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Evaluation of Genetic Variability in the Dopamine Receptor D2 in Relation to Behavioral Inhibition and Impulsivity/Sensation Seeking: An Exploratory Study With *d*-Amphetamine in Healthy Participants

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Abstract

The dopamine D2 receptor (DRD2) appears to be involved in impulsive behaviors, and particularly in behavioral inhibition. We sought to determine whether inhibition and impulsivity were related to genetic polymorphisms in the DRD2 gene (*DRD2*) in healthy volunteers ($N = 93$). Participants received placebo or *d*-amphetamine in random order. They performed the stop task, measuring behavioral inhibition, and rated their mood states on each session. They also completed the Zuckerman–Kuhlman Personality Questionnaire, including an Impulsivity subscale. We investigated the association between 12 single nucleotide polymorphisms (SNPs) and haplotypes in *DRD2* and stop task performance in the nondrug (i.e., placebo) session and on the personality measure of impulsivity. We secondarily evaluated the *DRD2* SNPs in relation to response to *d*-amphetamine on stop task performance and mood ratings. Mood was not related to genotypes in either the drug free condition or in response to drug. However, 2 SNPs, rs4648317 and rs12364283, and a haplotype block consisting of those SNPs, were associated with better performance on the stop task in the drug free condition and lower scores on the Impulsivity subscale. We also found that rs12364283 was associated with effects of *d*-amphetamine on stop task performance: *d*-amphetamine decreased stop reaction time (RT) in the A/A group but increased stop RT in the combined A/G + G/G genotype. Of the SNPs we evaluated, rs12364283, which has been associated with *DRD2* expression, was the most significantly associated with inhibition and impulsivity. The significant relationship between *DRD2* genotype and both behavioral inhibition and impulsivity suggests a possible common genetic influence on behavioral and self-report measures of impulsivity.

Keywords

DRD2; inhibition; impulsivity; amphetamine; Stop Task

Individuals vary in behavioral inhibition, or the predisposition to respond to stimuli without regard to negative consequences. These individual differences have been observed in healthy populations (de Wit, Crean, & Richards, 2000), as well as in psychiatric samples such as patients with attention deficit/hyperactivity disorder and substance use disorders (Colzato, van

den Wildenberg, & Hommel, 2007; Schachar, Tannock, & Logan, 1993). One possible source of the observed variability is genetic variation in the neurotransmitter systems responsible for the phenotype. Several lines of evidence suggest that dopamine plays an important role in inhibition in both humans (Friedel, 2004) and nonhumans (Cardinal, Pennicott, Sugathapala, Robbins, & Everitt, 2001; Dulawa, Grandy, Low, Paulus, & Geyer, 1999; Puumala, & Sirvio, 1998; Rubinstein et al., 1997; Winstanley, Theobald, Cardinal, & Robbins, 2004, 2006). Specifically, there is evidence that the dopamine receptor D2 (DRD2) is important for inhibition. Lower expression of *DRD2* in patients with Huntington's disease is associated with poor behavioral inhibition (Cropley, Fujita, Innis, & Nathan, 2006; Lawrence et al., 1998), and imaging studies with healthy participants demonstrate a relationship between DRD2 availability and performance on a measure of behavioral inhibition (Volkow et al., 1998). In addition, rats with lower DRD2 availability perform more poorly on the five-choice serial reaction time (RT) tasks, a measure of behavioral inhibition in animals (Dalley et al., 2007). Functional neuroimaging studies suggest that corticostriatal circuitry—especially the right inferior frontal gyrus and striatum, both rich in DRD2 receptors (Bertolino, Fazio, Caforio, Blasi, & Rampino, 2009)—plays an important role in behavioral inhibition (Aron, Dowson, Sahakian, & Robbins, 2003; Robbins, 2007; Rubia, 2002; Semrud-Clikeman, Steingard, Filipek, Bekken, Biederman, & Renshaw, 2000; Vaidya et al., 1998).

Recently, Zhang et al. (2007) evaluated 23 polymorphisms within *DRD2* to determine whether any of them controlled *DRD2* expression. Only a previously uncharacterized single nucleotide polymorphism (SNP), rs12364283, was directly associated with *DRD2* expression. It is interesting that Taq1A, a polymorphism that has been associated with alcoholism in some (Amadeo, Abbar, Fourcade, Waksman, & Leroux, 1993; Blum, Noble, Sheridan, Finley, & Montgomery, 1991; Comings, Comings, Muhleman, Dietz, Shahbahrani, & Test, 1991; Foley, Loh, Innes, Williams, & Tannenberg, 2004; Hietala, Pohljalainen, Heikkila-Kallio, West, Salaspuro, & Syvalahti, 1997; Higuchi, Muramatsu, Murayama, & Hayashida, 1994; Ishiguro et al., 1998) but not all studies (Dick et al., 2007; Gelernter & Kranzler, 1999; Gelernter et al., 1991; Gelernter et al., 2006), was not found to be associated with *DRD2* expression. Several recent studies have identified associations between rs12364283 and phenotypes such as working memory, brain activity, and negative symptoms in schizophrenic patients (Bertolino, Fazio, Caforio, Blasi, & Rampino, 2009) and avoidance-based decisions (Frank & Hutchison, 2009). In this study, we evaluated rs12364283 and 11 other SNPs including: rs4648318 and rs4274224, both of which have been weakly associated with nicotine dependence in European Americans (Huang et al., 2009); rs4648317, which has been associated with nicotine dependence in adolescents (Laucht et al., 2008); rs1079596, which has been associated with performance on the continuous performance test (Kollins et al., 2008); and rs1125394 and rs1799978, which have been associated with therapeutic responses to clozapine (Hwang et al., 2006) and risperidone (Ikeda et al., 2008).

We evaluated performance on a behavioral task as well as a self-report measure of impulsive personality in healthy volunteers. We used the stop task (Logan & Cowan, 1984), a standardized measure of behavioral inhibition. On this task, participants are instructed to respond to a “go” stimulus on most trials, but they are told to withhold their response when a “stop” signal is presented. The time between the stop signal and the go signal is systematically varied to determine the time needed to inhibit a response. More “impulsive” individuals require longer times to inhibit their responses on the stop task, although their go RTs may be normal. We measured impulsivity as a personality trait using the Impulsivity/Sensation Seeking scale on the Zuckerman–Kuhlman Personality Questionnaire (ZKPQ; Zuckerman, Kuhlman, Joireman, Teta, & Kraft, 1993). It is not clear whether the behavioral inhibition task measures the same underlying construct as the self-report questionnaire (Reynolds, Ortengren, Richards, & de Wit, 2006). Some studies have reported positive correlations between self-report measures of impulsivity and stop RTs (Gorlyn, Keilp, Tryon, & Mann, 2005; Logan, Schachar,

& Tannock, 1997), whereas others have not (Cheung, Mitsis, & Halperin, 2004; Lijffijt, Bekker, Quik, Bakker, Kenemans, & Verbaten, 2004). Thus, a genotype that is associated with performance on the inhibition task may or may not also be associated with the self-report measure of impulsivity.

In addition to the analysis of stop task performance on the placebo session, while participants were drug free, we also compared the genotypic groups on subjective and behavioral responses to acute doses of *d*-amphetamine (5, 10, and 20 mg). Several lines of evidence suggest that responses to *d*-amphetamine might be related to DRD2. For example, DRD2 availability has been associated with subjective responses to stimulants (Volkow et al., 1999): Participants who liked the effect of intravenous methylphenidate, an amphetaminelike drug, had significantly lower DRD2 levels than participants who disliked its effects. Therefore, we also evaluated the effect of *DRD2* genotype on both subjective rating and behavioral inhibition after acute *d*-amphetamine challenge.

Our primary goal was to investigate *DRD2* polymorphisms in relation to behavioral inhibition in a drug-free state (i.e., placebo condition) and a self-report measure of impulsivity. Secondly, we evaluated behavioral inhibition and mood responses to acute doses of *d*-amphetamine in relation to *DRD2* polymorphisms. We hypothesized that measures in both our primary and secondary analyses would depend on the *DRD2* genotype.

Method

Participants

Healthy Caucasian male and female volunteers ($N = 93$), ages 18–35 years were recruited by posters, advertisement, and word-of-mouth referrals. To reduce variability related to tolerance and withdrawal from nicotine or caffeine, we excluded participants who reported smoking more than 10 cigarettes per week or consuming more than three cups of coffee per day. At screening, volunteers underwent a structured clinical psychiatric interview and a physical examination, including electrocardiogram (EKG). They also completed a psychiatric Symptom Checklist (SCL-90; Derogatis, 1983), the Michigan Alcoholism Screening Test (Selzer, 1971), and a health questionnaire with a detailed section on current and lifetime drug use and personality questionnaires including the ZKPQ (Zuckerman et al., 1993). They were excluded if they were taking medication for a current condition, if they had any current Axis I psychiatric disorder including substance dependence (in accordance with the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders [DSM-IV]*; American Psychiatric Association, 1994), or any current or past medical condition considered to be a contraindication for *d*-amphetamine (e.g., abnormal EKG or hypertension). Candidates had to speak English and have at least a high school education. Their body mass index (BMI) had to be in the range between 19 and 26 kg/m². To minimize the influence of hormones, women were tested only during the follicular phase (White, Justice, & de Wit, 2002). Women who were pregnant, lactating, or planning to become pregnant during the study were excluded from participation. The study was approved by The University of Chicago Institutional Review Board.

Design and Procedure

Participants completed four 4-hr sessions in which they received *d*-amphetamine (5 mg, 10 mg, and 20 mg) or placebo in random order under double-blind conditions. Placebo and *d*-amphetamine (Mallinkrodt, MO) were placed in size 00 capsules with dextrose filler. Placebo capsules contained dextrose only.

Participants attended an orientation session to familiarize themselves with the procedures of the study, practice the questions, provide informed consent, schedule their study sessions, and

provide a 20-ml (2×10 ml) blood sample for genotyping. They were instructed to abstain from taking drugs (including alcohol, caffeine, and nicotine) 24 hr before each session and to fast from midnight the night before the sessions. On arrival at the laboratory for each session, urine was tested for recent drug use and pregnancy, and a breath alcohol level was obtained. Participants were tested individually and remained in a comfortably furnished room with TV and reading material for the 4-hr session. They could watch emotionally-neutral movies and read during the sessions when measurements were not being taken, but they were not allowed to study.

The four experimental sessions were conducted from 0900 to 1300 and were separated by at least 48 hr. Precapsule subjective reporting of mood was recorded at 0900. At 0930, participants ingested a capsule containing *d*-amphetamine (5, 10, or 20 mg) or placebo. For blinding purposes, they were informed that the capsule might contain a stimulant, sedative, or placebo. The stop task was administered by computer, 90 min after capsule administration, which is the expected time of peak *d*-amphetamine blood concentration. Mood measures were obtained 30, 60, 90, 150, and 180 min after ingestion of the capsule, and several other measures were obtained that are not reported here because of the specific nature of the hypothesis. These included the Digit Symbol Substitution Test (Wechsler, 1958), the Multidimensional Personality Questionnaire (Tellegen, 1982), Deviation From the Mode (de Wit, 2008), Addiction Research Center Inventory (Martin, Sloan, Sapira, & Jasinski, 1971) and the Drug Effects Questionnaire (Johanson & Uhlenhuth, 1980).

At the end of each session, participants also completed an end-of-session questionnaire reporting on their overall experience with the drug they received. After completing all four sessions, participants were debriefed and paid a total of \$120.

Dependent Measures

Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1971)—The POMS consists of 72 adjectives commonly used to describe momentary mood states. Participants rate from 0 (*not at all*) to 5 (*extremely*) the extent to which each adjective describes how they feel at that moment. The items on the POMS have been factor analyzed to yield eight mood state scales: Anger, Anxiety, Confusion, Depression, Elation, Fatigue, Friendliness, and Vigor. In addition, the POMS has two intuitively derived scales: Arousal ($[\text{Anxiety} + \text{Vigor}] - [\text{Fatigue} + \text{Confusion}]$) and Positive Mood ($\text{Elation} - \text{Depression}$).

Stop task (Logan et al., 1997)—The primary dependent measures on this task are the stop and go times. On each trial, participants are presented with a go signal (symbol on the computer screen) and instructed press a certain key as quickly as possible. The go signal appears at 2-s intervals, and the individual's RTs (go RTs) are recorded. On 25% of the trials, a tone (stop signal) is sounded after the presentation visual stimulus is presented, and participants are instructed to inhibit (stop) their go response on those trials. The delay from the onset of the go signal to the onset of the stop signal (stop-signal delay) is systematically adjusted in 50-ms increments. If the individual fails to stop, the stop-signal delay is decreased by 50 ms on the following stop-signal trial. If the individual successfully stops, the stop-signal delay is increased by 50 ms on the next trial. Trials continue to vary until the individual is able to inhibit (stop) his or her key press responses on approximately 50% of trials. Stop RT is computed by subtracting the average stop-signal delay at which the individual is able to inhibit the go response 50% of the time from the average go RT. Each administration of the stop task consisted of four blocks of 64 trials (256 total trials). Completion of all 256 trials with brief breaks between the blocks takes approximately 10 min.

At the beginning of each administration of the stop task, the stop delay is set at 200 ms. To ensure that the participants had adjusted their stop-signal delay to the point at which they

successfully stopped 50% of the time, we computed the stop RT (and go RT) from the last two blocks of 64 trials. Thus, the procedure provides a measure of the latency in milliseconds to respond to the letter presentation, or the go RT, and the time in milliseconds needed to inhibit a go response, or the stop RT.

The ZKPQ (Zuckerman et al., 1993)—The ZKPQ is a 99-item scale comprising the following subscales: Impulsive/Sensation Seeking (19 items), Neuroticism–Anxiety (19 items), Aggression–Hostility (17 items), Activity (17 items), Sociability (17 items), and Infrequency (10 items). We only evaluated the Impulsive/Sensation Seeking sub-scale of the ZKPQ in this analysis because the primary aim was to examine *DRD2* genotype in relation to impulsivity.

Genotyping—Participants were genotyped at 12 SNPs in the *DRD2*, which were part of the Addiction Array (Hodgkinson et al., 2008), based on the Illumina Golden-Gate platform. Arrays were imaged with an Illumina Bead-station GX500, and the data were analyzed with GenCall v6.2.0.4 and GTS Reports software v5.1.2.0 (Illumina). Criteria for sample exclusion and determining genotyping failure were previously described (Hodgkinson et al., 2008).

Population stratification—We genotyped all study participants for 186 ancestry informative markers (AIMs) that were included on the Addictions Array (Hodgkinson et al., 2008). The 186 AIMs represent a subset of a previously defined set of 204 AIMs (Enoch, Shen, Xu, Hodgkinson, & Goldman, 2006). We ran STRUCTURE (Pritchard, Stephens, & Donnelly, 2000) to identify subpopulations of individuals using these AIMs. All participants' self-reported Caucasian ancestry was confirmed.

Statistical Analysis

Drug-free state analyses—First, for each SNP, we checked whether genotype correlated ($p > .01$) with demographic measures including gender, BMI, education in years, age, current and lifetime substance use. We also evaluated whether any of the demographic factors correlated with stop RT or go RT. If they did, we included them as covariates in further analyses. If the minimum allele frequency was <0.1 we combined the rare homozygous genotype with the heterozygous genotype.

We assessed stop and go RTs for differences between genotypic groups without administration of drug (placebo), using a one-way analysis of variance (ANOVA). We repeated the same analysis for the Impulsivity/Sensation Seeking subscale of the ZKPQ. We assessed the significance of each SNP for each phenotype after adjusting for multiple testing (12 SNPs) while accounting for the correlations between SNPs.

We constructed a linkage disequilibrium (LD) map using Haploview software, Version 4.1, from which we defined haplotype blocks. We constructed the blocks using the method of Gabriel et al. (2002) but modified it to include SNPs for which $D' = 1$ regardless of lower confidence bound. Haplotypes that were observed fewer than five times were dropped from the analysis. We also checked that LD estimates were similar between our data and those of the HapMap CEU sample (i.e., Utah residents with Northern and Western European ancestry from the CEPH [Centre d'Etude du Polymorphisme Humain] sample). Using PLINK, we tested each haplotype within each block of *DRD2* for association with stop RT, go RT, and ZKPQ Impulsivity/Sensation Seeking subscale scores. We empirically assessed statistical significance while accounting for the testing of multiple haplotypes in each block separately using 5,000 permuted datasets.

A standard likelihood ratio test was used to determine whether haplotypes constructed from the haplotype blocks were better able to explain the trait variation than the most associated

SNP in the block. First, we regressed the trait value on predictors that count the number of each haplotype possessed by a participant. Individuals with rare haplotypes had the count for that haplotype equally distributed among the other haplotypes. This is akin to the method of Zaykin et al. (Zaykin, Westfall, Young, Karnoub, Wagner, & Ehm, 2002). Next, we regressed the trait value on the allele count of the most significantly associated SNP in the haplotype block. Multiplying two times the log ratio of the haplotype regression likelihood and the SNP regression likelihood produced a statistic that is asymptotically chi-square distributed with degrees of freedom equal to the number of unique haplotypes minus the number of unique genotypes at the SNP.

Response to d-amphetamine analyses—We conducted two-factor repeated measure ANOVAs (or analyses of covariance [ANCOVAs], with dose as a repeated measure) for outcome measures stop RT, go RT, and POMS to compare the effect of individual SNPs on responses to drug (0, 5, 10, 20 mg). Because mood was measured at multiple time points, we calculated the area under the curve relative to baseline (Time 0), for each drug dose. We conducted post hoc analyses to identify the source of genotype–drug interactions.

Results

Genotype Frequencies and Haplotype Construction

Table 1 shows the genotype frequencies for the 12 SNPs included in the study. The frequencies and LD between SNPs were similar to those calculated in the HapMap CEU sample (available in the International HapMap Genome Browser B36). Eleven SNPs had a minor genotype frequency of less than 0.1 (see Table 1). Participants in these groups were combined with the heterozygous group in the analysis. Only one SNP, rs4274224, was analyzed using all three genotype groups. All SNPs were in Hardy–Weinberg equilibrium. D' values between the 12 polymorphisms are shown in Figure 1. We formed two haplotype blocks: Haplotype Block 1 contained SNPs rs2242592, rs1079596, rs1125394, and rs27471857; and Haplotype Block 2 contained rs4648317, rs4350392, rs1799978, and rs12364283. SNPs rs71003679, rs4648318, rs4274224, and rs4581480 were not part of any haplotype block.

Demographic Characteristics

The sample included a similar number of men and women (see Table 2 for participant demographics). Participants were mostly in their 20s with either some college or a completed college education. They were moderate caffeine and alcohol drinkers and low cigarette and marijuana users.

Drug-Free Genotype Differences—Stop Task

Data from 4 participants were dropped because they were extreme outliers on either stop RT or go RT (scores outside of 3 standard deviations). The demographic characteristics of this subsample ($n = 89$) were similar to those of the overall sample (see Table 2) and did not vary significantly across genotypic groups. In general, stop and go RTs were not related to demographic variables included in the study, although the go RT was positively correlated with caffeine use and negatively with BMI. Therefore, caffeine use and BMI were included as covariates in further analyses with go RT.

Genotypic groups of three SNPs (rs4648317, rs4350392, and rs12364283—all in Haplotype Block 2) had significantly different stop RTs (see Table 3). The remaining SNPs in the analysis were not associated with stop RT. The most significantly associated SNP, rs12364283, had a p value of .005. After correcting for testing all 12 SNPs, the p value remained significant at .035 (see Table 4). None of the *DRD2* loci included in this study were associated with go RT.

Four haplotypes (TAAG, CCGA, TAAA, and CCAA) constructed from rs4648317, rs4350392, rs1799978, and rs12364283, were assessed for association with stop and go RTs. Haplotype TAAG was associated with faster stop RT ($p = .005$, indicating lower impulsivity) and remained significant after adjusting for multiple testing ($p = .02$). Haplotype CCAA was associated with slower stop RT ($p = .008$) and remained significant after adjusting for multiple testing ($p = .03$). (See Table 4 for the mean stop RT values for each haplotype.) Haplotypes in Block 1 were not associated with stop RT. None of the haplotypes (in Block 1 or Block 2) were associated with go RT.

We also tested whether using the haplotypes in Block 2 could improve the prediction of stop RT beyond fitting only the most significant single (rs12364283). The likelihood ratio test based on fitting stop RT as a function of rs12364283 genotypes and, separately, as a function of the four haplotypes observed in Block 2 was not significant. Thus, the other SNPs in Block 2 contain little additional information about the relationship between stop RT beyond what rs12364283 explains.

The ZKPQ—This analysis included only 86 participants because the questionnaire was added later in the study. In this subset, genotypic groups of the individual 12 *DRD2* loci were similar on the demographic variables included in this study. Of the 12 SNPs, 2 showed nominally significant differences on the Impulsivity/Sensation Seeking subscale of the ZKPQ (rs4648317 and rs12364283—both in Haplotype Block 2; see Table 3). However, the two SNPs did not remain significant after adjusting for multiple testing (see Table 4).

In addition, the haplotype TAAG, which was also associated with the fastest stop RT (indicating lower impulsivity), had the lowest mean impulsivity score ($p = .02$). After adjusting for testing all four haplotypes, this p value increased to .08 (see Table 4) and, hence, did not remain statistically significant.

Response to d-Amphetamine Analyses

Administration of *d*-amphetamine produced typical effects on mood, but none of the *DRD2* loci included in the study were associated with mood responses to the drug. The drug did not significantly alter stop RT, $F(3, 264) = 1.6$, $p = .18$; or go RT, $F(3, 264) = 0.23$, $p = .88$. However, the drug did influence stop RT when we stratified on the genotype of SNP rs12364283; for Dose $\times$ Genotype, $F(3, 258) = 4.0$, $p = .008$ (Figure 2A). None of the remaining SNPs showed a statistically significant differential pattern of response to *d*-amphetamine. Post hoc comparisons indicated that *d*-amphetamine decreased stop RT in the A/A group but increased stop RT in the combined A/G + G/G genotype. In comparison with the placebo condition, *d*-amphetamine decreased stop RT in the 5-mg ($p \leq .05$), 10-mg ($p \leq .001$), and 20-mg ($p \leq .05$) conditions in the A/A group. However, in the combined A/G + G/G genotype, 10-mg *d*-amphetamine ($p \leq .05$) increased stop RT in comparison with the placebo. Administration of other doses of *d*-amphetamine did not produce results that were different from placebo. Go RTs did not interact with any of the *DRD2* loci included in this study. (See Figure 2, Panels A and B, for stop and go RTs by rs12364283.)

Discussion

The results of this study support the idea that *DRD2* is implicated in inhibition and impulsivity. First, individual SNPs rs4648317 and rs12364283, as well as the haplotype block consisting of those SNPs, were associated with better performance on the response inhibition task in a drug-free condition and lower scores on self-reported measurement of impulsivity. Second, analyses of responses to *d*-amphetamine according to *DRD2* showed a significant interaction between the drug and rs12364283 on a response inhibition task, although the groups did not differ in subjective ratings of mood.

rs1236423, which is located in a conserved suppressor region of *DRD2*, is of particular interest because it was shown by Zhang et al. (2007) to influence the expression of *DRD2* in postmortem brain tissues. The minor allele of rs1236423 confers higher transcriptional activity compared with the major allele; a gain-of-function such as this might be expected to have functional consequences even in heterozygotes. The minor G allele enhances expression of *DRD2* (Zhang et al., 2007), and imaging studies show that enhanced *DRD2* expression is associated with better performance on inhibition tasks (for a review, see Cropley et al., 2006). These data are consistent with our finding that participants with genotypes A/G or G/G performed better on the stop RT in comparison with the A/A group. Analysis of the Block 2 haplotype was no better than rs1236423 alone at accounting for variability in stop RT. These data are consistent with the hypothesis that rs1236423 influences behavior because of its effect on *DRD2* gene expression.

Results of previous work assessing the relationship between impulsivity and inhibition provided mixed results. Although some studies found that higher self-reported impulsivity is associated with poor behavioral inhibition (i.e., higher stop RT; Gorlyn et al., 2005; Logan et al., 1997), others have shown no relationship (Cheung et al., 2004; Lijffijt et al., 2004). In our study, we found that the combined genotype T/C + C/C of rs4648317 and the combined genotype A/G + G/G of rs1236423, as well as the haplotype block consisting of these SNPs, were associated with lower self-reported impulsivity/sensation seeking, as well as lower stop RT (i.e., better behavioral inhibition performance). This finding is the first step in understanding the genetic basis of the neurobiological processes of the two phenotypes. However, the results need to be interpreted cautiously and replicated in future studies in light of the fact that self-reported measure of impulsivity/sensation seeking did not remain significant after adjusting for multiple comparisons.

Analyses of our secondary aim evaluating genetic determinants of subjective rating of mood and behavioral responses to *d*-amphetamine provided interesting results. Contrary to our hypothesis, the drug did not influence mood differentially in the *DRD2* genotypic groups. Results of a previous study indicated that *DRD2* availability may be associated with subjective responses to stimulants (Volkow et al., 1999). One possible explanation is that our study may have been underpowered to detect this effect. The finding that genotypic groups of rs1236423 showed a differential pattern of response on the stop task after administration of *d*-amphetamine is consistent with previous studies. Results of work in animals (Eagle, Tufft, Goodchild, & Robbins, 2007) and humans (de Wit et al., 2000; Mattay et al., 2003) have indicated an interesting pattern of response to psycho-stimulants. Eagle et al. (2007) divided rats into slow and fast responders and found that the administration of methyl-phenidate, a drug that is similar to *d*-amphetamine, reversed stop RTs only in slow-stopping rats, whereas it worsened stop RTs in fast-stopping rats. A similar pattern of response has been observed in humans (de Wit et al., 2000), where administration of *d*-amphetamine did not significantly change stop RT in the overall sample of participants, but when participants were divided into slow and fast stoppers by the median split, the drug improved stop RT only in participants with an initially long stop RT. With the use of genotype locus, rather than slow or fast RT, to segregate our participants into two groups, our finding that *d*-amphetamine improved stop RT in the rs1236423 A/A group (with initially longer stop RT) and worsened stop RT in the rs1236423 A/G + G/G group (with initially shorter stop RT) is consistent with the two previous studies.

This study also had limitations. It included a relatively homogenous population of Caucasian college students, and it is not known whether these findings would apply to more heterogeneous populations including participants of different ages or races/ethnicities. We only analyzed behavioral and mood outcome measures in our study: It would be interesting to determine whether these *DRD2* variations modulate brain activity corresponding to impulsive behavior, both in a drug-free condition as well as in response to *d*-amphetamine. One other limitation

concerns the interpretation of the interaction between drug and genotype on stop RT. It is possible that the differential effect of amphetamine in the A/G+/G/G and A/A groups was driven by differences in baseline (placebo) stop RTs. In addition, the multiple adjustment procedure for haplotype analyses included only haplotypes in Block 2 and not all haplotypes evaluated in the study.

In summary, we found an association between *DRD2* and two impulsivity phenotypes. This experiment was highly controlled and involved a sample of healthy volunteers. The findings add to our understanding of genetic effects on neurobiological mechanisms of inhibition and impulsivity. Our finding that the *DRD2* genotype—in particular, the recently discovered promoter SNP rs12364283—influences both behavioral inhibition and self-reported measure of impulsivity demonstrates a common genetic influence on experimentally and interview-based measures of impulsivity.

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Figure 1. Linkage disequilibrium (LD) plot of the 12 *DRD2* loci included in the analysis. LD values represented are D' . The haplotype structure of *DRD2* is similar to the haplotypes identified in the HapMap Project.

RS 12364283

Figure 2.

(A) Mean stop reaction time (RT) plus or minus standard error of the mean after placebo (0) and *d*-amphetamine (5, 10, 20 mg) in participants grouped by *DRD2* rs12364283 genotype. In the placebo condition, A/A carriers ($n = 75$) took longer to inhibit a response in comparison with the combined A/G + G/G group ($n = 14$; # $p \leq .01$). In comparison with the placebo condition, administration of 5 (* $p \leq .05$), 10 (** $p \leq .001$), and 20 mg (* $p \leq .05$) of *d*-amphetamine decreased stop RTs in the A/A group. In the A/G + G/G genotype, 10 mg of *d*-amphetamine increased stop RTs (* $p \leq .05$). (B) Mean go RT plus or minus standard error of the mean in participants grouped by *DRD2* rs12364283. Go RTs did not differ between the two genotypic groups of rs12364283. # $p \leq .01$. * $p \leq .05$. ** $p \leq .001$.

Table 1**Genotype Frequencies of the DRD2 Polymorphisms**

SNP	Genotype		
rs2242592 ^a	C/C 5 (5.4)	C/T 40 (43.5)	T/T 47 (51.1)
rs1079596	A/A 6 (6.5)	G/A 25 (26.9)	G/G 62 (66.7)
rs1125394	A/A 62 (66.7)	A/G 25 (26.9)	G/G 6 (6.5)
rs2471857	A/A 6 (6.5)	A/G 25 (26.9)	G/G 62 (66.7)
rs7103679	T/T 3 (3.2)	T/C 27 (29.0)	C/C 63 (67.7)
rs4648318	A/A 60 (64.5)	A/G 30 (32.3)	G/G 3 (3.2)
rs4274224	A/A 29 (31.2)	A/G 49 (52.7)	G/G 15 (16.1)
rs4581480	C/C 1 (1.1)	T/C 16 (17.2)	T/T 76 (81.7)
rs4648317	C/C 71 (76.3)	T/C 19 (20.4)	T/T 3 (3.2)
rs4350392	A/A 3 (3.2)	A/C 21 (22.6)	C/C 69 (74.2)
rs1799978	A/A 82 (88.2)	A/G 11 (11.8)	G/G 0
rs12364283	A/A 78 (83.9)	A/G 14 (15.1)	G/G 1 (1.1)

Note. Values are *ns* (and percentages). SNP = single nucleotide polymorphism.

^aOne participant's genotype data was missing

Table 2**Participant Demographic Characteristics and Current and Lifetime Nonmedical Drug Use**

Demographic characteristic	Value
<i>n</i>	93
Mean age in years ($\pm SEM$)	22.3 $\pm$ 0.3
Gender (male/female)	50/43
Mean BMI ($\pm SEM$)	22.5 $\pm$ 0.2
No. of years of education	
High school	1
Some college	39
College degree	39
Advanced degree	14
Current substance use	
Alcohol (mean number of drinks per week $\pm SEM$)	4.3 $\pm$ 0.4
Tobacco (mean number of cigarettes per week $\pm SEM$)	0.6 $\pm$ 0.1
Marijuana (mean number of times used per month $\pm SEM$)	0.8 $\pm$ 0.2
Caffeine (mean cups per week $\pm SEM$)	6.0 $\pm$ 0.5
Lifetime substance use (% ever used)	
Marijuana	74.2
Stimulants	32.3
Opiates	23.7
Hallucinogens	16.1
Inhalants	8.6

Summary of Significant Associations Between DRD2 Single Nucleotide Polymorphisms (SNPs) and Measures of Behavioral Inhibition (Stop Task) and Self-Reported Personality Measure of Impulsivity (on the ZKPQ)

SNP	Stop RT ^a (drug free)			Impulsivity/Sensation Seeking subscale of the ZKPQ				
	Mean ± SEM	p	F	Mean ± SEM	p	F		
rs4648317	C/C 194.3 ± 5.6	C/T + T/T 161.8 ± 10.3	.006	7.8	C/C 9.9 ± 0.5	C/T + T/T 7.8 ± 0.8	.045	4.2
rs4350392	C/C 193.7 ± 5.7	A/C 166.3 ± 10.1	.018	5.8	C/C 9.9 ± 0.5	A/C 8.0 ± 0.8	ns	ns
rs12364283	A/A 192.7 ± 5.3	A/G + G/G 153.9 ± 13.3	.005	8.2	A/A 9.8 ± 0.5	A/G + G/G 7.3 ± 1.1	.041	4.3

Note. ZKPQ = Zuckerman–Kuhlman Personality Questionnaire. Higher values represent higher self-reported impulsivity/sensation seeking.

^aStop reaction times are given in milliseconds.

Higher values indicate more impulsive responding on the stop task.

Table 4

Means for Stop Reaction Times (RTs, in Milliseconds) and Zuckerman–Kuhlman Personality Questionnaire Self-Reported Impulsivity/Sensation Seeking Score According to Single Nucleotide Polymorphisms (SNPs) in Block 2: rs4648317, rs4350392, rs179978, and rs12364283 and Haplotypes Formed by Them

SNP and haplotype	Values					
	Allele 1	n	Mean	Allele 2	n	Mean p Adjusted p
Stop RT						
SNP						
rs4648317	T	23	169.8	C	155	190.5 .0065 .0474 *
rs4350392	A	25	165.0	C	153	190.2 .0184 .1294
rs179978	G	11	178.5	A	167	187.2 .5517 .9972
rs12364283	G	15	154.9	A	163	189.6 .0052 .0352 *
Haplotype						
TAAA	10	180.2	.5083			.8872
TAAAG	13	145.8	.0047			.0186 *
CCAA	142	191.1	.0083			.0324 *
CCGA	11	178.5	.6869			.9718
Zuckerman–Kuhlman Personality Questionnaire Self-Reported Impulsivity/Sensation Seeking						
SNP						
rs4648317	T	23	7.2	C	149	9.8 .0448 .2950
rs4350392	A	24	7.4	C	148	9.8 .0715 .4258
rs179978	G	11	11.1	A	161	9.3 .1448 .6778
rs12364283	G	14	7.3	A	158	9.6 .0411 .2758
Haplotype						
TAAA	10	7.5	.1106			.3220
TAAAG	13	6.9	.0237			.0760

	Count	Mean	<i>p</i>	Adjusted <i>p</i>
CCAA	137	9.7	.1267	.3610
CCGA	11	11.1	.1309	.3654

Note. Count is the number of each allele or haplotype observed in all individuals. Mean is the average value among individuals possessing the allele or haplotype specified in the row, calculated as the sum of the values for each individual multiplied by 0, 1, or 2, depending on the number of alleles or haplotypes possessed by the participant, and divided by the total number of alleles or haplotypes observed. *p* values for SNP tests come from analysis of variance with SNP genotype as a factor. *p* values for haplotypes were determined with 5,000 permuted datasets. Adjusted *p* value for SNP tests corrects for testing 12 correlated SNPs with permutation testing. Adjusted *p* values in the haplotype table may be interpreted similarly, but the correction is for testing four haplotypes.

* Statistically significant at the .05 level.