Dopaminergic Genetic Variation in Young Adolescents: Associations with Sensation-Seeking

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Abstract:

Deficient reward functioning, including reward-related personality, is implicated in depression's etiology. A dopaminergic genetic multilocus genetic profile score (MGPS) has previously been associated with neural reward responsivity but, despite theoretical basis, has not been studied with reward-related personality. Such research is needed to elucidate associations between genetic variation and reward-related personality in a developmentally sensitive population. In the present study, we examined associations between dopaminergic MGPS's and self-report reward-related personality in two young adolescent samples aged 10–15 years old (Sample 1: N=100 girls, 82% White, 18% Other; Sample 2: N=141, 65 girls, 76 boys, 89.36% White, 10.64% Other) using an established MGPS and an augmented MGPS. A "mini" meta-analysis synthesized results across samples. In Sample 1, an exploratory mediation analysis intended to gauge effect size for future work tested a path between the MGPS and depression through significant reward traits. In each independent sample, both MGPS's showed significant associations with sensation-seeking but not social drive, a pattern that persisted following correction. Effect sizes of novel variants were at least as robust as established variants, suggesting their added utility. Additionally, the exploratory mediation analysis suggested no noteworthy indirect effect, but a small (R2=0.022), statistically non-significant direct effect of the MGPS predicting prospective depressive symptoms. Results suggest that dopaminergic genetic variation is associated with the reward-related personality trait of sensation seeking but not social drive. Additional work is needed to probe whether sensation seeking may be a path through which this genetic variation confers depression risk.

Keywords: dopamine | genetics | sensation-seeking | depression

Article:

Major depressive disorder affects around 17% of people in the United States in their lifetimes (Kessler et al., 2005), with major economic (Greenberg et al., 2015) and health (Moussavi et al., 2007) impact. Given that depression increases rapidly in mid-adolescence (Hankin et al., 1998; Rohde et al., 2013), it is critical to examine risk pathways prior to this increase (i.e., in early adolescence).

Additionally, evidence indicates that changes to reward-related brain pathways begin in early-adolescence (Fuster, 2002; Romer, 2010). Reward-related traits have been implicated in depression risk (Beevers & Meyer, 2002; Kotov et al., 2010; Loas, 1996). Moreover, the brain dopamine system is thought to contribute to reward-related traits (DeYoung, 2013; Wise & Rompré, 1989). Recent evidence links additive risk from multiple dopaminergic genetic variants with neural reward responsivity (Nikolova et al., 2011; Stice et al., 2012) and with self-report depressive symptoms (Pearson-Fuhrhop et al., 2014) in adults. Limited research, however, examines the relationship of additive dopaminergic genetic variation with reward-related traits, particularly in early adolescents. Here, using two early adolescent samples, we examined the relationship of additive dopaminergic genetic variation to reward-related personality traits.

Reward-Related Personality Traits

Reward-related personality (i.e., extraversion) reflects traits associated with seeking reward externally (Depue & Collins, 1999; Watson & Clark, 1997) and consists of two central components: "interpersonal engagement" and "impulsivity-sensation seeking" (for review see Depue & Collins, 1999). Though these traits are often labelled differently, here we call them "social drive" (i.e., anticipation of pleasure from relationships or social achievements; Patrick et al., 2002) and "sensation-seeking" (i.e., anticipation of pleasure from novel experiences; Zuckerman et al., 1964), respectively. In the present study, we use the term "reward-related personality" as a higher order construct synonymous with Extraversion and subsuming overlapping terms such as impulsivity, sensation-seeking, novelty-seeking, and the behavioral approach system (Gray, 1990). Indeed, in prior work, measures of these constructs show correlations with each other (e.g., sensation seeking and novelty seeking r=0.43; McCourt et al., 1993) as well as with measures of Extraversion (Watson & Clark, 1997).

The Link from Reward-Related Personality Traits to Depression Risk

Anhedonia, a core component of depression in both children and adults (see Weiss & Garber, 2003 for review), reflects reward-related dysfunction (Hasler et al., 2004) and blunted reward motivation (Treadway & Zald, 2011). Furthermore, low levels of reward-related personality traits such as low behavioral approach in adults (Beevers & Meyer, 2002) and low extraversion in children and adults (Kotov et al., 2010; Malouf et al., 2005) have been examined in relation to the development of anhedonia and depression in adults. The frst of these, BAS (Gray, 1990), reflects appetitive motivation (i.e., goal directed behavior) and positive incentive salience. The BAS system is theoretically similar to reward-related personality and indeed, shows robust correlations with other reward-related personality measures (e.g., sensationseeking and BAS fun seeking r=0.5; Smillie et al., 2006). In prior work in adults, low BAS strength in all three BAS subscales was cross-sectionally significantly associated with self-reports of anhedonia symptoms (fun-seeking: r=-0.25, drive: r=-0.20, reward responsiveness r=-0.19; Beevers & Meyer, 2002). In children, although work has largely not examined reward-related personality and depression symptoms prospectively, cross-sectional research suggests significant associations; Extraversion and depressive symptoms were significantly correlated in Spanish children (del Barrio et al., 1997), and blunted ventral striatal reactivity—a marker of low reward processing—was associated with low reward anticipation and outcome in depressed adolescents relative to non-depressed adolescents (Forbes et al., 2009a, b).

A second line of work has linked extraversion to depression risk. In one meta-analysis, extraversion predicted major depressive disorder (Malouf et al., 2005). A second meta-analysis indicated that extraversion significantly predicted dysthymia, but not major depressive disorder specifically, when adjusting for neuroticism (Kotov et al., 2010). These meta-analytic results suggest value in examining factors that may contribute to reward-related traits, such as molecular genetics. Indeed, studies examining potential molecular genetic bases for reward-related personality traits have found that sensation-seeking heritability ranges widely from 29%-60% (Stoel et al., 2006), and social drive heritability is estimated at 70% (Beatty et al., 2002), indicating at least modest and potentially robust genetic contributions to these personality traits. Thus, we focused on genetic prediction of two reward-related personality traits—social drive and sensation-seeking.

Dopaminergic Genetic Variation and Reward

To predict these reward-related traits, we focused on ventral striatal dopaminergic genetic markers, due to this brain region's role in reward-related processes (Forbes et al., 2009a, b). Evidence supports the roles of dopamine and ventral striatal activity in incentive salience or wanting/seeking rewards (Berridge, 2007), reward traits broadly (DeYoung, 2013), and sensation-seeking personality traits (Cohen et al., 2009). Recently, novel "multilocus" genetic profile scores (MGPS) have offered means to examine dopaminergic genetic variation in relation to reward traits, leveraging the additive effect of multiple polymorphisms chosen a priori, typically based on biological evidence of functionality. This MGPS methodology is consistent with polygenic, additive theoretical assumptions in behavioral genetics, which indicate that many polymorphisms, each with small effect sizes, collectively contribute to complex phenotypes (Plomin et al., 2009).

Studies using such a multilocus approach1 with dopaminergic genetic variants predicted activity in reward-related brain regions in White adults (Nikolova et al., 2011), and in a predominantly (i.e., 77.6%) European American sample (Stice et al., 2012), but examined task-related brain activation and not reward-related personality traits. Other work, however, suggests that a dopaminergic MGPS will also relate to reward-related traits: An additive dopaminergic genetic risk score derived from a genome-wide association study (i.e., not relying on candidate genetic variants) accounted for 4% of sensation-seeking variance in adults (White: 72.9%, African American: 18.9%, Hispanic: 8.2%; Derringer et al., 2010), and a candidate-derived MGPS similar to Nikolova et al.'s predicted the Eysenck Personality Inventory-R Addiction Scale—an empirically derived scale reflection impulsivity, stress and emotional reactivity, and negative affect in a predominantly White sample (80%; Davis & Loxton, 2013). Last, in a sample of all-White adults, a candidate-derived genetic profile score composed of five polymorphisms from two genes, DRD2 and ANNK1, coded toward lower sensation-seeking, aggressive tendencies, and putative dopamine functioning indirectly predicted physical aggression in a mediational model via sensation-seeking tendencies (Chester et al., 2016).

However, to date, no studies have predicted reward-related traits using a candidate-derived MGPS coded based on putative biological dopamine signaling. Given the relationship between ventral striatal reactivity and reward-related traits (Leyton et al., 2002; Lind et al., 2005), we hypothesized that a dopaminergic MGPS described by Nikolova et al. (2011) would predict reward-related traits. Further, utilization of a biologically informed MGPS will facilitate better understanding of the genetic pathways implicated in depression risk.

Table 1 Dopamine Polymorphisms Overview

Coding	DRD4 VNTR	COMT Val158Met	DAT1 VNTR	DRD2 141C Ins/Del	ANNK Taq1A	DRD2 C957T	DRD4 C521T
1	7-r carrier (n = 81)	Met/Met (n = 68)	9-r carrier (n = 101)	Del carrier (n = 38)	C/C (n = 153)	T/T (n = 65)	C/C (n = 54)
0.5		Val/Met (n = 119)			C/T (n = 68)	T/C (n = 112)	
0	0	0	0	0	0	0	0

The established MGPS is composed of the first 5 polymorphisms listed in the table. The additional polymorphisms (in gray) were added to create the 7 polymorphism "augmented" MGPS

Table 2 Functional evidence of dopamine polymorphisms

Genetic Variant	Evidence
DRD2 141C Ins/Del	Deletion allele in promotor region tied to increased ventral striatal reactivity (Forbes et al., 2009a, b)
DAT1 VNTR	9-repeat allele of 40 base pair VNTR in DA transporter gene linked to reduced DA reuptake and greater striatal DA signaling (Heinz et al., 2000)
DRD4 VNTR	7-repeat allele tied to reduced postsynaptic inhibition and increased DA signaling (Wang et al., 2004)
COMT Val158Met	Met allele associated with less degradation of DA and greater ventral striatal reactivity (Dreher et al., 2009)
DRD2 Taq 1a	C (A2) allele associated with greater DA signaling (Noble et al., 1991)
DRD2 C957T	T-allele homozygote associated with greater striatal D2 binding than C-allele homozygote or heterozygote genotype (Hirvonen et al., 2005)
DRD4 C521T	T-allele associated with 40% less DRD4 receptor activity than C-allele genotype (Okuyama et al., 2000)

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Established & Augmented Dopaminergic Multilocus Profile Polymorphisms

Here, we examined the role of a previously described dopaminergic MGPS (Nikolova et al., 2011) in reward-related traits. We augmented this with two additional polymorphisms. The established MGPS comprised five polymorphisms located in the genes DAT1, DRD2, ANNK, DRD4, and COMT (see Table 1 for individual variants and values assigned; Nikolova et al., 2011). Genotypes associated with greater dopamine signaling and ventral striatal reactivity to reward were assigned a value of 1, genotypes associated with lower dopamine signaling were coded as 0, and when functional evidence indicates that heterozygotes constitute intermediate signaling, these were assigned a value of 0.5 (COMT Val158Met, ANNK Taq1A, DRD2 C957T). Similarly, the augmented MGPS used these same five polymorphisms but also two additional functional polymorphisms, C957T within the DRD2 gene and C521T within the DRD4 gene. The C957T (rs6277) T-allele homozygote genotype is associated with greater striatal D2 binding potential than the C-allele homozygote genotype, with the heterozygote genotype conferring intermediate functioning (T/T > T/C > C/C; Hirvonen et al., 2005). This variant has been used in prior genetic profile scores to predict food addiction (Davis et al., 2013) and addiction-prone personality traits (Davis & Loxton, 2013). Similarly, carrying the DRD4 C521T (rs1800955) T-allele is associated with 40% less DRD4 receptor activity than the homozygote C-allele genotype (Okuyama et al., 2000). We are unaware of support for a heterozygote intermediate (see Table 1 for coding and Table 2 for review of evidence of functional effects of each variant). The C521T polymorphism was also implicated in reward-related personality traits by a meta-analysis (Munafò et al., 2008).

Early Adolescence

Examining relationships between dopaminergic genetic variants and reward-related personality in early adolescence is particularly useful. Prior work suggests a marked increase in depression during mid-adolescence (Hankin et al., 1998; Rohde et al., 2013); this pattern suggests utility in examining risk pathways prior to this increase. Notably, during this developmental period, rates of depression between boys and girls diverge, with girls experiencing higher rates (Nolen-Hoeksema, 1990); thus, studying reward-related personality in girls may be particularly informative. Second, beginning in early adolescence, reward related brain pathways (e.g., ventral striatum) "mature" (Fuster, 2002); however, executive control over these pathways and experience modulating reward drive is underdeveloped (Romer, 2010). Early-to-mid adolescence is characterized by increasing dopamine signaling and innervation and an increase in synaptic pruning in the prefrontal cortex. These changes may result in difficulties regulating high levels of motivation and exploratory behaviors (Wahlstrom et al., 2010), potentially contributing to the established pattern of heightened reward-seeking behaviors in adolescence (Urošević et al., 2012).

Given the potential importance of reward-related personality to depression risk (Malouff et al., 2005) and the development of both reward-related personality and depression risk during early adolescence, understanding genetic predictors of low reward-related personality in this population may yield useful insights into etiological factors in depression. Indeed, the associations between reward-personality and depression (Malouff et al., 2005) and the genetic associations between the dopaminergic genetic variation and reward functioning (Nikolova et al., 2011; Stice et al., 2012) suggest a model in which dopaminergic genetic variation may confer risk for depression through its effects on reward-related personality. Identification of these pathways prior to the increase in depression rates around age 15 (Hankin et al., 1998; Rohde et al., 2013) may

provide targets for preventative interventions and generate a better understanding of the development of risk pathways leading up to an abrupt increase in depression rates.

The Present Study

We examined the relationship between dopaminergic genetic variation and reward traits in two independent early adolescent samples to test replication of observed effects. In both samples, we tested the prediction that an established MGPS (Nikolova et al., 2011) would be associated with sensation-seeking and social drive, and we examined the contribution of two additional polymorphisms (DRD2 C957T and DRD4 C521T) in an augmented MGPS. We evaluated these predictions using a mini meta-analysis to synthesize results across two samples. Finally, as an exploratory analysis to provide estimates of sample sizes necessary to fully power tests of the dopaminergic MGPS on depression, in one sample in which prospective depression data was available, we conducted a mediation model examining prediction by the MGPS through baseline sensation seeking to prospective depression.

Methods

Sample 1 data come from the Project on Youth Stress and Coping at Williams College. Sample 2 data come from the Youth Emotion Regulation Project at Lawrence University. All procedures were approved by respective institutional review boards (IRB). The present analyses of archival data were approved by the IRB of the University of North Carolina at Greensboro.

Sample 1

Participants Participants were 100 adolescent girls aged 10–15 years old ($M = 12.39$, $SD = 0.76$). Participants were White ($n = 82$; 82%), Black ($n = 3$; 3%), Asian ($n = 5$; 5%), Native American ($n = 1$; 1%), and multiple or other races ($n = 9$; 9%). In both samples, race was self-reported and a SNP ancestry panel was not available. Eligible participants were in 6th, 7th, or 8th grade, and had a primary caregiver willing to participate. All were recruited from two New England counties by flyers, word-of-mouth, and from local schools; participants and caregivers provided informed assent or consent, respectively.

Measures

Trait Reward Sensitivity To determine subscales measuring sensation-seeking and social drive across different measures in each of these archival samples, all available item content was examined for similarity. Sample 1 reward-related measures were screened and nominated for consideration by CBS and SVS and Sample 2 by LMH. Final measures were chosen by consensus of the authorship team. Example items from each subscale are reported in Table 3. In Sample 1, participants completed the Multidimensional Personality Questionnaire Brief Form (MPQ-BF; Patrick et al., 2002), a 155-item questionnaire that measures positive and negative emotionality and constraint, each of which contain lower-order scales. Sensation-seeking was indicated by the reverse scored "Dislikes Risky Adventures" subfacet of the Harm Avoidance subscale of constraint (4-items; $\alpha = 0.63$). We chose this subfacet because the Harm Avoidance subscale showed the strongest correlation to Zuckerman et al. (1964)'s sensation-seeking scale (Patrick et al., 2002),

and because of strong content match between the reverse scored "Dislikes Risky Adventures" subfacet and the comparable measure in Sample 2. This subfacet reflects displeasure with novel activities (e.g., reverse scored, "I might enjoy riding in an open elevator to the top of a tall building under construction"). Social drive was measured by the Social Potency subscale (14 items; $\alpha = 0.77$), reflecting pleasure from leadership, visibility, and dominance (e.g., "I enjoy being in the spotlight").

Genetic Assays DNA was extracted using Oragene PrepIT L2P DNA Purification Kits. Genotyping was conducted using allele-specific polymerase chain reaction (PCR) and ascertained through fluorescent detection with a synergy II Plate reader (Biotek Instruments, Winooski, VT).

Multilocus Profile Score Following Nikolova et al. (2011), to compute the established "biologically informed" MGPS, each genotype was coded by its putative dopamine signaling level, with "high" scored as 1, "intermediate" scored as 0.5, and "low" scored as 0, and then scores across all 5 polymorphisms were summed. Each of these polymorphisms were chosen given their known associations with striatal dopamine signaling (see Nikolova et al., 2011 for review of polymorphisms), a key component of the brain reward system (Tanaka et al., 2016). An intermediate score was assigned if evidence indicated that dopamine signaling differed for heterozygotes relative to homozygotes (COMT Val158Met, ANNK Taq1A, DRD2 C957T). Additional polymorphisms were similarly scored for the augmented MGPS (Table 1). The DRD2 C957T heterozygote was coded at the intermediate level given evidence of heteroyzygote intermediate dopamine signaling (i.e., between that of each homozygote genotype) (Hirvonen et al., 2004). Higher MLPSs were expected to correspond to greater trait reward sensitivity. For frequency of participants by genotype, see Table 1.

K-SADS Prospective depression data were available in Sample 1. Participants completed the Schedule for Affective Disorders and Schizophrenia for School Age Children Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997). The K-SADS-PL is a semi-structured interview assessing depressive symptoms rated 0 (no symptoms), 1 (one to two symptoms), 2 (three to four symptoms), to 3 (meeting criteria DSM-IV criteria for depression). Participants completed K-SADS-PL interviews at Time 1 (at the time of collection of reward trait measures) and Time 2 (approximately 1 year after collection of personality measures). Interrater reliability was good and was assessed through audio-recordings for 27% of interviews (T1: current ICC: 1.00, past ICC: 0.97; T2: current ICC: 0.95, past ICC: 1.00).

Sample 2

Participants Participants were 141 youth (46.1% girls) aged 10–14 years old ($M = 12.74$, $SD = 1.05$). Paternal race was White ($n = 125$; 88.7%), African American ($n = 3$; 2.1%), Asian ($n = 1$; 0.7%), Native American ($n = 3$; 2.1%), Other ($n = 6$; 4.3%), and $n = 3$; 2.1% chose not to answer. Maternal race was White ($n = 136$; 96.5%), African American ($n = 4$; 2.8%), and $n = 1$; 0.7% chose not to answer. Participants were recruited from a small Midwestern community through local organizations, flyers, and mailing parents of children enrolled in the local school district.

Table 3 Examples of items from reward trait personality measures by sample

Sensation Seeking	
Sample 2	Sample 1
•Surgency scale of the EATQ-R (example items) • "Thinks traveling to Africa or India would be exciting and fun" • "Would be frightened by the thought of skiing fast down a steep slope" (Reverse) • "Thinks it would be exciting to move to a new city" • "Would like driving a racing car."	• Risky Adventures subscale of the MPQ-BF • "I might enjoy riding in an open elevator to the top of a tall building under construction" • "I would enjoy trying to cross the ocean in a small but seaworthy sailboat" • "Of the following two situations I would like least: Riding a long stretch of rapids in a canoe, or Waiting on someone who's late" • "It might be fun learning to walk a tightrope"
Social Drive	
• Shyness scale of the EATQ-R • "Can generally think of something to say, even with strangers." • "Is shy." (Reverse) • "Likes meeting new people." • "Feels shy about meeting new people." (Reverse)	• Social Potency subscale of the MPQ-BF • "I enjoy being in the spotlight" • "When I work with others I like to take charge" • "I am quite effective at talking people into things" • "People consider me forceful"

Procedure In a larger study, participants and a parent began by completing questionnaires at home prior to their laboratory visit. All completed informed assent or consent respectively.

Measures

Trait Reward Sensitivity Sensation-seeking was assessed by the Surgency subscale of the Early Adolescent Temperament Questionnaire – Revised Parent Version (EATQ-R; Ellis & Rothbart, 1999). The EATQ-R is a 62-item questionnaire measuring temperament and behavior. Responses are on a 5-point scale ranging from "Almost always untrue" to "Almost always true". The Surgency subscale (9-items; $\alpha = 0.72$) reflects pleasure from novel and intense activities (e.g. "Would be frightened by the thought of skiing fast down a steep slope" Reverse scored). Social drive was measured through the Shyness subscale (5 items; $\alpha = 0.89$), reverse scored. The Shyness subscale reflects inhibition to social novelty and challenge (e.g. "Likes meeting new people.").

Genetic Assays and Multilocus Profile Score See Sample 1 Methods.

Data Analytic Plan

Power Analysis

We conducted an a priori power analysis using GPower 3 (Faul et al., 2007) to assess sample sufficiency for examining the MGPS on reward-related traits in omnibus tests, converting Cohen's f2 to R2. The a priori plan was to synthesize results from the two samples by using a meta-analytic approach. Using a combined sample size ($N = 241$) to reflect analyses at the meta-analytic level, one predictor, and $\alpha=0.05$, power was deemed sufficient (≥ 0.8) to detect effect sizes above $R2 = 0.033$; this fully-powered effect size is smaller than an effect observed in a similar report ($R2 = 0.039$; Derringer et al., 2010). In Sample 1 ($N = 100$), power was sufficient (≥ 0.8) to detect effect sizes above $R2 = 0.074$, and in Sample 2 ($N = 141$), power was sufficient to detect effect sizes above $R2 = 0.057$. Further, though sample sizes were modest (separate Ns = 100, 141), prior MGPS research (e.g., N = 69, Nikolova et al., 2011; N = 160, Stice et al., 2012) suggests that these additive variables have larger effect sizes than individual variants, and thus even moderately-sized samples might provide sufficient power to detect effects (e.g., Starr & Huang, 2018). Overall, power analyses indicate sufficient power to detect effects at the meta-analytic level for associations between the MGPS and reward-related traits.

Reward-Related Traits

We conducted separate linear regression analyses using Mplus (Muthén & Muthén, 2010) to examine the effects of the MLPSs on sensation-seeking and social drive. We limited analyses to these constructs because both samples possessed appropriate measures of each and because both constructs are important to the broader trait—extraversion (Depue & Collins, 1999).

All analyses were first conducted with the established MGPS, followed by the augmented MGPS. In all models, a priori-chosen covariates were included due to their associations with depression risk: a socioeconomic status indicator (income; Lorant et al., 2003) in both samples, and gender (Nolen-Hoeksema, 1990) only in Sample 2 given participants in Sample 1 were all girls. Analyses re-run excluding the covariates showed an equivalent significance pattern.

Mini Meta-Analyses

In order to synthesize the results of both samples to increase power, we planned to aggregate effect sizes across samples in a mini meta-analysis approach using Comprehensive Meta-Analysis software (Borenstein et al., 2005). We favored this approach versus standardizing measures of reward-related traits in each sample and combining results across samples given the potential of sample-level differences such as gender (Cross et al., 2011) affecting reward-related personality. We ran four separate analyses using effect sizes (i.e., Hedges' g) from both samples (two MGPS, two reward measures in each sample) in random effects models. We made these a priori decisions given that 1) Hedges' g is more appropriate than Cohen's d when sample sizes vary (Ellis, 2010) and 2) random effects models take into account error due to differences between populations from which samples are drawn (Borenstein et al., 2010). Furthermore, we accounted for multiple testing through a single False Discovery Rate (FDR; Benjamini et al., 2001) correction across all four meta-analyses.

Post Hoc Analyses

Three post-hoc analyses were planned; results for individual samples and the meta-analysis are provided, but interpretations are made at the more statistically authoritative meta-analytic level. First, to inform whether any particular polymorphism was driving the profile score's effect, we conducted "N-1" analyses for significant omnibus MGPS outcomes using 7 separate profile scores, each removing one polymorphism (see Vrshek-Schallhorn et al., 2015). Second, as an additional means to gauge relative contributions of individual polymorphisms, separate regressions were run to inspect effects (as t-values) of each polymorphism on any significant reward-related trait. Third, primary analyses were re-run in the subset of White participants, the largest racial sub-group in both samples, to rule out the possibility of spurious findings arising from population stratification. To address multiple testing and examine results across samples, all post-hoc analyses were synthesized via meta-analysis. Throughout the paper, p-values of < 0.05 are characterized as statistically significant, and values < 0.10, but > 0.05 are characterized as approaching significance.

Novel MGPS Polymorphisms

To assess the impact of newly added polymorphisms in the augmented MGPS (DRD2 C957T and DRD4 C521T), we inspected their effect sizes relative to individual polymorphism effect sizes in the established MGPS. This is preferable to testing whether the newly added polymorphisms make significant incremental improvements to the model because polygenic, additive theoretical assumptions suggest that a limited number of additional polymorphisms will contribute small effect sizes that are not significant alone. Thus, in addition to reporting results with the augmented MGPS, we gauged added polymorphism value based on whether their individual effect sizes (a) were in the predicted direction, a modest indicator of added utility, and (b) had similar magnitude as polymorphisms in the established profile score, a stronger indicator of added utility. Due to missing genetic and questionnaire data for a single subscale, sample sizes for analyses (reported below) vary nominally across analyses; Ns are indicated in Table 4.

Exploratory Mediation Model to Gauge Effect Sizes

Although prior evidence suggests that psychopathology may be more distal than personality from genetic variation (e.g., Savitz et al., 2006), and thus analysis of dopaminergic MGPS predicting depression is bound to be underpowered and non-significant in samples of N = 100 and N = 141, exploratory analyses to estimate effect sizes can inform future work. Indeed, effect sizes provide a useful indication of the strength of relationships largely independent of sample size (Hojat & Xu, 2004). Thus, an exploratory analysis of depressive symptoms in Sample 1 was conducted to probe the potential indirect pathway between dopaminergic genetic variation depression risk via reward related personality. A mediation test, bootstrapped to 10,000 samples was conducted through PROCESS (Hayes, 2012) in IBM SPSS Statistics version 23 (IBM, 2015). The model predicted worst depressive symptoms between Time 1 and Time 2 from dopaminergic MLPS via sensation seeking. To decompose this model, linear regressions were conducted to estimate the effect sizes of each path, which are not provided by PROCESS for mediation models.

Results

Hardy–Weinberg Equilibrium

In Sample 1, apart from the Taq1A polymorphism in the ANKK gene, all polymorphisms were in Hardy–Weinberg Equilibrium (HWE; ANKK Taq1, $\chi2 = 5.257$, $p = 0.022$, all remaining $\chi2 \leq 0.753$, $ps \geq 0.385$). When the ANKK Taq1A polymorphism was excluded in both samples to address the possibility of genotyping errors indicated by HWE violation, the meta-analytic results across samples remained consistent with the primary results (full results available upon request from first author). Primary analyses include the ANKK Taq1A polymorphism throughout. In Sample 2, all polymorphisms were in Hardy–Weinberg Equilibrium ($\chi2 \leq 2.919$, $ps \geq 0.088$).

MGPS Predicting Reward-Related Traits

Individual Samples

Linear regression analyses were conducted separately in Sample 1 and Sample 2. In both samples, the established MGPS approached significance (i.e., $p < 0.10$) in predicting sensation-seeking (Sample 1: $b = 0.058$, $p = 0.080$; Sample 2: $b = 0.108$, $p = 0.082$). However, for both samples, the augmented MGPS significantly predicted sensation-seeking (Sample 1: $b = 0.061$, $p = 0.032$; Sample 2: $b = 0.108$, $p = 0.037$; see Fig. 1)Footnote2Footnote3. Notably, R2 estimates of the relationship between the augmented MGPS and sensation-seeking was similar across both Samples (Sample 1 R2: 0.043, 95% CI of ß = [0.004, 0.119]; Sample 2 R2: 0.030) 95% CI of ß = [0.004, 0.212]. Neither the established (Sample 1: $b = 0.003$, $p = 0.917$, Sample 2: $b = 0.011$, $p = 0.745$) nor the augmented MGPS (Sample 1: $b = 0.007$ $p = 0.756$, Sample 2: $b = 0.026$, $p = 0.357$) were significant predictors of social drive in separate linear regressions for either individual sample (Table 4).

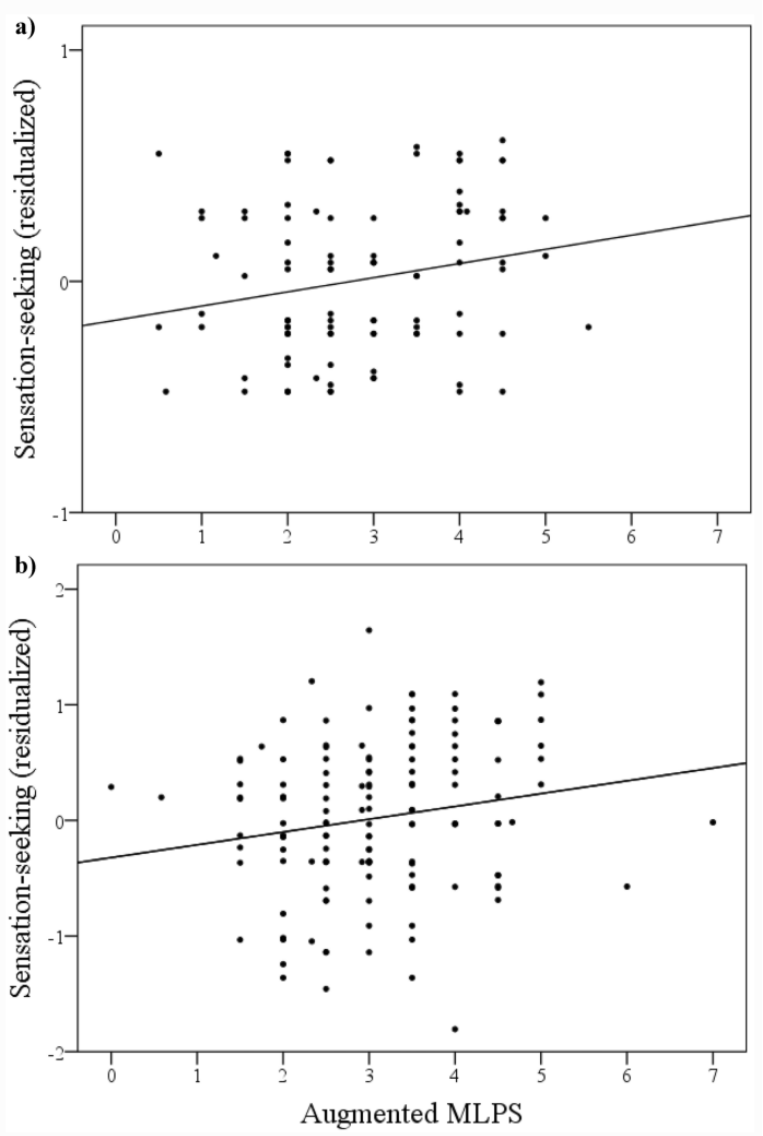

Figure 1 Scatter plots depicts results from a Sample 1 (N=100) and b Sample 2 (N=141). Sensation-seeking is residualized with respect to covariates income and gender. The augmented MGPS is a significant predictor and captures 5.9% of variance in sensation-seeking in Sample 1 and 3.8% of variance in Sample 2.

Mini Meta-analyses

Mini meta-analyses aggregating sample data revealed that both the established (Hedges' g = 0.318, p = 0.016) and the augmented (Hedges' g = 0.384, p = 0.004) MGPS significantly predicted sensation-seeking, but not social drive (established: Hedges' g = -0.041, p = 0.753; augmented: Hedges' g = -0.116, p = 0.369; see Table 4). FDR correction across the four meta-analyses provided consistent results: The established (p = 0.032) and the augmented (p = 0.016) MGPS significantly predicted sensation-seeking, but not social drive (established: p = 0.753; augmented: p = 0.492)Footnote4.

Table 4 Linear Regression Results Predicting Sensation-Seeking and Social Drive Using the Established and Augmented MGPS in the Individual Samples and Mini Meta-Analysis

	Sample 1 (all girls)				Sample 2 (boys and girls)				Mini Meta-Analysis		
Sensation Seeking	b	SE(b)	t	p-value	b	SE(b)	t	p-value	Hedges' g	SE(g)	p-value
Established Profile Score	0.058	0.033	1.752	0.08	0.108	0.062	1.742	0.082	0.318	0.131	0.016
Augmented Profile Score	0.061	0.029	2.145	0.032	0.108	0.052	2.087	0.037	0.384	0.132	0.004
Social drive	b	SE(b)	t	p-value	b	SE(b)	t	p-value	Hedges' g	SE(g)	p-value
Established Profile Score	0.003	0.025	0.104	0.917	0.011	0.034	-0.325	0.745	-0.041	0.129	0.753
Augmented Profile Score	0.007	0.022	0.311	0.756	0.026	0.028	-0.921	0.357	-0.116	0.130	0.369

Sample 1: N 100 for sensation-seeking, N 101 for social drive (Ns differ due to missing data); Sample 2: N 141 throughout. Gender and Income are included in all models but were not significant predictors. Full models are available from the first author upon request

Table 5 N-1 Sensitivity Analyses: Prediction of Sensation-seeking in Linear Regression (MGPS Lacking Each SNP in Succession)

	Sample 1			Sample 2			Meta-Analytic Results		
	N	t	p-value	N	t	p-value	Hedges' g	SE(g)	p-value
MGPS without DRD2—141C Ins/Del	100	1.663	0.096	141	1.739	0.082	0.310	0.131	0.018
MGPS without DAT1 VNTR	101	2.024	0.043	142	1.332	0.183	0.297	0.131	0.023
MGPS without DRD4 VNTR	100	1.663	0.096	142	1.962	0.050	0.331	0.131	0.012
MGPS without COMT Val158Met	101	1.650	0.099	141	2.489	0.013	0.382	0.132	0.004
MGPS without ANNK Taq1A	100	2.374	0.018	141	2.230	0.026	0.317	0.133	0.002
MGPS without DRD2 C957T	100	2.153	0.031	141	1.560	0.119	0.332	0.132	0.012
MGPS without DRD4 C521T	100	1.734	0.083	141	2.259	0.024	0.367	0.132	0.005

For space, gender and income effects are not presented but are included in each of the seven models above for both samples. Full models available from the first author. Ns vary nominally due to missing genetic calls across polymorphisms

N-1 Sensitivity Analyses

At the meta-analytic level, all N-1 sensitivity analyses were significant suggesting that results do not depend upon any one polymorphism, consistent with polygenic, additive assumptions. However, in individual samples, sensitivity analyses revealed mixed effects of each "N-1" MGPS predicting sensation-seeking (See Table 5).

Individual Polymorphism Sensitivity Analyses

In meta-analyses, individual polymorphisms were not significant predictors of sensation-seeking with the exception of DAT1 VNTR (Hedges' $g = 0.284$, $p = 0.032$; full results available upon request). In each sample, analyses examining individual polymorphism effect sizes predicting sensation-seeking, revealed a mixed pattern of results. In Sample 1, no individual polymorphism showed a significant effect on its own (as expected). In Sample 2, results were consistent, with the exception of the DAT1 VNTR ($b = 0.222$, $SE(b) = 0.111$, $p = 0.046$; Fig. 2). Further, results for additional polymorphisms in the augmented MGPS, DRD4 C521T (Sample 1: $b = 0.099$, $p = 0.266$; Sample 2: $b = 0.038$, $p = 0.756$) and DRD2 C957T (Sample 1: $b = 0.038$, $p = 0.666$; Sample 2: $b = 0.291$, $p = 0.061$) were similar to polymorphism effects from the established MGPS.

Population Stratification

To rule out that results were spuriously driven by population stratification, the primary analyses were conducted with White participants (Sample 1 N: 77, Sample 2 N: 124). At the meta-analytic level, results were consistent with primary analyses (established MGPS: Hedges' $g = 0.329$, $p = 0.022$; augmented MGPS: Hedges' $g = 0.393$, $p = 0.007$). In Sample 1, neither the established MGPS ($b = 0.052$, $p = 0.173$) nor the augmented MGPS ($b = 0.052$, $p = 0.127$) predicted sensation-seeking. In Sample 2, the established MGPS approached significance in predicting sensation-seeking ($b = 0.134$, $p = 0.059$) whereas the augmented MGPS was a significant predictor ($b = 0.144$, $p = 0.019$).

Exploratory Analyses to Estimate Effect Sizes

The effect size of the direct effect of the MGPS on depressive symptoms was ($R2 = 0.022$, $p = 0.121$; 95% CI: [-0.2413, 0.1020]). A follow up power analysis conducted in GPower 3 (Faul et al., 2007) suggested that required sample size to be sufficiently powered (i.e., at least 0.8) to detect an effect of this size was $N = 351$. The 95% confidence interval of the indirect effect of the MGPS through sensation seeking on T2 depressive symptoms was [-0.0621, 0.0555], indicating the indirect path was not significant. The regression of sensation seeking predicting depressive symptoms revealed an effect size of ($R2 = 0.003$, $p = 0.562$).

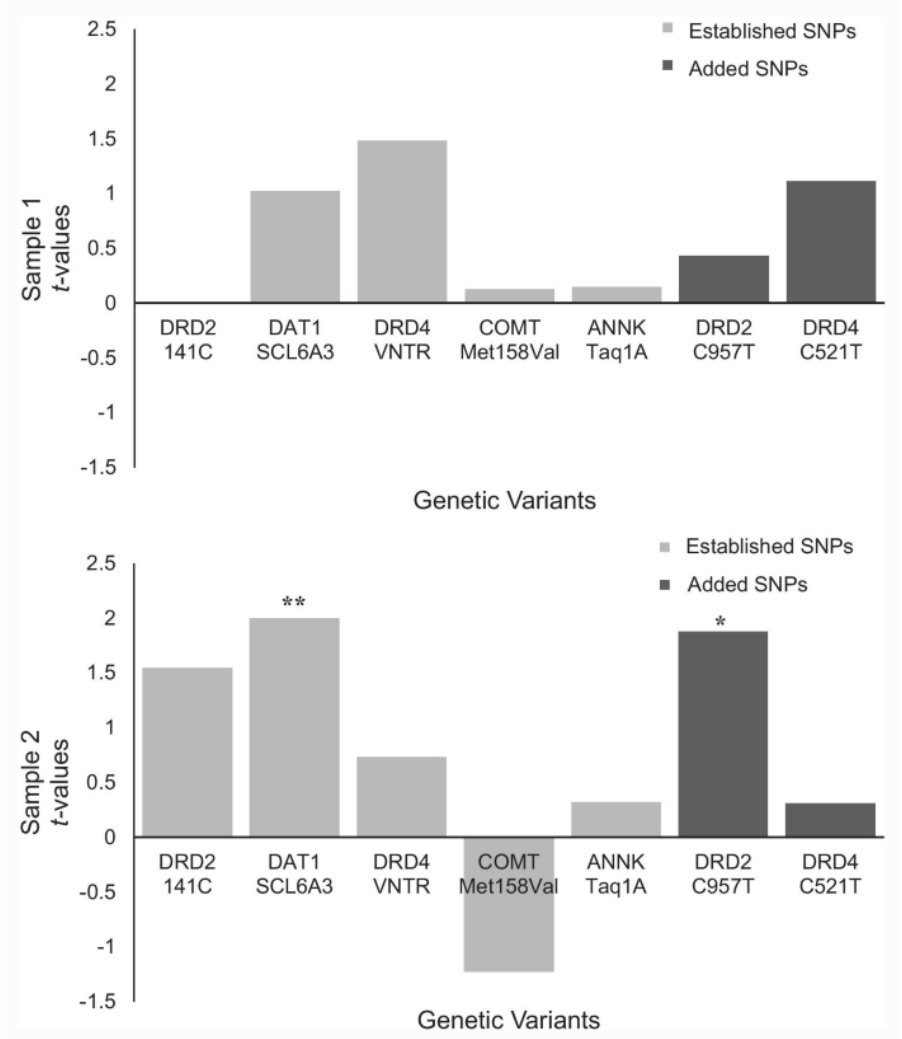

Figure 2. Individual polymorphisms predicting sensation-seeking in samples (using separate linear regressions for each polymorphism) with income and gender as covariates. *p < .10, **p < .05.

Discussion

We presented novel evidence—consistent across two independent samples of early adolescents—that an established and an augmented dopaminergic MGPS both relate to sensation-seeking but not to social drive. Results extend evidence linking this MGPS to ventral striatal reward task activation (Nikolova et al., 2011) to one form of trait reward sensitivity and suggest how the profile score might be augmented with additional genetic variants for future research. In addition, we provide effect sizes for prospective depression in one sample with available data, indicating an inverse association between the augmented dopaminergic MGPS and depression. Furthermore, given the developmental period of the samples, results suggest important implications for understanding risk for depression.

Dopaminergic MGPS and Reward-Related Personality Traits

The MGPS was associated with trait sensation-seeking, consistent with striatal dopamine modulating reward seeking. Thus, in linking the dopaminergic MGPS to trait sensation-seeking, the present results extend prior evidence linking the dopaminergic MGPS to state-like neural reward responsivity (i.e., activation in response to a monetary reward task; Nikolova et al., 2011; Stice et al., 2012). The link between the dopaminergic MGPS and sensation-seeking suggests a role for this MGPS in reward-related personality in a developmental period preceding a spike in depression (Hankin et al., 1998). Though a link between the dopaminergic MGPS and depression is not tested in primary analyses (but is tested as part of an exploratory effort to gauge effect sizes), the implied pathway between the dopaminergic MGPS and depression through reward related traits warrants further examination.

Ultimately, although speculative, it may be that "risky" levels of additive dopaminergic genetic variation contribute to an "anhedonic personality," (i.e., low levels of sensation seeking) which in prior work has been linked to depression risk under stressful environmental circumstances (Beevers & Meyer, 2002; Loas, 1996) by dampening positive salience of life experiences (Beevers & Meyer, 2002). Furthermore, the association between the dopaminergic MGPS and sensation-seeking suggests a potential role for this dopaminergic MGPS not only in risk for depression, but perhaps also in other disorders characterized by either low reward seeking (e.g., schizophrenia; Simon et al., 2010) or high reward seeking (e.g., bipolar disorder, substance abuse; Zuckerman & Neeb, 1979). Though longitudinal research is needed to understand the long-term effects of this MGPS in clinical populations, prior work has demonstrated relationships between dopaminergic MGPS's and depressive symptoms (Pearson-Fuhrhop et al., 2014)—suggestive of a link between dysfunction in the dopamine system and depression.

The present study builds upon prior work by suggesting a pathway for future research to examine which dopaminergic genetic markers may relate to risk for depression. Identification of dopaminergic risk markers and their associations with personality traits permits a greater understanding of the etiology of personality and depression at a molecular, cellular, and neural level. Furthermore, given the developmental level of the samples examined, associations between dopaminergic genetic risk and low sensation-seeking are clinically important: Identification of patterns of genetic markers may help identify at-risk, early adolescents that may benefit from interventions focused on enhancing adaptive sensation-seeking (e.g., employing behavioral activation training as a preventative tool). Indeed, preventative interventions in early adolescents, prior to an epidemiological spike in depression risk (Hankin et al., 1998; Rohde et al., 2013) may be particularly beneficial as prior work suggests that sensation-seeking may be malleable in childhood, though such work has focused on enhancing control over impulsivity rather than improving adaptive sensation-seeking (see Romer, 2010 for review). Furthermore, prospective research is needed to examine the incremental contributions of sensation seeking traits and genetic variation to clinical outcomes, which could then guide earlier intervention.

The lack of evidence linking the MGPS and social drive may be either methodological effects or substantive. Methodologically, it is possible that there is indeed a very small effect, which the present study was underpowered to detect; however, per a priori power analyses, there was sufficient power (≥ 0.8) to detect a small to medium effect size—$R2 = 0.033$ or greater—at the meta-analytic level. Substantively, however, the lack of effect may be genuine. Indeed, it is consistent with a prior meta-analysis linking one polymorphism in the augmented MGPS, DRD4

C521T, to sensation-seeking traits, but not significantly to extraversion broadly, which is more similar to the social drive construct examined here (Munafò et al., 2008).

Additionally, social drive may be more associated with other neurotransmitter and hormone systems (e.g., serotonergic, oxytocinergic, and vasopressin systems). Experimental research demonstrates an effect of a selective serotonin reuptake inhibitor on increased affiliative behavior (Knutson et al., 1998). Further, the S/S genotype of the 5-HTTLPR polymorphism in the serotonin transporter gene is associated with reduced self-ratings of extraversion (Gillihan et al., 2007), differences in sensitive parenting to infants (Bakermans-Kranenburg & van IJzendoorn, 2008), and in interaction with stress, predicts neural responding in regions associated with social cognition (for review, see Canli & Lesch, 2007). Similarly, evidence suggests a role of oxytocinergic and vasopressin systems in affiliative behavior. In humans, oxytocin administration increases willingness to trust and accept social risks (Kosfeld et al., 2005), prerequisites for increased social affiliative behavior. Likewise, vasopressin administration affects perceptions of friendliness in neutral, same-sex faces in both males and females (Thompson et al., 2006). Thus, genetic markers of striatal dopamine may play a secondary or non-significant role relative to other neurotransmitter and hormonal systems in modulating social drive.

Methodological Advancements for the Dopaminergic Multilocus Genetic Profile Scores

Results support the addition of two polymorphisms to the established MGPS. Across all models tested, effect sizes for the augmented MGPS were descriptively larger than for the established MGPS. Based on additive polygenic theoretical assumptions in which each polymorphism contributes minimal variance to associations (Plomin et al., 2009), we would not expect two additional polymorphisms to make statistically significant incremental improvements over the established MGPS. Instead, we focused on effect sizes in evaluating the contributions of additional polymorphisms. Post-hoc analyses support that both added polymorphisms' effects were in the expected direction. In particular, the effect size of the newly added DRD2 C957T variant is among the strongest descriptively relative to established MGPS polymorphisms. This adds to growing evidence (Davis & Loxton, 2013; Davis et al., 2013) supporting its use in future MGPSs. Although the effect size of newly added variant DRD4 C521T (Sample 1: $t = 1.11$; Sample 2: $t = 0.31$) was not the most robust compared to the established MGPS, it was in the hypothesized direction and was descriptively larger than the smallest established polymorphism's effect (i.e., Sample 1: DRD2 141C $t = 0.01$; Sample 2: ANNK Taq1A $t = 0.31$). Thus, results suggest utility in including these polymorphisms in future MGPS research.

Pathways from Dopaminergic MGPS to Depression

An exploratory mediation analysis of dopaminergic MGPS predicting prospective depression via baseline sensation seeking was conducted in Sample 1 for the purpose of gauging effect sizes to inform future work. Although knowingly underpowered in the present sample, regression effect size estimates of each path may be valuable to future research. Notably, the direct effect of the MLPS on Depression yielded an R2 of 0.022 ($p = 0.121$). Though not significant, this effect size is remarkable in light of prior work in the related area of Gene x Environment research, where effect sizes for a single genetic variant on psychopathology may be considered moderate at $R2 = 0.001$ (Duncan & Keller, 2011). Though the observed effect size of 0.022 reflects a genetic main effect utilizing the additive effect of multiple polymorphisms, it is notable that the observed

effect size of 0.022 is 22 × the estimate of a moderate effect size of a GxE for a single variant. This suggests utility in the additive, multilocus approach and mirrors results obtained by Pearson-Fuhrhop et al. (2014) noting a significant correlation between a similar dopaminergic MGPS and depressive symptoms (N = 273; ß = -0.80, SE(ß) = 0.27). Taken together, although we could not provide evidence linking sensation seeking with depression in Sample 1, we provide significant evidence for a pathway from a dopaminergic MGPS to sensation seeking in two samples, and evidence of a noteworthy effect size for the direct effect of the dopaminergic MGPS predicting prospective depression in the one sample with this data available.

Limitations

Despite strengths including sampling a sensitive developmental period and using a cutting-edge additive genetic approach and independent replication of results across samples, the present study has several limitations. Reward sensitivity measures across samples were not identical; however, item content was examined to ensure that subscales were sufficiently similar, and the pattern of results was consistent across individual samples. Despite this, only a moderate match emerged between item content in social drive measures in Sample 2 (i.e., the Shyness subscale may have tapped into affiliation aspects of social reward whereas the social potency subscale may have tapped into desire for social dominance). Additional replication utilizing developmentally sensitive measures, specifically designed to assess sensation seeking (e.g., Sensation Seeking Scale; Zuckerman et al., 1964) and social drive and social affiliation (e.g., Affiliative Tendencey Scale; Mehrabian, 1970) would advance these findings.

Second, though similar to those obtained in prior work (e.g., R2 = 0.04; Derringer et al., 2010), the effect sizes of the association between MGPS and sensation-seeking (Sample 1: R2 = 0.04 Sample 2: R2 = 0.03) were small. This indicates that there are other substantive factors that influence sensation-seeking, including both environment factors, such as parenting style (e.g., Hartos et al., 2002) and peer networks (Donohew et al., 1999), as well as genetic factors in other neurotransmitter systems (e.g., serotonergic influences on sensation-seeking; Netter et al., 1996). Though an exploration of these factors is beyond the scope of the current study, the magnitude of the observed effect size indicates caution in interpreting the implications of this MGPS on sensation seeking.

Third, the sample sizes (Ns = 100, 141) were modest relative to some genetic studies, although an a priori power analysis and prior MGPS research (e.g., N = 69, Nikolova et al., 2011; N = 160, Stice et al., 2012) suggested sufficient sample size to detect effects above R2 = 0.033 with power of 0.8. Third, community samples were used; thus, extension of these results to clinical populations and outcomes is important (e.g., Pearson-Fuhrhop et al., 2014). Despite exploratory analyses, sufficient data were not available in both samples to test the putative pathway implied by the present results—an indirect effect of sensation seeking traits in the pathway between dopaminergic genetic variation and anhedonic symptoms provoked by objective stress. This remains an important future direction. Specifically, prospective data is necessary to understand whether relationships between dopaminergic genetic variation and sensation seeking predict onset of depression in later adolescence. Though exploratory analyses from the present study suggest reasonable effect sizes for a relationship between the dopaminergic MLPS and depression, prospective studies with data in mid-adolescents are needed before conclusions can be drawn. Fourth, despite the importance of establishing the relationship between sensation-seeking at the MGPS in early adolescence, further research is needed to identify whether results would replicate

in adult samples. Prior work demonstrating links between dopamingeric genetic variation and reward-related behavior in adults (Derringer et al., 2010; Nikolova et al., 2011) points to this relationship in adulthood, but this has not been directly tested with this MGPS.

Fourth, consistent with prior work (e.g., Starr et al., 2019; Vrshek-Schallhorn et al., 2015), the present study addressed population stratification by conducting analyses in the largest racial sub-sample. However, a limitation of this approach is that small differences in ancestry may potentially impact population stratification even within racial subgroups (Barnholtz-Sloan et al., 2005). In the present study, we lacked genome-wide data necessary to measure ancestry. However, examination of genome wide markers of ancestry is considered the gold-standard assessment for population stratification (Price et al., 2006). Notably, examination of population stratification via racial subgroup analyses is consistent with prior work (e.g., Starr et al., 2019; Vrshek-Schallhorn et al., 2015).

Fifth, a limitation of this and other dopaminergic MGPS studies (e.g., Chester et al., 2016; Davis & Loxton, 2013; Nikolova et al., 2011; Stice et al., 2012) is the examination of primarily White and "WEIRD" samples (Muthukrishna et al., 2020; Schulz et al., 2018). Important directions of future work include replicating and extending these findings within diverse samples and better understanding how sociocultural factors may interplay with genetic variation.

Conclusions

The present study finds support for associations between the dopaminergic MGPS and a reward-related personality trait, sensation-seeking, in early adolescents, but provides no evidence to support a relationship between this genetic variation and social drive. Results also suggest how the MGPS may be augmented for future research and highlight the role of the dopaminergic MGPS approach in developmental personality research. Additionally, results may help identification of at-risk individuals—based on genetic risk—that may benefit from interventions focused on reducing depression risk (though further prospective research is needed to understand whether sensation seeking is the key mediator between the dopaminergic MLPS and depression). Future research should test a model in which additive dopaminergic genetic risk might relate to depression risk in part via sensation seeking personality traits.

Notes

1 The two profile scores differ in their coding of genetic variants: Stice et al. (2012) codes the COMT Val158Met and DRD4 VNTR genotypes opposite to Nikolova et al. (2011) and includes intermediate genotypes for DRD2 141C Ins/Del and DAT1 VNTR.

2 Per reviewer recommendation, age was added a covariate given its relationship to both depression and reward sensitivity and was not a significant predictor of either sensation seeking or social drive and did not alter pattern of results. Full results available upon request.

3 Per reviewer recommendation, significant primary analyses of the MGPS predicting sensation seeking were re-run covarying social drive. Associations between sensation seeking and the Augmented MGPS remained generally consistent (Sample 1: ß = 0.063, SE(ß) = 0.028, p=0.030; Sample 2: ß =0.10, SE(ß) =0.052, p=0.057).

4 Though we planned to examine results using a meta-analytic approach, results were consistent when reward-related trait measures were standardized and combined across samples. Both the established (b=0.176, SE(b)=0.069, p=0.011) and the augmented MGPS (b=0.181, SE(b)=0.058, p=0.002) significantly predicted sensation-seeking. Neither the established (b=-0.018, SE(b)=0.071, p=0.798) nor the augmented MGPS (b=-0.048, SE(b)=0.060, p=0.567) significantly predicted social drive.

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