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Is Marijuana Use Linked to Your Genes?

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Abstract

Marijuana is the most commonly used illicit drug in the United States and refers to the dried parts of the hemp plant, *Cannabis sativa*, that are consumed to give mind-altering effects. The perception that marijuana is dangerous has decreased and this correlates with increased use among college-aged people with the prevalence of those reporting daily use rising from 3.5% in 2007 to 4.6% in 2015. Contrary to common belief, research suggests that thirty percent of users may develop addiction to cannabis. With the current increase in legalization of the drug for medical and recreational purposes, it is essential to understand where the desire to use the drug. While environment may prompt marijuana use, personality traits, that are in part heritable, also influence marijuana consumption. Novelty seeking (NS) is one personality trait that is associated with drug use. Higher NS scores are associated with drug use, and specifically, more frequent marijuana use. There is a strong correlation between NS and a polymorphism in the promoter region of the serotonin transporter gene (5-HTTLPR). The purpose of the current study is to discover whether correlations exist between NS, the 5-HTTLPR genotype, marijuana use, and estimations of the physical risk of using marijuana in college students. Results show that as novelty seeking scores increase, the frequency of marijuana use also increases ($n= 199$, $r= 0.22$, $p<0.05$). We found that as the frequency of marijuana use increases, the assessment of the risk of use of marijuana decreases ($n= 199$, $r= -0.39$, $p<0.001$). Preliminary trends suggests individuals with the L/L genotype ($n=13$) use marijuana more often than individuals with the L/S genotype ($n=18$, $p<0.05$). At the time of submission, genotyping had not been completed so only preliminary results are discussed.

Keywords: Marijuana, Novelty Seeking, 5-HTTLPR

1. Introduction

Marijuana is the most commonly used semi-illicit drug in the United States, with over 94 million people stating that they have used the drug at least once[1]. Marijuana refers to the dried parts of the hemp plant, *Cannabis sativa*, which are smoked or consumed for their mind-altering and physical effects including a change in perception, a feeling of euphoria and increased appetite[1]. Next to alcohol marijuana is the second most frequently found substance in the bodies of drivers involved in fatal car accidents[2]. However, it has a myriad of health benefits including appetite stimulation in cancer patients, decreased eye pressure in glaucoma patients and decreased muscle weakness in patients with spinal cord injuries[3]. In the last decade several states have voted to legalize marijuana use in some form resulting in a total of eight states currently having legal recreational use of the drug and 21 states having legal medicinal use of the drug[4].

Other than its national and political importance, marijuana use is also highly relevant to college students as long-term use of the drug has been linked to higher likelihood of dropping out of school and more job absences and injuries[1]. Smoking marijuana reduces cognitive, memory and learning functions[1]. Contrary to common belief, research suggests that 30% percent of marijuana users may develop addiction to the drug[5]. Thus, it is essential to determine where the desire to use marijuana may stem.

While environmental factors may influence an individual to engage in certain behaviors, one's personality traits, which are genetically heritable, may also influence their choice[6]. Robert Cloninger established four independently heritable personality traits (temperaments): novelty seeking, harm avoidance, reward dependence and persistence[7]. These four dimensions of personality can be quantified and measured by the 226-item Temperament and Character Inventory (TCI) questionnaire[7]. Novelty seeking (NS) is defined as the likelihood of an individual to try new and stimulating activities. Individuals who are high novelty seekers are characterized as being easily bored, curious and quick tempered[8]. Higher novelty seeking scores are associated with drug use and more specifically, more frequent marijuana use[9,10,11]. Indeed, 70% of the genetic liability of marijuana use in males is shared with the novelty seeking personality trait[12].

Alterations in levels of brain monoamines, such as serotonin, dopamine, epinephrine and norepinephrine, contribute to behavioral and psychological traits such as novelty seeking, impulsivity and anxiety[13]. These monoamines are neurotransmitters that regulate synaptic and neural activity[14]. Serotonin interacts with the reward center of the brain influencing mood and social behavior, appetite and digestion, sleep, memory and sexual desire and function[15].

The amount of serotonin in the synaptic cleft is regulated by the serotonin transporter protein (SLC6A4 or 5-HTT). The transporter is an integral membrane reuptake protein[18]. A polymorphism in the serotonin transporter gene is correlated with novelty seeking[16,17]. The gene is located on chromosome 17q11.1-12 and its transcription is modulated by a polymorphism in the promoter region termed the 5-hydroxytryptamine transporter-linked polymorphic region (5-HTTLPR).

A polymorphism in the promoter region of SLC6A4 results in different versions of the gene. The most predominant versions of this allele are termed short (S) if the gene contains 14 repeats of a 20-23 base pair repeat or long (L) if there are 16 repeats[19]. Transcriptional activity is decreased with the S/S genotype as compared to the L/L or the S/L genotypes thus, less serotonin uptake occurs in individuals with the S genotype compared to individuals with the L variant[20,21]. Individuals who have the S/S or S/L genotypes may have more serotonin in the synaptic cleft than those with the L/L genotype.

Marijuana consumption affects the endocannabinoid system, which is closely linked with the serotonergic system as they are located in the same parts of the brain and affect many of the same body functions[22]. When marijuana is consumed it has two main active ingredients: delta-nine-tetrahydrocannabinol (THC) and cannabidiol[23]. These interact with the serotonergic system resulting in the increase of serotonin in the synaptic cleft. Some studies have shown that THC binds with serotonin transporters through non-competitive inhibition resulting in the increase of serotonin in the synaptic cleft[24]. Also, cannabidiol inhibits re-uptake of serotonin by 5-HT[25]. The overall impact of marijuana use is an increase of serotonin in the synaptic cleft. Therefore, this further implies a potential link between marijuana use and the 5-HTTLPR polymorphism.

There is some contradiction in the literature as to which allele might be more prevalent in people who use drugs. Most studies analyze potential correlations between general drug use and the serotonin transporter genotype. Studies done on different ethnic groups have reported an association of the S allele with drug dependence, specifically heroin and alcohol[26,27]. One study done on a Jordanian Arab population found an association between the L allele and drug use, but only when in the presence of a certain marker, i.e. the rs25531 polymorphism[28]. The differences between these studies could reflect the different populations being tested. Other studies analyzed the correlation between the 5-HTTLPR genotype and novelty seeking but in the presence of another polymorphism, such as DRD4, and found that individuals with the L allele are more novelty seeking than individuals with the S allele[29,30]. However, not many studies have been done to analyze correlations between marijuana use and the 5-HTTLPR genotype. The purpose of this study is to determine whether a correlation exists, in a sample of the Georgia Gwinnett College population of students, between the personality trait of novelty seeking, marijuana use, perceived risk of marijuana use and the 5-HTTLPR marker. Finding a correlation between these factors may contribute to a better understanding of marijuana use, at least in novelty seeking personalities. The effects of gender were also analyzed. However, at the time of submission of this paper, genotyping of the individuals had not been completed and therefore only preliminary results are incorporated into this paper.

2. Methodology

2.1. Participants

One hundred and ninety-nine student participants (137 females and 62 males) from Georgia Gwinnett volunteered to participate in this study. Students were recruited from Introductory Psychology, Introductory Biology, and Genetics courses and were incentivized to participate via credit or extra credit.

2.2. Procedures

Subjects were read the same instructions verbatim and then completed an informed consent form. Next, they were asked to donate DNA using a buccal swab using standard techniques. Each participant was given a random number that was associated both with their DNA and their survey responses. Students then completed questionnaires including the physical risk assessment inventory (PRAI), physical risk frequency inventory (PRFI) and the temperament and character inventory (TCI). All surveys were completed on computers using SONA and these procedures were approved by the GGC IRB prior to the study induction.

2.3. Surveys

2.3.1. physical risk assessment inventory (PRAI)

The PRAI was comprised of 28 risky activities that participants were asked to grade on a seven-point Likert scale with 0 being no risk, 1 being little risk, 2-4 being moderate risk and 5-6 being extreme risk, based off their perceived risk to the average participant. The activities were grouped into three categories: eleven for adventurous sport, seven for drug use (which included marijuana use), and ten for general risky activities. For this study only marijuana use was analyzed.

2.3.2. physical risk frequency inventory (PRFI)

The PRFI was comprised of the 28 risky activities from the PRAI and was used to measure the participants' frequency in those activities. The participants were prompted to indicate how many times per year they engaged in each activity, based on an eight category sequence of responses with: 0= never tried it, 1= tried it one to three times in lifetime, 2= 1-10 days per year, 3= 11-20 days per year, 4= 21-30 days per year, 5= 30-40 days per year, 6= 41-50 days per year and 7= >51 days per year. For this study, only the frequency of marijuana use was analyzed.

2.3.3. the temperament and character inventory (TCI)

The TCI, developed by Cloninger *et al.* (2004), consists of 240 true/false statements that measure four dimensions of temperament ((1) Novelty Seeking (NS), (2) Harm Avoidance (HA), (3) Reward Dependence (RD) and (4) Persistence)) and three dimensions of character ((1) Self-Directedness, (2) Cooperativeness and (3) Self-Transcendence)). It gives a summative numerical value for each temperament and character trait. For this study, only novelty seeking scores were analyzed. Thus, low scores indicated personalities who are not novelty seekers compared to individuals with high novelty seeking scores.

2.3.4. sociodemographics

Sociodemographic questions assessed the participants' age, occupation, marital status, and also included questions on current and potential future drug addictions. For the purpose of this study, only gender was analyzed in correlation with marijuana use, novelty seeking and perceived risk of marijuana use.

2.4. Genotyping

Genomic DNA was obtained from the participants via the buccal cheek swab method (Epicenter Biotechnologies). After collecting DNA from the cheek and allowing the swab to dry for at least 15 minutes, the swab was stored between 1 week to 1 month at -20°C. The swab was rolled in DNA extraction solution (Epicenter Biotechnologies) for approximately 1 minute. The tube was vortexed for ten seconds, incubated at 65°C for 1 minute, vortexed for 15 seconds and then incubated at 98°C for 2 minutes. The extract was vortexed and stored at -20°C.

PCR was performed using primers JP (sequence: 5' - ATG CCA GCA CCT AAC CCC TAA TGT – 3') and GR (sequence: 5' - GG ACC GCA AGG TGG GCG GGA – 3'). The PCR master mix included 2 µM dNTP (10mM Invitrogen), 1µL of each primer (20mM, SIGMA), 1 µL Go Taq enzyme, 10 µL 5X Go Taq Buffer, 31 µL of ultra-pure water and 4 µL of DNA. The thermocycler was run at 95°C for 2 minutes and then cycled forty times: (1) 95°C for 30 seconds, (2) 62°C for 30 seconds and (3) 72 °C for 30 seconds, followed by a final 10 minute extension at 72°C. PCR samples were run on a 2% agarose gel for 2-3 hours at 120 V. The bands were visualized using Sybr Green (Fisher) and UV fluorescence where the 'S' and 'L' bands were expected at 484 and 528 base pairs, respectively.

2.5. Statistical Analysis

All graphs were plotted in Microsoft Office Excel and SPSS statistical analysis was used in all data analyses. Quantitative data were described as a mean ± standard deviation (SD) and average differences were compared using ANOVA, *t*-tests, and post-hoc comparisons. Pearson product moment correlations (r-values) were used to assess relationships between variables. A value closer to 1.0 or -1.0 suggested a strong positive or negative correlation, respectively. The alpha level for statistical significance was set at 0.05 for each analysis.

2.6. Hypotheses

We hypothesized the following:

(1) The more novelty seeking an individual, the more frequently they participate in marijuana use.
(2) As novelty seeking increases, the individual's assessment of the risk of marijuana use decreases.
(3) The more frequently an individual participates in marijuana use, the lower their perceived risk of use of marijuana.
(4) Individuals with the L/L genotype are more novelty seeking and have a higher frequency of marijuana use than individuals with the S/S genotype.

3. Data

3.1. Descriptive Statistics

The 199 students included 137 females and 62 males. Out of all the participants, 55% of people claimed to have never used marijuana (n=108), 20% claimed to have tried it (n=40) and 25% of the individuals reported frequent to extreme use of the drug (n=49). Moreover, in 199 subjects, 22% classified marijuana use as extremely risky (n=43), 38% as moderate risk (n=75), 42% as little risk (n=42) and 19% as having no risk (n=18). The average age of all of the subjects was found to range from 18-65 years old with the average age being 22.65 ± 7.6 years.

3.2. Associations Between Key Variables

3.2.1. association between novelty seeking and marijuana use

There was a positive correlation found between novelty seeking and marijuana use (n=199, r = 0.22, p <0.05), supporting the hypothesis that the more novelty seeking an individual, the more frequent their use of marijuana (figure 1). While it is clear from the scatterplot that those in the "never tried it" category regarding marijuana use were from

the full NS score range, it is noteworthy that none of the most frequent marijuana users (scoring 7) scored below 15 on NS.

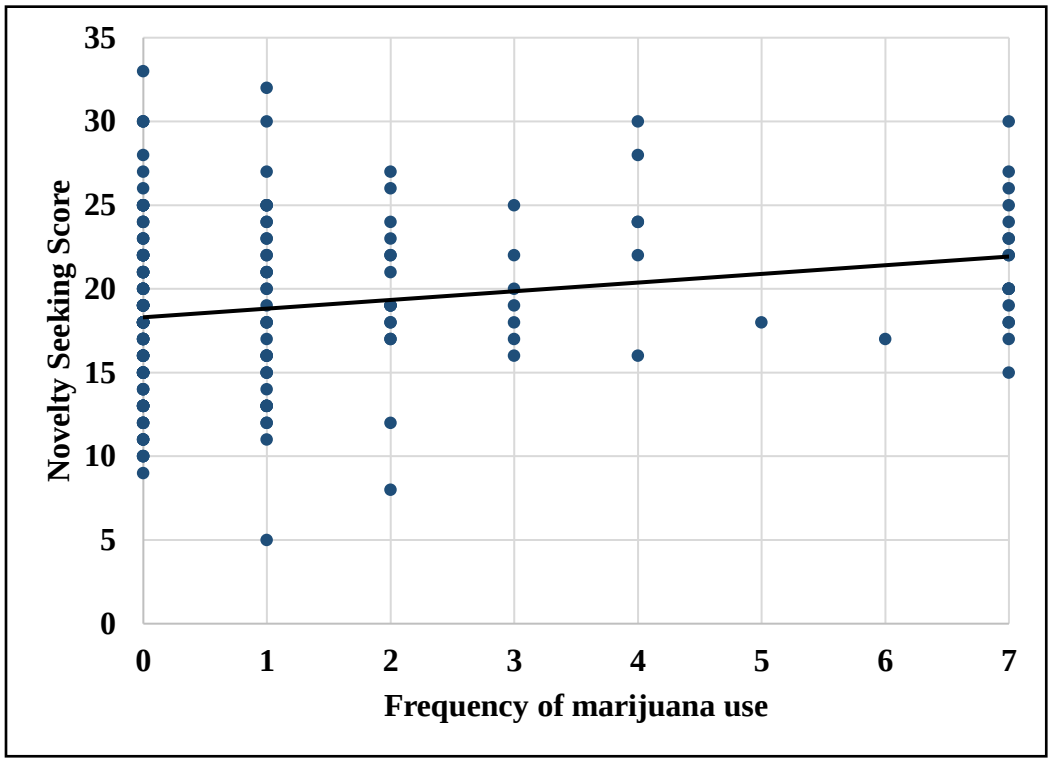

Figure 1. Scatterplot showing the weak positive correlation ($r=0.22$, $p<0.05$, $n=199$) between novelty seeking and the frequency of marijuana use where 0= never tried it; 1= tried it one to three times in lifetime; 2= 1-10 days/year; 3= 11-20 days/year; 4= 21-30 days/year; 5= 30-40 days/year; 6= 41-50 days/year; 7= >51 days/year.

Therefore, the higher an individual's novelty seeking score, the higher their frequency of marijuana use.

3.2.2. association between novelty seeking and the assessment of the risk of marijuana use

The negative correlation between novelty seeking and assessment of the assessment of the risk of use of marijuana trended in the direction hypothesized but was not significant ($r = -0.11$, $p = 0.07$).

3.2.3. association between frequency of marijuana use and assessment of the risk of marijuana use

A negative correlation was found between the frequency of marijuana use and assessment of the risk of marijuana use ($r=-0.39$, $p<0.001$) (Figure 2). Thus, there is enough statistical evidence to support the claim that as the frequency of the use of marijuana increases, the assessment of the risk of use decreases. While many of the individuals who had never used marijuana or only tried it 1-3 times in their lives assessed the risk of marijuana as high (3-6), none of the individuals reporting 5-7 on frequency of use agreed, instead reporting the risk of use as 0 (none), 1 (little), or moderate on the low end (2).

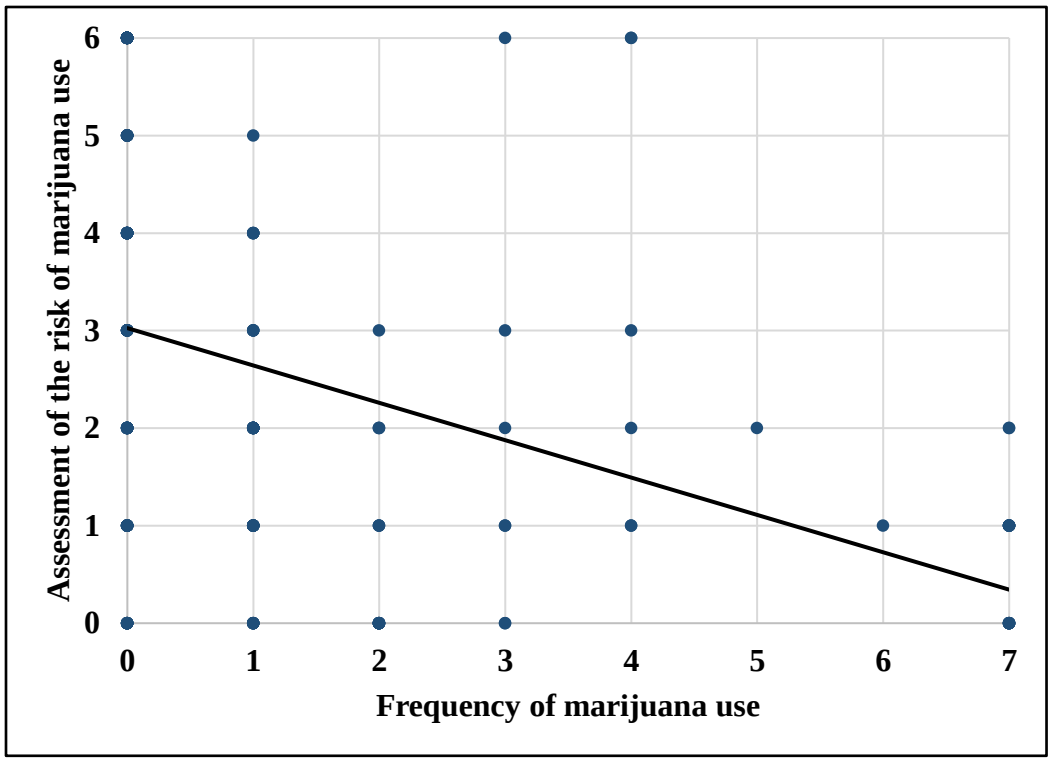

Figure 2. Scatterplot showing a negative correlation (r=-0.39, p <0.001, n=199) between the assessment of the risk of marijuana use (0= No risk; 1= Little risk; 2-4= Moderate risk; 5-6= Extreme risk) and the frequency of marijuana use (0= never tried it; 1= tried it one to three times in lifetime; 2= 1-10 days/year; 3= 11-20 days/year; 4= 21-30 days/year; 5= 30-40 days/year; 6= 41-50 days/year; 7= >51 days/year).

3.3. genotype

Genotyping is still in progress so only preliminary trends are discussed in this paper. Genotyping has been completed on a total of 42 individuals. A total of 13 individuals had the L/L genotype, 11 individuals had the S/S genotype and 18 individuals were heterozygotes with the L/S genotype. Preliminary results are shown in table 1.

Table 1. Genotype table for average novelty seeking score, frequency of marijuana use, or assessment of risk of use for each genotype.

Genotype (*n*=42)	Number of Participants	Average NS Score	Average Frequency of Marijuana Use	Average Assessment of Risk of Marijuana Use
L/L	13	17.62	1.85	2.54
L/S	18	17.33	0.11	3.61
S/S	11	16.64	0.82	2.09

One-way ANOVAs comparing NS scores and risk of marijuana use, respectively, across the three genotypes were not significant ($p>0.05$). A one-way ANOVA for the frequency of marijuana use across the three genotypes was statistically significant ($p<0.05$) and a *post hoc* analysis showed the L/L participants average score was statistically greater than the L/S group ($p<0.05$).

There is insufficient statistical evidence to support the hypothesis that individuals with the L/L genotype are more novelty seeking *and* have higher a higher frequency of marijuana use than individuals with the S/S genotype.

3.4. Gender Comparisons

3.4.1. average differences in key variables

There were a total of 137 females and 62 males that volunteered to participate in this study. There was no significant difference found between the novelty seeking scores, frequency of marijuana use or in the assessment of the risk of marijuana use of males and females ($p>0.05$).

3.4.2. gender differences in associations between key variables

When analyzed by gender, the positive correlation between NS and frequency of marijuana use was essentially identical for males and females. Similarly, the negative correlation between marijuana use and the risk assessment was demonstrated in males and females, though the strength of relationship was more pronounced in the latter. However, while NS and risk assessment showed a negative correlation in females, these variables showed no relationship for males.

Table 2. Correlations of key variables by gender. Significance is present at the $p<0.05$ level. Assessment was done on 137 females and 62 males.

Correlation tested	Sex	r-value	p-value
Novelty Seeking and the Assessment of the Risk of Marijuana Use	Female	-0.18	<0.05
	Male	0.04	0.78
Novelty Seeking and the Frequency of Marijuana Use	Female	0.21	<0.01
	Male	0.23	<0.05
Assessment of the Risk of Marijuana Use and Frequency of Marijuana Use	Female	-0.44	<0.01
	Male	-0.31	<0.01

4. Conclusion

Although studies have been conducted to examine correlations between 5-HTTLPR and novelty seeking and between novelty seeking and marijuana use, a consensus about correlations between genotype and phenotype are lacking and importantly, few studies focus on college age students. The purpose of this study was to determine what correlation exists between the 5-HTTLPR genotype, marijuana and novelty seeking in college students.

It was hypothesized that the more novelty seeking an individual, the more frequent their use of marijuana, that the higher an individual's novelty seeking score, the lower their assessment of the risk of use of marijuana, that the more frequent an individual's frequency of marijuana use, the lower their perceived risk of use and that individuals with the L/L genotype are more novelty seeking and have higher a higher frequency of marijuana use than individuals with the S/S genotype.

This study found that (1) on average, females are just as novelty seeking as males, (2) some individuals assume there is no risk associated with marijuana use, (3) individuals with high novelty seeking scores tend to be more frequent marijuana users, consistent with the findings of previous studies[9,10,11], (4) individuals who use marijuana more frequently assess it to be less risky than individuals who use it less often and (5) individuals with the L/L genotype use marijuana more frequently than individuals with the L/S genotype. 45% of our students have claimed to have used marijuana, which is consistent with the findings of other recent studies[31].

4.1 Females are as novelty seeking as males

These results are consistent with the majority of published studies examining novelty seeking by gender[7]. One study did report novelty seeking scores of females to be higher than males[30]. However, this may be due to the fact that the study analyzed individuals from only Sweden. Although men and women tend to have the same average novelty seeking scores, women do tend to have higher harm avoidance scores than men, and this could partially explain why men often report and demonstrate higher levels of physical risk-taking[32,33].

4.2 Some individuals (n=38) think that there is no risk associated with marijuana use (Figure 2)

This is interesting because next to alcohol, marijuana is the second most frequently found substance in the bodies of drivers involved in fatal car accidents[2]. Also, marijuana use has been shown to be linked with an increased risk of a form of testicular cancer in young adult males and a range of cognitive impairments are associated with long-term use[5,34].

4.3 Individuals with high novelty seeking scores tend to be more frequent marijuana users

This finding is consistent with the literature where some studies have found that novelty seeking is positively correlated with higher use of marijuana and other drugs[9,10,11]. This result is notable as levels of novelty seeking may be established at a fairly young age and novelty seeking may serve as a predictive risk factor for drug use.

4.4 As frequency of marijuana use increases, the perceived risk of use of marijuana decreases

There was a negative correlation found between the frequency of marijuana use and the assessment of the risk of use of marijuana, which is consistent with the literature[35]. Similar findings were discovered when the data was divided by gender and analyzed. Several alternate hypotheses could explain this result. One explanation could be that people who do not assess marijuana to be risky are more prone to try it or to use it frequently. Preconceived notations may influence exploratory behavior. Alternatively, it might be that continued use of marijuana leads people who initially felt that the drug carried some risk to down-grade their risk assessment, perhaps misjudging the lack of immediate harm as equivalent to no possible future harm. Continued use itself could lead to reducing risk assessment. Some third variable, such as age, neural development, social learning, etc., could contribute to the demonstrated association.

4.5 Individuals with the L/L genotype use marijuana more often than individuals with the L/S genotype (n L/L=13, n L/S = 18)

Individuals with the L/L genotype had a higher average frequency of marijuana use (M=1.85) than individuals with the L/S genotype (M=0.11). The literature documents that the presence of the L allele may be the factor that causes a higher novelty seeking personality, so if this is analyzed in the future, similar correlations may arise[16,30].

Many researchers studied the 5-HTTLPR genotype in the presence of additional polymorphisms, such as those in the serotonin transporter gene (e.g. Stin2) or dopamine receptor or monoamine oxidase (MAO) genes[16,30]. Some studies that examined novelty seeking behavior and drug use did not entirely focus on marijuana use and instead studied general drug use, but still found correlations between the two[10,36]. The majority of these studies found stronger correlations between novelty seeking and drug use in males compared to females[37]. There is a lack in the literature studying direct correlations between the 5-HTTLPR polymorphism and marijuana use. However, one study that analyzed the polymorphism and general drug use found that the L allele was correlated with drug dependence[28].

The factors that contribute to drug use are multiple and much more complex than the actions of a single gene. Drug use behavior has been related to other genes and certainly involves neural mechanisms in multiple neurotransmitter system pathways beyond the serotonin pathway[40,41]. It is also important to note that environmental factors such as drug availability, culture, peer pressure, and socioeconomic factors also play a strong role[38]. Thus, it is the multiplex effect of genes and environment that may indicate an individual's potential drug usage[39].

The limitations of this study could have contributed to the lack of correlations found. This was a preliminary study as there were only a total of 199 participants and higher sample sizes are frequently needed to gain statistical power for analyzing the contribution of a single genetic polymorphism. All of the participants were incentivized and were from Georgia Gwinnett College's Introduction to Psychology, Introduction to Biology and Genetics courses. Furthermore, there is an inherit limitation in the nature of survey data. We are aware that the surveys asked extremely personal and intimate questions and although the participants were informed of the anonymity of their responses, there is no way to guarantee that all the questions were answered honestly by the participants. Finally, we only analyzed one gene in our study. Because behavior interactions are complex and involve multifaceted pathways studying one genetic polymorphism limits the scope of the study. Also, genotyping in this study is ongoing, and data is currently available from only 42 of the 199 participants.

In conclusion, we plan to expand the study and incorporate the results of more participants from more diverse classes and ages so that our current results will have greater statistical power and may be generalized to a larger population.

We also plan to study whether there is a correlation between other polymorphisms such as the DRD4 dopamine receptor polymorphism on marijuana use, perceived risk of use and novelty seeking. Finally, in the future, we will complete genotyping of the existing participants. This will allow us to analyze whether a correlation exists between marijuana use, perceived risk of marijuana use, the 5-HTTLPR marker and the personality trait of novelty seeking. Finding a correlation between these factors may contribute to a better understanding of marijuana use, specifically in novelty seeking individuals.

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