency toward approach behavior and exploration of potential rewards (including social rewards), and considerable biological evidence indicates that Extraversion is associated with dopaminergic function (Depue & Collins, 1999; DeYoung & Gray, 2009). Thus, Extraversion can be considered the behavioral or concrete manifestation in personality of the drive to explore, whereas Openness/Intellect might be the cognitive or abstract manifestation, with both influenced by dopamine. Consistent with this interpretation, dopamine has also been linked to traits like Sensation Seeking and Novelty Seeking (Cloninger, 1987; Zuckerman, 2005), which are typically related to both Extraversion and Openness/Intellect (e.g., Aluja, Garcia, & Garcia, 2003; Costa & McCrae, 1992).

Finally, both Openness/Intellect and Extraversion are associated with reduced latent inhibition (Peterson & Carson, 2000; Peterson, Smith, & Carson, 2002). Latent inhibition is an automatic pre-conscious process whereby stimuli previously categorized as irrelevant are blocked from entering awareness. Dopamine appears to be the primary modulator of latent

inhibition, with increased dopaminergic activity producing reduced latent inhibition (Kumari et al., 1999).

These four lines of evidence, though suggestive, are indirect, and stronger support for the association of Openness/Intellect with dopamine must come from biological research on the dopaminergic system. Molecular genetics is one promising approach to investigate the association of personality traits with neurotransmitter systems, because functional variations have been discovered in genes that produce many of the elements of those systems, such as the receptors to which neurotransmitters bind and the enzymes that catalyze production and degradation of neurotransmitters. Two genes in the dopaminergic system are particularly likely to be related to Openness/Intellect because they are uniquely important for the functioning of dopamine in the PFC. These are the dopamine D4 receptor gene (*DRD4*) and the catechol-*O*-methyltransferase gene (*COMT*).

There are five dopamine receptors that respond to dopamine released into the synapse, and they form two groups with opposed functions: excitatory (D1, D5) and inhibitory (D2, D3, D4). Of the inhibitory receptors, D4 is the only one strongly expressed in PFC; by contrast, in the area of the brain where dopamine is most directly involved in signaling reward and triggering approach behavior (the striatum), D4 is minimally expressed (Lahti et al., 1998; Meador-Woodruff et al., 1996). Neither of the two excitatory dopamine receptors (D1 and D5) is expressed in the PFC but not the striatum, in the way that D4 is. Thus, D4 is the dopamine receptor most likely to be specifically involved in the prefrontal cognitive processes associated with Openness/Intellect.

A locus of variation or *polymorphism* exists in the *DRD4* gene, consisting of a variable number of tandem repeats (VNTR) of a 48 base-pair sequence. This VNTR contains between 2 and 11 repeats, with the most common alleles being 4- and 7-repeat. The 7-repeat allele produces D4 receptors that are less efficient than those produced by the 2, 4, or 10 repeat variants (Asghari et al., 1995; Jovanovic, Guan, & Van Tol, 1999) and appears to be associated with reduced D4 expression (Schoots & Van Tol, 2003). Thus, the 7-repeat allele should act like a natural D4 antagonist, reducing the inhibitory function of D4 receptors in PFC. A number of traits related to disinhibited behavior and risk taking have been associated with the 7-repeat allele, with the best established findings being that the 7-repeat allele is associated with risk for attention deficit/hyperactivity disorder (ADHD; Faraone et al., 2005). Additionally, however, multiple studies have linked presence or absence of the 7-repeat allele to variation in cognitive functions associated with Openness/Intellect, including attention and intelligence (Bellgrove et al., 2005; DeYoung et al., 2006; Gornick et al., 2007; Swanson et al., 2000), which suggests that the 7-repeat allele may affect Openness/Intellect (but see Benjamin et al., 1996; Tochigi et al., 2006).

Predicting the direction of the effect of the 7-repeat allele on Openness/Intellect is difficult. On the one hand, the 7-repeat allele has been linked to novelty seeking (Benjamin et al., 1996; Ebstein et al., 1996; but see Munafo, Yalcin, Willis-Owen, & Flint, 2008), which would suggest it might be associated with higher levels of Openness/Intellect. On the other hand, the best replicated association of the 7-repeat allele is with risk for ADHD, and Openness/Intellect predicts better performance on tests of attention (DeYoung et al., 2005, 2009), just the opposite of an "attention deficit." Thus, one might expect the 7-repeat allele to be associated with reduced Openness/Intellect. Because the likely direction of effect is ambiguous, we predicted simply the presence of any effect, on the logic that an effect in either direction provides evidence for the involvement of the D4 receptor in the biological substrate of Openness/Intellect.

The *COMT* gene produces the COMT enzyme, which breaks down the catecholamine neurotransmitters, dopamine and norepinephrine. COMT is the primary mechanism of dopamine clearance in the PFC because the dopamine transporter, which also clears dopamine from the synapse, is only weakly expressed in PFC (Tunbridge, Harrison, & Weinberger, 2006). In the striatum, in contrast, the dopamine transporter is strongly expressed, and COMT has relatively little effect on levels of dopamine. Thus, *COMT* variation is likely to be particularly important for the functions of PFC and hence for Openness/Intellect.

The *COMT* gene contains a single nucleotide polymorphism (SNP), known as Val¹⁵⁸ Met, which determines whether a methionine (Met) or a valine (Val) molecule is inserted at a particular point in the construction of the enzyme. The Met allele is associated with reduced enzyme efficiency and therefore reduced dopaminergic turnover, leaving higher levels of dopamine available in the synapse. Numerous studies have shown that Val¹⁵⁸ Met genotype predicts variation in cognitive function and associated brain function, especially in PFC (Meyer-Lindenberg et al., 2006; Tunbridge et al., 2006). The Met allele therefore seems likely to be associated with greater Openness/Intellect, although this prediction is tentative because the effect of dopamine on PFC function exhibits an inverted U-shape, with both high and low levels of dopamine associated with reduced function (Arnsten & Robbins, 2002).

The present study examined the relation of *COMT* and *DRD4* to Openness/Intellect, with three main considerations. First, because both of these genes affect dopaminergic function in PFC, their variation may interact in its effect on the phenotype; we therefore examined gene-gene interactions (epistasis) as well as main effects. Second, although the Big Five model was developed to describe adult personality, considerable evidence has accumulated that the same five traits afford a good description of personality in childhood (Caspi & Shiner, 2006). One study found that *COMT* Val¹⁵⁸ Met genotype was associated with Openness/Intellect in a cohort of 385 79-year-olds (Harris et al., 2005). Demonstrating that *COMT* predicts Openness/Intellect across the lifespan would provide stronger evidence of the importance of prefrontal dopamine for the trait. The present study therefore examined *COMT*, *DRD4*, and their interactions in one sample of children and one of adults.

Finally, although *DRD4* and *COMT* are the two dopaminergic genes most specific to PFC, they might nonetheless be related to Extraversion as well as Openness/Intellect because they are expressed in regions involved in processing reward information and linked to Extraversion, including the amygdala and orbitofrontal cortex (DeYoung & Gray, 2009). Several studies have reported significant effects of *COMT* on Extraversion (e.g., Hoth et al., 2006; Reuter & Hennig, 2005). However, a meta-analysis indicated that *DRD4* variation is not associated with Extraversion (Munafo et al., 2008). To explore the specificity of effects of *COMT* and *DRD4* on Openness/Intellect, we performed secondary analyses predicting the other Big Five traits from genotypes.

Sample 1

The first sample in which we tested the hypothesis that *COMT* and *DRD4* variation would affect Openness/Intellect consisted of disadvantaged children who attended a week-long summer camp research program. A large number of these children had been maltreated, and we investigated the possibility of gene-by-environment (GxE) interactions in the prediction of Openness/Intellect, using maltreatment status as the environmental predictor. However, we did not formulate any specific predictions regarding the presence of GxE effects. Interactions of genotype with sex were also tested, as effects of *COMT* variation have been

found to be sexually dimorphic for several phenotypes (Biederman et al., 2008; Harrison & Tunbridge, 2008).

Participants

Participants were 614 children from an urban setting in upstate New York, who attended a day camp research program designed for maltreated and nonmaltreated, low-income, disadvantaged children (Cicchetti & Manly, 1990). Of this sample, 339 were maltreated (160 girls, 170 boys) and 275 were nonmaltreated (142 girls, 133 boys). Children ranged in age from 8 to 13 years ($mean = 11.3$, $SD = 1.0$). The sample was ethnically and racially diverse, and we used the Add Health system to code race and ethnicity in a single variable (www.cpc.unc.edu/projects/addhealth/data/code/race; accessed Apr. 11, 2010), with the exception that “American Indian” was coded as “other” because only two participants were identified as such. This variable, which had four categories in our sample (68% Black, 10% White, 18% Hispanic, and 4% other), was used as a categorical covariate in all analyses to control for potential population stratification (in which specific genetic effects can be confounded by ancestry). Parents provided informed consent for their child’s participation and for investigation of any Department of Human Services (DHS) records associated with the family. Children provided assent.

Maltreatment

Children in the maltreated group were identified by DHS records as having experienced maltreatment, whereas those in the nonmaltreated group were not so identified and were additionally screened through checks of the child abuse registry and interviews with their mothers to verify lack of DHS involvement. Families who received preventive services through DHS due to concerns over risk for maltreatment were excluded from the study to avoid inclusion of children with unidentified maltreatment in the comparison group. Trained raters coded DHS records of maltreatment to identify, for each child, the presence of sexual abuse, physical abuse, neglect, and/or emotional maltreatment, using criteria developed by Barnett, Manly, and Cicchetti (1993). Most maltreated children (59%) had experienced more than one type of maltreatment. Categorizing maltreated children according to the most severe type of abuse they had experienced did not produce results more informative than those reported below using the binary indicator of presence or absence of maltreatment.

Personality

The Big Five personality traits were assessed using two instruments: the Big Five scales derived from the California Child Q-sort (CCQ; John, Caspi, Robbins, Moffitt, & Stouthamer-Loeber, 1994) and a set of 46 trait descriptive adjectives (TDA) designed for assessment of the Big Five in children (Hagekull & Bohlin, 1998). The CCQ comprises 100 personality descriptive items that are sorted according to a fixed distribution into 9 categories, representing the degree to which each is characteristic of the child. The TDA comprises 46 items rated on a 5-point Likert scale. These instruments were completed by two adult camp counselors, trained in use of the instruments but unaware of research hypotheses and maltreatment status, after a week (35 hours) of extensive observation and interaction with participants. Interrater agreement was high, with the average intraclass correlation among pairs of raters ranging from .85 to .87 for the CCQ and from .74 to .89 for the TDA scales. Ratings for each item by each of the two raters were averaged in order to derive scale scores for each instrument.

Big Five scores from the CCQ and TDA were standardized in order to combine scores across the two instruments. Composite scores from these two inventories were very reliable, with Cronbach’s Alphas as follows: Extraversion: .95 (18 items), Agreeableness: .96 (25 items), Conscientiousness: .91 (18 items), Neuroticism: .90 (20 items), Openness/Intellect: .

75 (10 items). (The lower Alpha for Openness/Intellect is attributable to its relatively fewer items.) Three items (one each from Agreeableness, Conscientiousness, and Openness/Intellect) were excluded from the calculation of trait scores because their correlations with the scale total (calculated without the item in question) were near zero and their inclusion reduced Cronbach's Alpha. Scores calculated without these items correlated at .99 or higher with scores including them.

Genotyping

DNA was collected using the Buccal Amp Kit (Epicentre, Cat. No. BQ0901SSC) and amplified using the Repli-g kit (Qiagen Cat. No. 150043). The *COMT* SNP was genotyped using TaqMan Genotyping Master Mix (Applied Biosystems, Cat. 4371357). The *DRD4* exon 3 VNTR length determination was made by PCR amplifying DNA with primers *DRD4* F3 (5'CGGCCTGCAGCGCTGGGA3') and *DRD4* R2 D4 (5'CCTGCGGGTCTGCGGTGGAGT3') on a MasterCycler Gradient (Eppendorf, Inc). The resulting products were analyzed for length using a CEQ8000 (Beckman Coulter, Inc.). For *DRD4* genotype, participants were grouped according to whether they did or did not have at least one copy of the 7-repeat allele. *DRD4* genotype could not be determined for 6 participants.

COMT genotype frequencies did not deviate significantly from Hardy-Weinberg equilibrium (HWE), $\chi^2_{(1)} = 0.93$, $p = .34$. However, *DRD4* genotype frequencies did deviate significantly from HWE (tested using the Markov Chain algorithm of Guo and Thompson, 1992), $p < .001$. Deviations from HWE indicate either a violation of the assumptions of the Hardy-Weinberg principal or errors in genotyping (Xu, Turner, Little, Bleecker, & Meyers, 2002). In this case, the likely explanation is that deviation from HWE was due to violation of the assumption of no assortative mating. The Hardy-Weinberg principal assumes that all mating is random; however, this sample is ethnically diverse and thus subject to substantial assortative mating (in which individuals with similar genotypes are more likely to mate). Deviation from HWE in ethnically diverse samples is particularly likely for the *DRD4* VNTR because there are 10 possible alleles (with 7 were represented in this sample) and considerable ethnic variation in frequency of minor alleles (Chang, Kidd, Livak, Pakstis, & Kidd, 1996). As long as deviation from HWE does not reflect genotyping error, it is not problematic for our analyses, and genotyping error is unlikely here, given strict quality controls, including use of previously genotyped samples as control samples to ensure that our genotyping replicated previous results. Further, the frequencies of all alleles by race (Table 1) were consistent with previously published reports (Chang et al., 1996; Roman, Bau, Almeida, & Hutz, 1999), which suggests accurate genotyping.

Results

Genotype frequencies appear in Table 2 with mean scores on the Big Five for each genotype. To assess the significance of genotype differences for Openness/Intellect we performed ANOVA with *COMT* and *DRD4* genotype as predictors, controlling for age, race, sex, and maltreatment status. (As reported elsewhere, maltreated children in this sample exhibited higher Neuroticism and lower Agreeableness, Conscientiousness, and Openness/Intellect than nonmaltreated children; DeYoung, Cicchetti, & Rogosch, 2011). Both *COMT* and *DRD4* had significant main effects (Table 2). For *COMT*, the Met/Met genotype was associated with increased Openness/Intellect, whereas for *DRD4*, the 7-repeat allele was associated with reduced Openness/Intellect.

Following examination of main effects, we then additionally entered terms for the interaction of the two genotypes and for interactions of genotype with sex and maltreatment. The only significant interaction was a three-way interaction of *COMT*, maltreatment, and

sex, $F_{(2)} = 4.05$, $p < .05$. The effect of *COMT* on Openness/Intellect was more pronounced in boys if they were maltreated but more pronounced in girls if they were not (see Figure 1).

Finally, we used MANOVA to predict the other four personality traits simultaneously by genotypes, age, race, sex, and maltreatment status (Table 2). *COMT* had a significant main effect on Agreeableness. Children homozygous for the Met allele had higher levels of Agreeableness than the other two genotypes. *DRD4* had a significant main effect on Extraversion, with reduced Extraversion in the presence of the 7-repeat allele. Following examination of main effects, we tested interactions of the two genotypes and of genotype with sex and maltreatment, but none were significant.

Sample 2

In our second sample, we examined the prediction of Openness/Intellect by *COMT* and *DRD4* in a population of adults. Here, we were additionally able to test whether genetic effects on Openness/Intellect were independent of intelligence. Despite the fact that Openness/Intellect is the one Big Five trait positively associated with intelligence (Ackerman & Heggestad, 1997; DeYoung, 2011), the exploratory tendency that Openness/Intellect shares with Extraversion appears to be independent of intelligence (DeYoung et al., 2005, 2008). It was therefore an open question whether the effects of dopaminergic genes on Openness/Intellect would remain significant when controlling for intelligence. If they did not, this would suggest that variance related to intelligence explains the influence of *COMT* and *DRD4* on Openness/Intellect; if they did, this would suggest that motivational or attentional processes, rather than intelligence, are influenced by variation in these genes.

Participants

Participants were 238 white men recruited from the community around New Haven, Connecticut, primarily through Internet sites. They ranged in age from 18 to 40 years ($M = 23.6$, $SD = 5.0$). About half of the sample (124) were students, with 48 attending Yale University and the other students attending nearby colleges and universities. Because students may differ systematically from the rest of the population in Openness/Intellect, we controlled for student status in our analysis (results remained significant and substantively identical when not controlling for this variable and when controlling for enrollment at Yale specifically). The rest of the sample had a wide range of mostly lower- and middle-class occupations, with 20 indicating that they were currently unemployed. All participants were given monetary compensation for their participation.

Personality

The Big Five were assessed by the average of three measurements. Self-ratings were obtained using both the Big Five Inventory (BFI; John & Srivastava, 1999) and the Big Five Aspect Scales (BFAS; DeYoung et al., 2007). Additionally, participants were requested to give the peer-rating version of the BFI to two people who knew them well and who would return the questionnaire by mail (at which time participants received additional compensation). One or two BFI peer ratings were returned for 131 participants. Scores from all instruments were standardized. To achieve the most accurate personality measurement possible from our data, peer ratings were averaged with each other (if two were available—otherwise the single peer rating was used) and then averaged with the two self-ratings. Agreement between peer and self-ratings of the BFI was in the standard range, $r = .43$ to $.58$ ($M = .50$). A dummy variable representing whether or not peer ratings were available for each participant was included in our analyses, to control for the possibility of systematic differences between participants with and without peer ratings. All significant findings

remained significant if the peer-rating scores were excluded from our assessment of the Big Five.

Intelligence

Intelligence was assessed using the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999), which uses four subtests from the Wechsler Adult Intelligence Scale, third edition (WAIS-III), to provide extremely accurate estimates of full scale IQ ($r > .95$). The four subtests are Matrix Reasoning, Block Design, Vocabulary, and Similarities. Estimated IQ ranged from 92.5 to 148.0 ($M = 121.9$, $SD = 11.7$).

Genotyping

Saliva samples were collected using Oragene™ kits (Genotek, Inc.). The *COMT* SNP was genotyped using TaqMan technology (see above). The *DRD4* polymorphism was genotyped using agarose gels, following amplification using Kapa Biosystems 2G Robust Hotstart PCR Kit (cat no. KK5522). Genotypes were grouped as in Sample 1. *DRD4* genotype could not be determined for 16 participants, and *COMT* genotype could not be determined for 10 participants. *COMT* genotype frequencies did not differ significantly from HWE, $\chi^2_{(1)} = 0.07$, $p = .79$, nor did *DRD4* genotypes, $p = .85$.

Results

Genotype frequencies appear in Table 3 with mean scores on the Big Five for each genotype. (Differences between this sample and Sample 1 with respect to *COMT* genotype frequencies are due to the different ethnic compositions of the samples. In both samples the allele frequencies are typical for the different ethnicities involved; see dbSNP for *COMT* frequencies: <http://www.ncbi.nlm.nih.gov/projects/SNP/>.) To assess the significance of genotype differences for Openness/Intellect we performed ANOVA with *COMT* and *DRD4* genotype as predictors, controlling for age, use of peer ratings, and student status. Neither *COMT* nor *DRD4* had significant main effects. However, we next additionally entered the interaction of the two genotypes into the model, and this interaction was significant, $F_{(2)} = 3.69$, $p < .05$. The effect of *COMT* was strongest for participants carrying the 7-repeat allele of *DRD4*, with homozygotes for both Val and Met showing considerably higher Openness/Intellect than heterozygotes (Figure 2).¹

We repeated our analysis of the model including the *COMT*-by-*DRD4* interaction term, adding IQ as a covariate. When controlling for IQ, the effect of the genetic interaction remained significant and largely unchanged, $F_{(2)} = 3.83$, $p < .05$. Additionally, IQ positively predicted Openness/Intellect independently of the genetic effect, $F_{(1)} = 17.20$, $p < .001$. (The zero-order correlation of IQ with Openness/Intellect was $r = .24$, $p < .001$.)

Finally, we used MANOVA to predict the other four personality traits simultaneously, with genotypes, age, use of peer ratings, and student status as predictors. Main effects of genotype were not significant, and neither was the interaction of *COMT* and *DRD4*, for any trait.

Discussion

In two samples, we confirmed our hypothesis that genes involved in prefrontal dopaminergic function would be associated with the personality trait Openness/Intellect. Variation in *COMT* and *DRD4* predicted Openness/Intellect as main effects in disadvantaged children

¹Because this interaction was found in an all male sample, whereas Sample 1 was mixed sex, we tested whether a *COMT*-by-*DRD4* interaction was significant in just the male portion of Sample 1. It was not, $F_{(2)} = 0.24$, $p = .79$.

and in interaction in male adults. These findings support the theory that dopamine is a key part of the biological substrate of Openness/Intellect, driving the cognitive exploration that characterizes this trait (DeYoung et al., 2002, 2005).

Dopamine has been similarly implicated in the behavioral and social exploration associated with Extraversion (Depue & Collins, 1999; DeYoung & Gray, 2009), and the role of dopamine in both traits may account for their regular correlation (DeYoung et al., 2002, 2005). Whereas dopaminergic function in the PFC may specifically influence Openness/Intellect, biological factors influencing rate of dopamine synthesis or activity levels of all dopaminergic neurons might affect both Openness/Intellect and Extraversion.

Replication is crucial in genetic association studies, so it is important that *DRD4* and *COMT* were associated with Openness/Intellect in both children and adults, despite major demographic differences between samples. However, this was only a partial replication; the child sample showed main effects of both genes, whereas the adult sample showed only an interaction between the two genes. Because the two samples are so different demographically, we cannot draw strong conclusions about the role of age in the genetic effects. It is certainly possible, however, that the consequences of particular genotypes change over the course of development, as dopaminergic function changes over the lifespan. Dopamine activity increases dramatically in adolescence, and then declines slowly as adults age (Chambers, Taylor, & Potenza, 2003; Volkow et al., 1998).

In the adults, we found that *COMT* variation was strongly associated with Openness/Intellect only in the presence of the *DRD4* 7-repeat allele, and the 7-repeat allele was associated with differences in Openness/Intellect in opposite directions depending on *COMT* genotype. The effects in the child sample were much simpler: the *COMT* Met/Met genotype predicted higher Openness/Intellect and the *DRD4* 7-repeat allele predicted lower. Nonetheless, the existence of epistatic interactions like that seen in the adult sample is not particularly surprising given that the products of these two genes interact through physical processes in the brain. Receptor densities change in response to levels of neurotransmitters in the synapse (which for prefrontal dopamine are regulated by the COMT enzyme), and this should increase the likelihood of statistical interaction effects (Arnsten & Robbins, 2002). Such interactions may be more likely to influence phenotypic traits as development progresses. Our finding of an interaction effect in adults suggests that studies that do not examine variation in *DRD4* and *COMT* simultaneously are less likely to detect the effects of these genes on Openness/Intellect (e.g., Benjamin et al., 1996; Tochigi et al., 2006).

Two previous studies of adult personality have examined interactions of the same *COMT* and *DRD4* polymorphisms (Benjamin et al., 2000; Strobel, Lesch, Jatzke, Paetzold, & Brocke, 2003). Both studies focused on the trait of Novelty Seeking (Cloninger, 1987), a complex trait reflecting primarily low Conscientiousness and high Extraversion, but also high Openness/Intellect (Costa & McCrae, 1992; Markon, Krueger, & Watson, 2005). Parallel to the results for Openness/Intellect in our Sample 2, in the study of Strobel et al. (2003) higher Novelty Seeking was found in the presence of the 7-repeat allele, for *COMT* heterozygotes only. A similar pattern, though slightly less clear, was found by Benjamin et al. (2000). (Also, note that the analyses in both studies are more complicated than ours because they test a 3-way interaction also involving variation in the serotonin transporter gene.) Both reports argued that failure to consider interactions among multiple genes might be responsible for null results in the study of genetic effects on personality.

In the child sample, *DRD4* was also associated with Extraversion and *COMT* was also associated with Agreeableness.² However, no trait other than Openness/Intellect was significantly associated with genotype in the adult sample. Thus the association of *COMT*

and *DRD4* genotypes with Openness/Intellect was the only finding in this study that was at least partially replicable.

The presence of a complex interaction between sex, maltreatment, and *COMT*, in the child sample, suggests a potential avenue for future research. Sex has been found to moderate the effects of *COMT* in relation to other phenotypes (Harrison & Tunbridge, 2008), and maltreatment has profound effects on many aspects of personality (Cicchetti & Rogosch, 2007; Rogosch & Cicchetti, 2004). Our results suggest that *COMT* variation may moderate the effect of maltreatment on Openness/Intellect very differently for boys and girls.

In the adult sample, we demonstrated that the association of Openness/Intellect with *COMT* and *DRD4* (in interaction) was independent of intelligence, suggesting that these genes are related to motivational or attentional features of the trait, rather than to variance shared with intelligence. Intelligence receives a great deal of attention in psychological research, but much less is known about the broader personality trait of Openness/Intellect.

Conclusion

Our finding that two dopaminergic genes particularly influential in PFC predict variance in Openness/Intellect furthers the attempt to characterize Openness/Intellect both psychologically and biologically (DeYoung et al., 2005, 2009). Perhaps no trait is more central to the uniqueness of human beings, as a species, than our capacity to explore the world in thought and imagination. Dopamine is the neurotransmitter most implicated in exploration, and this study supports the theory that prefrontal dopamine is crucial for individual differences in the cognitive exploratory tendency central to Openness/Intellect. Nonetheless, given that our two samples were very different and that replication was only partial, our results should be seen as preliminary, and more research should be conducted on the role of dopamine in Openness/Intellect.

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²In Sample 1, genotypes were available for the *TaqIA* polymorphism associated with the dopamine D2 receptor gene (*DRD2*), which has previously been found to interact with *COMT* to predict the Extraversion-related trait, behavioral activation system (BAS) sensitivity (Reuter, Schmitz, Corr, & Hennig, 2005). We do not report analysis of this polymorphism in detail because it was not available in Sample 2, but it provides an interesting contrast because, unlike *DRD4* and *COMT*, the action of *DRD2* is more influential on the motivational systems of the striatum, rather than on the functioning of prefrontal cortex (Zald et al., 2010). This makes *DRD2* variation more likely to effect Extraversion than Openness/Intellect, according to our model. Adding *DRD2 TaqIA* to the analyses in Sample 1, we did not find that it predicted Openness/Intellect or Extraversion, either as a main effect or in interaction with *COMT*.

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Figure 1. Interaction between *COMT* Val¹⁵⁸Met, maltreatment, and sex predicts Openness/Intellect in children ($N = 608$). A constant (1) was added to scores to facilitate graphical representation.

Figure 2. Interaction between *DRD4* 7-Repeat allele and *COMT* Val¹⁵⁸Met predicts Openness/Intellect in adult males ($N = 214$). A constant (1) was added to scores to facilitate graphical representation.

Table 1

Allele frequencies (%) by race for Sample 1.

	<i>N</i>	<i>DRD4</i> Exon III VNTR								<i>COMT</i> Val ¹⁵⁸ Met	
		2R	3R	4R	5R	6R	7R	8R	Val	Met	
Black	415	6	1	73	5	1	13	1	70		30
White	63	7	3	77	0	0	13	0	44		56
Hispanic	108	9	0	71	3	0	16	1	59		41
Other	22	9	2	70	0	5	14	0	63		37

Genotype frequencies and Big Five means (and standard deviations) for Sample 1, with significance tests controlling for maltreatment, sex, race, age, and other genotype.

	DRD4			COMT					
	7R-absent	7R-present	$F_{(1)}$	p	Val/Val	Val/Met	Met/Met	$F_{(2)}$	p
Frequency	76%	24%			43%	44%	13%		
Openness/Intellect	0.06 (0.89)	-0.16 (0.86)	7.12	<.01	-0.02 (0.86)	-0.05 (0.90)	0.25 (0.91)	3.16	.04
Extraversion	0.05 (0.94)	-0.20 (1.04)	7.35	<.01	-0.05 (0.99)	-0.01 (0.93)	0.16 (1.03)	1.51	.22
Neuroticism	-0.02 (0.91)	0.06 (0.95)	1.36	.24	0.02 (0.88)	0.04 (0.95)	-0.10 (0.94)	0.63	.53
Agreeableness	-0.01 (0.98)	0.03 (0.97)	0.02	.89	0.01 (0.97)	-0.08 (1.02)	0.22 (0.81)	3.62	.03
Conscientiousness	-0.01 (0.96)	0.07 (0.92)	0.24	.62	0.03 (0.93)	-0.05 (0.98)	0.13 (0.92)	1.41	.25

Genotype frequencies and Big Five means (and standard deviations) for Sample 2, with significance tests controlling for age, student status, use of peer ratings, and other genotype.

Table 3

	<i>DRD4</i>			<i>COMT</i>			
	7-R-absent 67%	7-R-present 33%	$F_{(1)}$	p	Val/Val 25%	Val/Met 49%	Met/Met 26%
Frequency							
Openness/Intellect	0.03 (0.85)	-0.06 (0.86)	0.64	.43	-0.07 (0.96)	-0.06 (0.89)	0.08 (0.80)
Extraversion	0.00 (0.82)	0.03 (0.94)	0.23	.63	0.10 (0.87)	0.01 (0.86)	-0.09 (0.91)
Neuroticism	0.09 (0.84)	-0.08 (0.91)	3.31	.07	-0.14 (0.85)	0.11 (0.86)	0.03 (0.89)
Agreeableness	-0.01 (0.80)	-0.03 (0.94)	0.06	.81	0.03 (0.86)	-0.13 (0.87)	0.12 (0.77)
Conscientiousness	-0.05 (0.86)	0.02 (0.93)	0.71	.40	0.10 (0.84)	-0.09 (0.84)	-0.04 (0.95)
							1.46
							.23