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Tobacco and cannabis use in college students are predicted by sex-dimorphic interactions between *MAOA* genotype and child abuse

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Summary

Background: Postsecondary students in Western countries exhibit a high prevalence of cannabis and tobacco use disorders. The etiology of these problems is contributed by several psychosocial factors, including childhood adversity and trauma; however, the mechanisms whereby these environmental determinants predispose to the use of these substances remain elusive, due to our poor knowledge of genetic and biological moderators. Converging evidence points to the monoamine oxidase A (*MAOA*) gene as a moderator of the effects of lifetime stress on the initiation of substance use.

Aims: Building on these premises, in this study, we analyzed whether *MAOA* upstream variable number tandem repeat (*uVNTR*) alleles interact with child maltreatment history to predict for lifetime cannabis and tobacco consumption.

Materials and methods: Five hundred college students (age: 18–25 years) from a large Midwestern University were surveyed for their child maltreatment history (encompassing emotional, physical, and sexual abuse, as well as emotional and physical neglect) and lifetime consumption of cannabis and tobacco. Saliva samples were obtained to determine the *MAOA uVNTR* genotype of each participant.

Results: In female students, lifetime tobacco and cannabis use was predicted by the interaction of physical and emotional abuse with high-activity *MAOA* allelic variants; conversely, in males, the interaction of low-activity *MAOA* alleles and physical abuse was associated with lifetime use of tobacco, but not cannabis.

Discussion: These findings collectively suggest that the vulnerability to smoke tobacco and cannabis is predicted by sex-dimorphic interactions of *MAOA* gene with childhood abuse.

Conclusion: These biosocial underpinnings of tobacco and cannabis use may prove important in the development of novel personalized preventive strategies for substance use disorders in adolescents.

KEYWORDS
cannabis, child maltreatment, college students, *MAOA*, tobacco

1 | INTRODUCTION

Epidemiological surveys in the USA and other Western countries have documented that students enrolled in postsecondary institutions display a high prevalence of problematic use of alcohol, tobacco, and cannabis.[1-8] The abuse of these substances results in enduring and severe consequences, including neurocognitive problems, poor academic performance, financial and legal repercussions, health concerns, as well as unintentional injuries and mortality.[9-14] Better interventional strategies are needed for the prevention of substance use in this population, but these efforts are severely hampered by our inadequate understanding of the etiology of substance use vulnerability.

Early initiation of drug use is arguably one of the most critical risk factors for abuse, dependence, and other substance-related problems in adulthood[15,16] and has been shown to be influenced by shared genetic and environmental vulnerability factors.[17-22] Accordingly, the vulnerability for early substance use in adolescents is increased by child adversity and trauma,[22-30] as well as shared and drug-specific genetic factors.[31-33]

A growing body of evidence indicates that the risk of substance use (and particularly its early onset) is influenced by the gene encoding monoamine oxidase A (*MAOA*).[34-48] This enzyme catalyzes the oxidative deamination of brain monoamine transmitters, including serotonin, norepinephrine, and dopamine,[49] which play a key role in the mechanisms of stress response as well as the pathogenesis of substance abuse and dependence. The *MAOA* gene is located on the short arm of the X chromosome (Xp11.4-p11.23).[50,51] The best-characterized genetic variants of *MAOA* are related to an upstream variable number tandem repeat (*uVNTR*), featuring different numbers (2, 3, 3.5, 4, 5 and 6) of 30-bp repeats located in the gene promoter.[52,53] Alleles harboring 2 and 3 repeats are associated with lower transcriptional efficiency than the other variants.[52,54-56]

Numerous studies have shown that *MAOA uVNTR* alleles exert a sex-dimorphic influence on the pathogenesis of alcohol-related problems, often through gene × environment (G × E) interactions with early-life psychosocial stress.[35-42] In males, low-activity *uVNTR* variants (hereafter denominated *MAOA-L*) predispose to earlier onset of alcoholism,[34] alcohol dependence,[34,35] and antisocial alcoholism.[36] In females, high-activity alleles (*MAOA-H*) predispose to alcohol consumption by interacting with poor-quality family relations and a positive history of sexual abuse; conversely, maltreated *MAOA-L* male carriers are at higher risk for alcohol use.[42]

TABLE 1 Participant demographics and descriptive statistics

	Overall sample (n = 470)	Males (n = 231)	Females (n = 239)
M (SD) Age	18.95 (1.19)	19.14 (1.25)	18.76 (1.10)
Year in school			
% 1st year student	61.1	55.8	66.1
%2nd year student	27.4	29.4	25.5
% 3rd year student	8.9	11.7	6.3
% 4th year student	1.9	2.6	1.3
% 5th year or more student	0.7	0.5	0.8
Race/Ethnicity			
% Caucasian	71.1	72.7	69.5
% African American	3.6	3.0	4.2
% Hispanic/Latino	6.2	4.8	7.5
% Native American	1.3	.9	1.7
% Asian	10.6	10.4	10.9
% Mixed or other	7.2	8.2	6.2
Medical History			
% Psychological disorder	13.2	10.4	15.9
% Current illness/injury	3.4	3.5	3.3
% Currently medications	43.4	25.1	61.1
Parental education at birth			
% Fathers greater than high school	80.9	81.0	78.4
% Mothers greater than high school	79.7	83.8	78.2

The involvement of *MAOA uVNTR* alleles in G × E interactions is in agreement with rich evidence on other psychopathological states. In males, the interplay of *MAOA-L* alleles with child maltreatment has been extensively shown to predispose to aggression, delinquency, and antisocial behavior[57-64]; conversely, the interaction of *MAOA-H* and early adversity has been shown to heighten the proclivity for antisocial and violent responses in females,[65-67] likely due to an enhancement in emotional reactivity during adolescence.[68] The interaction of *MAOA-L* alleles and childhood adversity in females may influence depression vulnerability.[69,70] These sex-dimorphic effects may reflect different influences of the *MAOA-uVNTR* variants on monoamine metabolism between males and females.[56,71]

In contrast with the rich evidence on alcohol-related problems and other psychiatric disorders, little is currently known about the specific role of the G × E interaction of *MAOA uVNTR* alleles and early-life maltreatment in use of tobacco and cannabis. Here, we surveyed 500 college students in a large Midwestern University to investigate whether tobacco and cannabis lifetime consumption may be predicted by the interaction of *MAOA* genotype, sex, and child maltreatment. Our rationale for focusing on lifetime cannabis and tobacco use was based on prior findings showing that: (i) uVNTR alleles may be particularly relevant in influencing the onset of substance use in early life[34,35]; and (ii) cannabis lifetime use is largely influenced by genetic factors,[33] and these factors largely overlap with those for cannabis abuse or dependence[72-74]; (iii) early substance use and misuse have been broadly linked to impulsivity and poor inhibitory control,[75-77] behavioral domains widely influenced by *MAOA* genotype.[38,78,79]

TABLE 2 *MAOA* variants

	MAOA	
	Low activity	High activity
Males	94	137
Caucasian	58	110
African American	3	4
Hispanic/Latino	6	5
Native American	1	1
Asian	16	8
Mixed or other	10	9

	MAOA		
	Low activity	Heterozygous	High activity
Females	44	121	74
Caucasian	25	84	57
African American	3	4	3
Hispanic/Latino	3	12	3
Native American	0	1	3
Asian	12	10	4
Mixed or other	1	10	4

2 | METHODS

2.1 | Participants

Five hundred students were recruited from introductory undergraduate Psychology courses at a large Midwestern University through a research recruitment system (SONA). However, due to missing data, analyses only included 470 participants (239 female). Demographic information (including age, sex and race/ethnicity) and descriptive statistics of this final sample are reported in Table 1. The majority of students (61.1%) were in their first year of college, identified as Caucasian (71.1%), and had parents with greater than a high school education (80.9% of fathers and 79.7% of mothers). *MAOA* genotype information broken down by sex and race/ethnicity is reported in Table 2. The *MAOA-H* genotype was more common than *MAOA-L* for males. The majority of females exhibited a heterozygous genotype (*MAOA-LH* = 121); 44 and 74 were homozygous *MAOA-L* and *MAOA-H* carriers, respectively. According to power tables, our samples of >200 males and females had adequate power ($\alpha = 0.80$) to detect moderate to larger *MAOA* × maltreatment effects for each sex.[80]

2.2 | Procedures

This study was approved by the researchers' institutional review board. Participants were asked to refrain from eating 1 hour before, as well as smoking, taking drugs (including prescription), caffeine, and alcohol at least 3 hours before their study appointment time. Written informed consent was obtained from all participants prior to study participation. At the beginning of the appointment, participants rinsed their mouths with water, and, approximately 10 minutes later, provided 2 mL of saliva via passive drool for genetic analysis. Participants then completed an online survey in approximately 1 hour, using Qualtrics software. To preserve the anonymity of all participants, they were given a unique ID number and no identifying information was collected. Due to the inclusion of items pertaining to a history of trauma, all participants received a list of local mental health care providers upon study completion. All subjects were compensated with a $5 debit card and 3 SONA course credits for study participation.

2.3 | Measures

The survey encompassed the following measures:

2.3.1 | Demographics

Participants answered several questions regarding demographic information, including their age, sex, and race/ethnicity.

2.3.2 | Child maltreatment

Child maltreatment was assessed via the Childhood Trauma Questionnaire (CTQ;[81]), a self-reported instrument that retrospectively measures exposure to abuse and neglect during childhood and adolescence. The measure includes 5 subscales (physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect) consisting of 5 items each, along with an overall child maltreatment score. Items are rated on a 5-point Likert scale ranging from "Never True" to "Often True." Mean scores were obtained and used for analyses, with higher scores indicating higher amounts of trauma exposure. Reliability and validity of the CTQ has been demonstrated in prior research.[81] The physical neglect subscale yielded the lowest reliability coefficient ($\alpha = 0.56$) in the current sample; conversely, internal consistencies for the remaining 4 subscales had $\alpha s > 0.81$.

2.3.3 | Lifetime substance use

Participants completed 2 dichotomous (0 = "no", 1 = "yes") items from the Center for Substance Abuse Prevention (CSAP) Student Survey,[82] which assessed lifetime tobacco (ie, "Have you ever smoked a cigarette, even just a few puffs, or used chewing tobacco, snuff, or dip?") and cannabis use (ie, "Have you ever tried marijuana?").

2.4 | *MAOA uVNTR* variants genotyping

DNA was extracted from salivary samples, using Saliva DNA Collection, Preservation, and isolation Kit (Norgen Biotek Corp, ON, Canada). *MAOA-uVNTR* allelic variants were genotyped by PCR-based amplification, with the following primers: forward, 5′-ACAGCCTGACCGTGGAGAAG-3′ labeled with the FAM fluorophore; and reverse, 5′-GAACGGACGCTCCATTCGGA-3′ PCR reactions contained 100 ng of template DNA, 1X PCR Master Mix (Thermo Scientific, Waltham, MA) 500 nmol/L of each primerin a total volume of 20 μL. After 2 minutes at 95°C, 35 cycles were carried out at 94°C for 30 seconds, at 60°C for 30 seconds, and at 72°C for 40 seconds, with a final extension at 72°C for 5 minutes. PCR products were assayed by sending 15 μL of PCR product to GENEWIZ LLC (Frederick, MD) for fragment analysis. Results were analyzed using Peak Scanner program (Applied Biosystems, Thermo Fisher, Waltham, MA). All laboratory procedures were carried out by operators blinded to experimental conditions and demographic data.

Male carriers of 2 and 3 repeat variants were designated as *MAOA-L*; conversely, male carriers with 3.5 and 4 repeat alleles were considered *MAOA-H* (see Table 2).

Females were designated as either *MAOA-L* or *MAOA-H* homozygous (depending on the same variants mentioned above), or heterozygous *MAOA-LH*, if they carried a copy of each variant. To allow for comparability between males and females, however, we combined *MAOA-L* homozygous and *MAOA-LH* female participants, in agreement with previous functional studies on sex-dimorphic effects of *MAOA uVNTR* variants.[83-87] To confirm the validity of this approach with respect to our study, analyses were conducted with female participants in which G × E interactions between the *MAOA* genotype variants (*MAOA-L*, *MAOA-H*, and *MAOA-LH*) and maltreatment types were evaluated. Results indicated that *MAOA-LH* genotype operated in an equivalent fashion as the *MAOA-L* genotype in its interaction with maltreatment types to predict tobacco and cannabis use.

Our analyses did not include carriers of 5-repeat *uVNTR* alleles, as the actual functional significance of this variant remains controversial[52,54]; in fact, the exclusion of 5-repeat variant is in agreement with numerous previous studies on *MAOA uVNTR*.[60]

2.5 | Data analysis

Analyses were conducted on 470 participants, as *MAOA* genotyping could not be undertaken for 11 participants, and an additional 11 participants were missing CTQ and/or substance use data; finally, 8 participants carrying 5-repeat *uVNTR* alleles were excluded from the analyses. Chi-square and mean difference tests indicated that there were no differences regarding sex or age for those whose data was included in analyses versus those who were excluded ($ps > 0.48$). Additionally, no differences in mean levels the child maltreatment variables were found ($ps > 0.16$). Logistic regression models were estimated using SPSS statistical software (IBM Corporation, Harmonk, NY) to evaluate proposed associations. The dichotomous lifetime substance use items were the dependent variables with sex, *MAOA* variants, the maltreatment types, and their interactive effects included as independent variables. Specifically, 3-way interactions were evaluated one at a time (eg, sex × *MAOA* variants × physical abuse) to determine if child maltreatment-*MAOA* interactive effects depended on sex. Note that all independent variables were mean centered prior to analyses to aid in interpretation of interaction effects. Statistically significant interactions were probed using simple slope analyses. Specifically, models were conditioned based on sex (male vs female) and for *MAOA* variants to determine the nature of the interactions, consistent with standard procedures.[80]

When a large number of analyses are conducted, Bonferroni's correction and other statistical methods aimed at reducing Type 1 error rates have been found to overcorrect and greatly reduce power to detect effects; in these cases, it has been therefore recommended to focus on effect sizes when interpreting results.[88] Accordingly, significance was set at $P \leq 0.05$ and odds ratios were reported as an indicator of the magnitude of effects for statistically significant associations. Odds ratios (OR) are reported for significant effects to provide a measure of the magnitude of the effect. OR greater than 1 suggest an increase in odds of the outcome (ie, substance use) per 1 unit increase in the independent variable (ie, maltreatment type), and OR less than 1 indicate a decrease in odds of the outcome per each unit increase in the independent variable.[89]

3 | RESULTS

3.1 | Descriptive analyses

Approximately 41.9% reported tobacco use, and 55.8% indicated cannabis use. According to clinical cutoff scores recommended by

Bernstein and Fink,[81] approximately 46.5% of the sample had experienced at least low levels of at least one maltreatment type. These data are consistent with previous reports on undergraduate, emerging adult samples.[90] Correlations between maltreatment types ranged from 0.23 to 0.59, suggesting that these maltreatment types share up to 35% of their variance with one another.

3.2 | Lifetime tobacco use

A marginally significant 3-way interaction involving any type of maltreatment × *MAOA* variants × sex was found ($B = 1.89$, $P = 0.059$; See Table 3). For *MAOA-L* males, maltreatment exposure was associated with lifetime tobacco use ($B = 1.143$, $P = 0.049$), such that for every unit increase in trauma exposure the log of the odds of ever using tobacco increased by 3.14. However, for *MAOA-H* males, trauma exposure was unrelated to tobacco use ($B = 0.088$, $P = 0.84$). In contrast, for females, trauma exposure was unrelated to tobacco use at *MAOA-L* variants ($B = 0.382$, $P = 0.25$), but positively associated with *MAOA-H* alleles ($B = 1.214$, $P = 0.041$). For *MAOA-H* females, for every unit increase in trauma exposure, the log of the odds of ever using tobacco increased by 3.37.

When examining specific maltreatment types, only one significant 3-way interaction emerged: physical abuse × *MAOA* variants × sex. Physical abuse was unrelated to lifetime tobacco use for *MAOA-H* males ($B = -0.30$, $P = 0.34$). However, for *MAOA-L* males, there was a trend for physical abuse to increase the likelihood of tobacco use ($B = 1.54$, $P = 0.055$), such that for every unit increase in physical abuse the log of the odds of using tobacco increased by 4.70 times. In contrast, physical abuse was unrelated to tobacco use for *MAOA-L* females ($B = -0.43$, $P = 0.31$), but positively associated for *MAOA-H* females ($B = 2.81$, $P = 0.03$). For *MAOA-H* females, for every unit increase in physical abuse the log of the odds of ever using tobacco use increased by 16.67. Follow-up 2-way interactions were also evaluated; however, no significant 2-way interactions emerged (ps > 0.17).

3.3 | Lifetime cannabis use

When examining lifetime cannabis use, a significant 3-way interaction involving any type of maltreatment × *MAOA* variants × sex was found ($B = 3.04$, $P = 0.00$; See Table 4). The probing of simple slopes indicated that an interactive effect between maltreatment and *MAOA* variants was unique to females; that is, trauma exposure was unrelated to lifetime cannabis use for both *MAOA-L* ($B = 0.65$, $P = 0.23$) and *MAOA-H* ($B = -0.67$, $P = 0.15$) males. Trauma exposure was also unrelated to cannabis use for *MAOA-L* females ($B = -0.31$, $P = 0.34$); however, in *MAOA-H* females, trauma exposure was associated with lifetime cannabis use ($B = 1.42$, $P = 0.041$), such that for every unit increase in trauma exposure, the log of the odds of ever using cannabis increased by 4.13 for females.

When examining specific maltreatment types results indicated 3-way interactions for all maltreatment types but sexual abuse (See Table 4). However, the probing of simple slopes for both emotional neglect and physical neglect indicated that these maltreatment types were not associated with lifetime cannabis use for males or females at either *MAOA-H* and *MAOA-L* (Males *MAOA-H* Bs = −0.27 & −0.41, ps > 0.29; males *MAOA-L* Bs = 0.45 & 0.15, ps > 0.16; females *MAOA-H;* Bs = 0.35 & 0.96, ps > 0.27; females *MAOA-L* Bs = −0.31 & −0.56, ps > 0.23). This pattern of results indicates that, although results vary for males and females, no meaningful associations between child maltreatment type and risk for cannabis use are evident for males or females at high- or low-activity *MAOA* alleles.

In contrast, the probing of simple slopes of the physical abuse and emotional abuse indicated that the interactive effects between maltreatment and *MAOA* variants depended on sex. For males, emotional abuse was positively associated with lifetime cannabis use at *MAOA-L* ($B = 0.86$, $P = 0.045$) but unrelated at *MAOA-H* ($B = -0.02$, $P = 0.95$). Physical abuse was negatively associated with lifetime marijuana use for *MAOA-H* males ($B = -0.76$, $P = 0.03$) and unrelated for *MAOA-L* males ($B = 0.23$, $P = 0.60$). For *MAOA-L* females, physical and emotional abuse were also unrelated to lifetime cannabis use ($B = -0.75$ & -0.02, ps > 0.06). However, in *MAOA-H* females, physical abuse increased the likelihood of cannabis use ($B = 2.66$, $P = 0.04$), such that, with every unit increase in physical abuse, the log of the odds of using cannabis increased by 14.25. Additionally, in *MAOA-H* females, emotional abuse increased the likelihood of cannabis use ($B = 0.83$, $P = 0.021$), such that for every unit increase in emotional abuse, the log of the odds of using cannabis increased by 2.30 for females. Finally, 2-way interactions revealed no significant 2-way interactions (ps > 0.49).

TABLE 3 Tobacco use 3-way interaction estimates

	Lifetime tobacco use	
	B	*P*
Sexual abuse	1.70	0.15
Emotional neglect	0.13	0.82
Physical abuse	5.09	0.00
Emotional abuse	0.68	0.28
Physical neglect	0.44	0.65
Any maltreatment	1.89	0.059

TABLE 4 Marijuana use 3-way interaction estimates

	Lifetime marijuana use	
	B	*P*
Sexual abuse	−0.21	0.81
Emotional neglect	1.37	0.02
Physical abuse	4.40	0.00
Emotional abuse	1.39	0.03
Physical neglect	2.07	0.051
Any maltreatment	3.04	0.00

4 | DISCUSSION

The results of this study show that, in a sample of 470 students enrolled in a large Midwestern University, lifetime tobacco and cannabis use were predicted by the interaction between *uVNTR* allelic variants of *MAOA* gene and specific components of child maltreatment in a sex-dimorphic fashion. Specifically, a positive history of physical abuse increased risk of lifetime tobacco consumption in *MAOA-L* male and *MAOA-H* female carriers; furthermore, *MAOA-H* variants exacerbate the link between physical and emotional abuse and risk of cannabis use in females.

These findings extend and complement previous evidence on the link between early-life adversities and substance use,[91-93] as well as the role of *MAOA* as a vulnerability gene for substance use [34-48] and a mediator of child maltreatment with respect to psychopathological outcomes associated with substance abuse, including aggression and antisocial behavior.[57-68] Furthermore, the finding that child abuse interacts with *MAOA* genotype to predispose to tobacco and cannabis use helps qualify previous findings on the role of this gene as a moderator for the impact of lifetime stress on early substance use initiation.[34,35,48]

Our finding that the effects of *MAOA* are most evident among the individuals with a history of child physical abuse is consistent with prior research indicating that this type of maltreatment has greater effects on substance use than other forms of abuse (including sexual).[94] Note that in the current study, we controlled for the statistical overlap in the maltreatment types, suggesting that physical abuse impacts the effects of *MAOA* in a specific fashion. Prior research also indicates that females exposed to physical abuse exhibit a greater risk of substance use than males[94-99]; this sex-specific vulnerability may account for the greater impact of physical abuse on cannabis use in female carriers of *MAOA-H* variants. On the other hand, it is possible that this sex-specific vulnerability may be confounded by different rates of physical abuse and substance use among males and females. With respect to these issues, it should be noted that physical abuse appears to be more common in boys than girls.[100] Furthermore, Caucasian young females have been found to be at greater odds of lifetime use than males.[101] It is important to note, however, that the severity level of maltreatment experienced in our sample is lower than the average rates observed in other populations, raising potential issues of representativeness of the general population.

Most studies on the phenotypic impact of *MAOA* have focused on aggression, violence, and antisocial behavior [57-68] as well as depression [69-72,102,103] and anxiety disorders.[104-106] Similar to these findings, prior studies have shown a sex-dimorphic effect of *MAOA* variants on psychopathology vulnerability, with *MAOA-L* males and *MAOA-H* females exhibiting a predisposition to antisocial responses.[35-42,69-72]

Neuroimaging studies have highlighted the key role of *MAOA* in shaping the function of the anterior cingulate cortex (ACC).[79,107] This region is a major component of the brain circuitry subserving the control of executive functions, impulse control, and reward-related behaviors.[108-111] The effects of *MAOA* on ACC activation patterns are sex-dimorphic[84]; specifically, *MAOA-L* male and *MAOA-H* female carriers with a history of stress were shown to exhibit alterations in the activation of the ACC in response inhibition tasks.[112] Functional impairments of the ACC (such as those predicted by the interaction of childhood stress and either MAOA-H females or *MAO-L* alleles in males) have been shown to lead to poor inhibitory control [113,114] and increase substance use predisposition by facilitating the responses of the ventral striatum to incentive stimuli.[115,116] From this perspective, it is likely that these deficits in inhibitory control may arguably facilitate use of cannabis and tobacco in adolescence. Thus, our studies may suggest that sex-dimorphic interactions of *MAOA* alleles and early maltreatment may facilitate inhibitory dyscontrol in adolescence and/or early adulthood, ultimately increasing the risk for tobacco smoking. Future analyses will be needed to verify whether specific domains of impulsivity may mediate the link between these G × E interactions and lifetime substance use.

One of the most commonly used frameworks to explain G × E interactions is the diathesis-stress model, which posits that certain genotypic variants may predispose to a greater effect of stress (when it exceeds a given threshold) during a critical developmental window.[117] In this case, the predisposition of *MAOA-H* females and *MAOA-L* males to a greater effect of stress may lead to a greater disinhibition phenotype, which may augment the likelihood to use substances in early developmental stages. From this perspective, it is worth mentioning that *MAOA-L* male carriers have been shown to exhibit a greater neuroendocrine response to stress.[118] An alternative model is afforded by the differential susceptibility hypothesis,[119,120] which postulates that genetic proneness accounts for sensitivity to both unfavorable and supportive environments.[121] In line with this hypothesis, emerging evidence has pointed to the possibility that *MAOA-L* variants may serve as "plasticity alleles" that may confer differential susceptibility to substance use depending on the sex and rearing environment.[122,123] For example, several authors have shown that boys carrying *MAOA-L* variants are at greater risk for ADHD and conduct disorder if they had been subjected to high levels of adversity, but fewer mental problems if they were raised in nurturing environments.[58,124] Specifically, in males, *MAOA-L* variants were found to predict for more or less criminal behavior, depending on different adversity histories.[125]

Previous studies have shown that *MAOA* variants can predict for higher risk of tobacco use disorder. Although our study was not focused on tobacco abuse or dependence, our data may suggest that the role of *MAOA* in increasing the risk for cigarette smoking may be influenced by early tobacco initiation. Indeed, previous studies have documented that early initiation of tobacco can predict higher risk for abuse and dependence in adulthood. This possibility, however, is partially challenged by the finding that *MAOA-H*, rather than *MAOA-L*, variants have been shown to increase the risk and severity for cigarette smoking in men.[45,47]

The mechanisms of the interaction between sex and *MAOA* variants remain unclear, but may reflect a differential pattern of epigenetic inactivation, considering the sex-specific methylation patterns of this gene.[126,127] This effect may be particularly relevant with

respect to the escalation of tobacco use, given that smokers have lower methylation at two CpG islands associated with the *MAOA* promoter, in a fashion dependent from the *uVNTR* genotypes.[44,126] Similar effects were shown in relation to alcohol-related problems in young adult males, in relation to both the interaction of *MAOA uVNTR* alleles and maltreatment.[128]

Androgens have been shown to modify the transcription of *MAOA* gene[129]; furthermore, testosterone has been shown to interact with *MAOA uVNTR* variants to predispose for aggression and risk-taking behavior.[65,130] Future studies will be needed to verify the impact of testosterone and estrogens on the role of *MAOA* variants in substance abuse.

Several limitations of this study should be acknowledged. First, the study was conducted on 500 college students of predominantly Caucasian ethnic background. In consideration of the conceptual and methodological limitations of current research on G × E interactions in psychiatry,[131,132] these findings should be confirmed by further studies with larger, more ethnically diverse cohorts, which may increase their robustness and ascertain their generalizability. Second, the 3-way interactions examined in this study do not reflect the full complexity of either genetic or environmental mechanisms in substance use. Future studies will also need to examine other environmental factors directly implicated in substance use in emerging adults, including parental rule setting, educational attainment, neighborhood characteristics, and peer influence.[133-135] Third, our survey on tobacco and cannabis use was only limited to ascertain whether participants ever consumed any of these substances, but did not measure frequency and problematic patterns of use; future studies will be necessary to verify whether and how these aspects can be influenced by *MAOA* genotype. Fourth, current findings are based on retrospective self-reports of child maltreatment; additionally, there was a low internal consistency associated with our measure of emotional neglect, which may have limited our ability to detect effects for this maltreatment type. Although several findings were evident in the current population and our measure of child maltreatment has been found to be psychometrically sound and widely used,[82,86] additional research in samples with more internally consistent measurement and have experienced elevated levels of maltreatment is warranted. Fifth, our analyses combined *MAOA-L* and *MAOA-LH* females; several studies have shown that, in females, the *MAOA* gene shows monoallelic expression due to Lyonization. Several studies suggest that X-linked genes undergo variable inactivation,[136] and thus, *MAOA-LH* carriers may exhibit intermediate phenotypes between *MAOA-L* and *MAOA-H* carriers (see[137] for a thorough analysis of this issue). Nevertheless, our analyses failed to show any statistically significant difference between MAOA-LH and female MAO-L carriers; thus, we adopted this analytical strategy to enable direct comparisons between sexes, in conformity with previous studies.[84-88]

These limitations notwithstanding, our data point to sex-dimorphic G × E interactions in shaping the vulnerability for tobacco and cannabis use in college students. To the best of our knowledge, although G × E interactions are posited to play a central role in the pathogenesis of cannabis and tobacco use, very few studies have examined these mechanisms with most analyses focusing on serotonergic and dopaminergic genes.[138] From this perspective, our recent analyses underscore the importance of gender as a factor in these analyses. In addition to *MAOA*, only very few genes have been shown to interact with environmental factors to influence the risk for psychopathology in a sex-dimorphic fashion.[139] On the one hand, sex remains a widely overlooked factor in most research on the genetic etiology of substance use[139]; on the other hand, it is possible that sex factors may be critical in differentiating the response to stress only with respect to specific gene pathways, such as those related to monoaminergic regulation. Our findings may have critical implications for the prevention of substance use, as they underscore the relevance of childhood trauma as an environmental determinant that may increase the vulnerability to tobacco use in *MAOA-L* males and *MAOA-H* females. Future studies confirming the involvement of MAOA as a differential susceptibility factor may be particularly critical to highlight the importance of good rearing environment for *MAOA-L* boys and *MAOA-H* girls.

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