



Article

Association between Polymorphism rs1799732 of *DRD2* Dopamine Receptor Gene and Personality Traits among Cannabis Dependency

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Abstract: Compared to other addictive substances, patients with cannabis addiction are significantly outnumbered by those who report dependence on other, more addictive substances. Unfortunately, most cannabis addiction goes untreated, and among those who choose treatment, the requirements are much higher for adolescents and young adults. The aim of the study: To examine the relationship of cannabinoid dependency in the genetic context—the association between the rs1799732 polymorphism of the *DRD2* gene and psychological traits and anxiety. Methods: The study group consisted of 515 male volunteers. Of these, 214 patients were diagnosed with cannabis addiction and 301 were non-addicted. Patients were diagnosed with NEO Five-Factor Personality Inventory (NEO-FFI), and State-Trait Anxiety Inventory (STAI) questionnaires. The interactions between personality traits and polymorphisms in the *DRD2* rs1799732 gene were investigated in a group of cannabis-addicted patients and non-addicted controls using the real-time PCR method. Results: Compared to the control group, the case group obtained significantly higher scores on the STAI State, STAI Trait, Neuroticism and Openness scales, as well as lower scores on the Extraversion, Agreeableness, and Conscientiousness scales. There was no statistically significant difference between addicts and the control group in the frequency of genotypes, but there was a statistically significant difference between addicts and the control group in the frequency of the *DRD2* allele rs179973. The multivariate ANOVA analysis showed a statistically significant influence of the *DRD2* rs1799732 genotype on the NEO-FFI agreeableness scale and a statistically significant effect of addiction to cannabinoids or its absence on the NEO-FFI agreeableness scale score. Conclusions: Studying homogeneous subgroups—as in our study—seems reasonable, particularly when combined with genetic determinants and psychological traits. In multigenic and multifactorial entities, such a strategy has a future.

Keywords: addiction; *DRD2* gene

1. Introduction

The most commonly used illegal drug in Western societies is marijuana (*Cannabis sativa*) [1–4]. According to the United Nations, in 2018, as many as 192 million people, or 3.9% of the world's adult population, used cannabis in the preceding year [5]. Cannabis use disorder (CUD) is the inability to stop using cannabis despite the physical and psychological

damage. According to data from 2016, as many as 22.1 million people met the CUD diagnostic criteria, and two-thirds were men [6–9]. CUD is one of the most common SUDs.

Despite the widespread use of cannabis, only the group of adolescents (25.4%) and young adults (19.0%) who use cannabis have seen a development of abuse or even addiction [10]. As many as 10% of cannabis users become daily users [11]. Day-to-day use is the best predictor of CUD, and as many as one-third develop an addiction. Although, compared to other drugs cannabis addiction occurs after prolonged use; people at a young age are more likely to become dependent on cannabis [12].

Of the neurotransmitter systems linked with addiction, dopamine has received the most attention, given its strong role in reward, motivation, and goal-directed behavior. Similarly to other substances of abuse, acute THC increases dopamine release in the striatum of healthy subjects [13]. Following chronic use, there is a reduction in stimulated dopamine levels in CUD [14], as in other SUDs (e.g., psychostimulants, nicotine, alcohol, and opioids). Early age of onset or longer duration of cannabis use correlates with reduced stimulated striatal dopamine release (evoked by psychostimulant administration) [15]. The lower striatal dopamine release apparent in heavy cannabis users relates to inattention and more significant negative symptoms [16], and it inversely correlates with negative emotionality and addiction severity [17]. The reduced release also corresponds with decreased dopamine synthesis in cannabis-dependent individuals [18], an effect associated with greater apathy [19,20].

Compared to other addictive substances, patients with cannabis addiction are significantly outnumbered by those who report dependence on other, more addictive substances [21]. Unfortunately, most cannabis addiction goes untreated, and among those who choose treatment, the requirements are much higher for adolescents and young adults [11]. Annual remission is around 17% among those not seeking treatment [22]. Early onset and intensity of use, early life trauma, mental health problems, and genetic susceptibility play an essential role in the development and severity of CUD [23–25].

In our study, it is for this reason that we decided to investigate the problem, but with a special focus on genetic determinants and personality traits. The problem is still huge, and despite numerous studies, we do not yet know the specific biological and psychological determinants (particularly when analyzed simultaneously). The dopamine receptor gene *DRD2* was selected as the genetic factor. The dopamine D2 receptor gene is located on chromosome 11q23 and covers an area of 65.56 kb. Eight coding regions (exons) within the gene are transcribed into 2713 kb mRNA. As a result of translation, the protein D2 receptor is 443 amino acids in size. As a result of the exclusion of exon six at the stage of transcription, a receptor variant is created that is 29 amino acids shorter [26]. The research results indicate at least a partial role of polymorphisms in the regions not coding the *DRD2* gene in shaping the risk of developing drug addiction throughout life [27].

One *DRD2* gene polymorphism that has been investigated extensively is a cytosine (C) insertion/deletion (Ins/Del) at nucleotide position −141C (−141C Ins/Del, rs1799732) in the promoter region, which may regulate *DRD2* transcription by modulating the binding of transcription factors [28]. Arinami et al. [28] show that variation in the genomic sequence of the promoter region of the D2 receptor gene (*DRD2*) could affect the expression or regulation of the gene. The *DRD2* 5′-promoter fragments drove the transcription of heterologous luciferase constructs in the Y79 cell line expressing *DRD2* as well as in *DRD2* non-expressing 293 cells. The fragment that contained the −141C Del allele showed a decrease in promoter strength as compared with the fragment that contained the −141CIns allele in Y-79 and 293 cells. The position of the polymorphism is part of a putative binding site for the transcription factor Sp-1, 5′-CCAGGCCCGGGATCGCC.

In an in vivo study, Jönsson et al. [29] found a significant association between the presence of a putative functional *DRD2* promoter allele (−141C Del) and high striatal DA receptor density in healthy subjects. These studies suggested that the rs1799732 polymorphism may be involved in the regulation of *DRD2* expression (mRNA level and/or protein level).

Previous publications have described the relationship of the rs1799732 polymorphism of DRD2 with nicotine [30], alcohol addiction [31–34], and opioid dependence [35]. Therefore, in our research, we decided to examine the relationship of the rs1799732 polymorphism of DRD2 with cannabis dependency and with personality traits.

Personality traits were an additional factor that was analyzed in our study. Personality affects many aspects, such as behavior, lifestyle, and maintenance of normal functions throughout life. The Big Five-factor model is most often used in personality research [36–38]. It consists of five traits: Openness, Conscientiousness, Extraversion, Agreeableness, and Neuroticism. Human differences are determined by these characteristics and related to behavior, emotions, motivation, and cognition [39]. Higher levels of anxiety are associated with susceptibility to substance addiction. Several studies describe the correlation of addiction with drug traits as measured by the STAI questionnaire [40]. The NEO Personality Inventory (NEO-FFI) is most often used to analyze personality traits [38]. The State and Trait Anxiety Inventory (STAI) is another tool used in addiction research. It allows to measure both the state, the reaction to a given situation, and the trait, the general tendency to react in a certain way in a state of anxiety [41]. As described above, both genetics and personality are factors that influence addiction. Therefore, our current study aimed to evaluate the effects of both of these components on cannabis use and the influence of the interaction of certain genetic variants with personality traits and anxiety. The analysis was carried out by comparing the polymorphism in the *DRD2* gene and personality traits measured by the Big Five Questionnaire (NEO FFI) and anxiety measured by the Anxiety Trait Inventory (STAI) in two study groups—cannabis-dependent and non-addicted.

2. Materials and Methods

2.1. Materials

The study group consisted of 515 male volunteers. Of these, 214 patients were diagnosed with cannabis addiction (mean age = 27.46, SD = 6.12) and 301 were non-addicted (mean age = 22.14, SD = 4.57). The Bioethics Committee previously approved the study of the Pomeranian Medical University in Szczecin (KB-0012/106/16). All participants gave their written consent to participate in the study, and the studies were conducted in the Independent Health Promotion Laboratory. Addicts were recruited after at least three months of abstinence in addiction treatment centers. Patients diagnosed with polysubstance use disorder with a depressive episode and the control group were examined by a psychiatrist using the Mini International Neuropsychiatric Interview (MINI), NEO Five-Factor Personality Inventory (NEO-FFI), and State–Trait Anxiety Inventory (STAI) questionnaires.

The interactions between personality traits and polymorphisms in the *DRD2* rs1799732 gene were investigated in a group of cannabis-addicted patients and non-addicted controls.

2.2. Measures

MINI-International Neuropsychiatric Interview is a structured diagnostic interview designed to evaluate the diagnoses of psychiatric patients according to the DSM-IV and ICD-10 criteria.

STAI measures anxiety as a trait of anxiety (trait A), which can be described as a persistent predisposition to having worries, stress, and discomfort, and anxiety states (A-states) such as anxiety, fear, and momentary stimulation of the autonomic nervous system in response to specific situations.

The Personality Inventory (NEO-FFI Five-Factor Inventory, NEO-FFI) contains six components for each of the five traits—neuroticism (anxiety, hostility, depression, self-awareness, impulsivity, susceptibility to stress), extroversion (warmth, sociability, assertiveness, activity, emotion seeking, positive emotions), openness to experience (fantasy, aesthetics, feelings, actions, ideas, values), agreeableness (trust, straightforwardness, altruism, compliance, modesty, tenderness), and conscientiousness (competence, order, duty, striving for achievements, self-discipline, consideration) [38].

The results of both inventories, i.e., NEO-FFI and STAI, were reported as the sten scores. The conversion of the raw score to the sten scale was carried out following the Polish standards for adults, where it was assumed that 1–2 corresponded to very low results; 3–4 was responsible for low results, 5–6 was responsible for average results; 7–8 was responsible for high results; and 9–10 sten was responsible for very high results.

2.3. Genotyping

The genomic DNA was isolated from venous blood by using standard procedures. Genotyping was conducted with the real-time PCR method. Details have been described previously [41]. The fluorescence signal was plotted as a function of temperature to provide melting curves for each sample. The *DRD2* gene peaks are read (rs1799732), 56.64 °C for the C allele and 62.85 °C for the (-) allele.

2.4. Statistical Analysis

A concordance between the genotype frequency distribution and Hardy–Weinberg equilibrium (HWE) was tested using the HWE software (<https://wpcalc.com/en/equilibrium-hardy-weinberg/>) (20 March 2021). The relations between *DRD2* gene (rs1799732) variants, Cannabis Dependency and control subjects, and the NEO Five-Factor Inventory were analyzed using a multivariate analysis of factor effects ANOVA [NEO-FFI/scale STAI $\times$ genetic feature $\times$ control and Cannabis Dependency $\times$ (genetic feature $\times$ control and Cannabis Dependency)]. The condition of homogeneity of variance was fulfilled (Levene test $p > 0.05$). The analyzed variables were not distributed normally. The NEO Five-Factor Inventory (Neuroticism, Extraversion, Openness, Agreeability, and Conscientiousness) was applied and compared using the U Mann–Whitney test. The *DRD2* gene (rs1799732) genotype frequencies between healthy control subjects and Cannabis Dependency were tested using the chi-square test. All computations were performed using STATISTICA 13 (Tibco Software Inc., Palo Alto, CA, USA) for Windows (Microsoft Corporation, Redmond, WA, USA).

3. Results

These frequency distributions were in accordance with the HWE both in the Cannabis Dependency and control subjects (Table 1).

Table 1. Hardy–Weinberg’s law for patients diagnosed with polysubstance use disorder comorbid with a depressive episode Cannabis Dependency and control subjects.

Hardy–Weinberg Equilibrium Calculator, Including Analysis for Ascertainment Bias		Observed (Expected)	Allele Freq	χ^2 (p Value)
DRD2 rs1799732 Cannabis Dependency n = 214	ins/ins	158 (155.64)	p (ins) = 0.853 q (del) = 0.147	1.656 (>0.05)
	ins/del	49 (53.73)		
	del/del	7 (4.64)		
DRD2 rs1799732 control n = 301	ins/ins	241 (240.40)	p (ins) = 0.894 q (del) = 0.106	0.132 (>0.05)
	ins/del	56 (57.20)		
	del/del	4 (3.40)		

p—statistical significance χ^2 test.

No statistically significant differences were found in the frequency of *DRD2* rs1799732 genotypes in the tested cannabis addicts compared to the control group (del/del 0.03 vs. del/del 0.01, ins/ins 0.74 vs. ins/ins 0.80, ins/del 0.23 vs. ins/del 0.19, $\chi^2 = 3.97$, $p = 0.138$). However, statistically significant differences in the frequency of *DRD2* rs1799732 gene alleles were found between cannabinol-dependent subjects and the control group (del 0.15 vs. del 0.11, ins 0.85 vs. ins 0.89, $\chi^2 = 3.87$, $p = 0.049$) (Table 2).

Table 2. Frequency of genotypes of the *DRD2* gene rs1799732 gene polymorphisms in the Cannabis Dependency and control subjects.

	<i>DRD2</i> rs1799732				
	Genotypes			Alleles	
	Del/Del n (%)	Ins/Ins n (%)	Ins/Del n (%)	Del n (%)	Ins n (%)
Cannabis Dependency n = 214	7 (3.27%)	158 (73.83%)	49 (22.90%)	63 (14.72%)	365 (85.28%)
Control n = 301	4 (1.33%)	241 (80.07%)	56 (18.60%)	64 (10.63%)	538 (89.37%)
χ^2 (<i>p</i> value)		3.966 0.138		3.870 (0.049) *	

n—number of subjects. *—significant statistical differences.

The means and standard deviations for all the NEO-FFI results and the STAI scale state and trait scale variant interactions for the Cannabis Dependency and control subjects are presented in Table 3.

Table 3. STAI and NEO Five-Factor Inventory sten scores between healthy controls and Cannabis Dependency.

STAI/NEO Five-Factor Inventory	Cannabis Dependency (n = 214)	Control (n = 301)	Z	(<i>p</i> -Value)
STAI trait/scale	7.10 ± 2.35	5.16 ± 2.18	8.619	0.0000 *
STAI state/scale	5.82 ± 2.44	4.69 ± 2.14	5.418	0.0000 *
Neuroticism/scale	6.70 ± 2.25	4.68 ± 2.02	9.472	0.0000 *
Extraversion/scale	5.66 ± 2.15	6.37 ± 1.97	−3.667	0.0002 *
Openness/scale	5.04 ± 2.00	4.53 ± 1.61	2.835	0.0045 *
Agreeability/scale	4.29 ± 1.97	5.60 ± 2.09	−6.825	0.0000 *
Conscientiousness/scale	5.49 ± 2.25	6.08 ± 2.15	−2.845	0.0044 *

p, statistical significance with Mann–Whitney U-test; n, number of subjects; M ± SD, mean ± standard deviation; * statistically significant differences.

The test subjects addicted to cannabis compared to the control group obtained higher scores in the assessment of anxiety (STAI) as a state (5.82 vs. 4.69; $Z = 5.418$; $p \leq 0.000$) and trait (7.10 vs. 5.16; $Z = 8.619$; $p \leq 0.000$), NEO-FFI neuroticism scale (6.70 vs. 4.68; $Z = 9.472$; $p \leq 0.000$), and NEO-FFI openness scale (5.04 vs. 4.53; $Z = 2.835$; $p = 0.004$). On the other hand, lower results were found for the NEO-FFI extraversion scale (5.66 vs. 6.37; $Z = -3.667$; $p \leq 0.000$), the NEO-FFI agreeableness scale (4.29 vs. 5.60; $Z = -6.825$; $p \leq 0.000$), and the NEO-FFI conscientiousness scale (5.49 vs. 6.08; $Z = -2.845$; $p = 0.004$).

The results of the 2×3 factorial ANOVA of the NEO Five-Factor Personality Inventory (NEO-FFI) and the State–Trait Anxiety Inventory (STAI) sten scales are summarized in Table 4.

Table 4. Differences in the *DRD2* gene rs1799732 and NEO Five-Factor Inventory, STAI scale between healthy control subjects and cannabinoid dependence.

STAI/NEO Five-Factor Inventory	Group	DRD2 Gene rs1799732			ANOVA			
		Del/Del n = 11 M ± SD	Ins/Ins n = 397 M ± SD	Ins/Del n = 104 M ± SD	Factor	F (p Value)	η^2	Power (Alfa = 0.05)
STAI trait/scale	Cannabinoid dependence (CD); n = 214	7.57 ± 1.81	6.95 ± 2.33	7.52 ± 2.45	Intercept	$F_{1,507} = 597.45$ ($p < 0.0001$)	0.541	1.000
					CD/control	$F_{1,507} = 27.02$ ($p < 0.0001$)	0.051	0.999
					DRD2	$F_{2,507} = 0.16$ ($p = 0.844$)	0.001	0.076
	Control; n = 301	4.50 ± 1.91	5.33 ± 2.16	4.48 ± 2.17	CD/control × DRD2	$F_{2,507} = 4.39$ ($p = 0.013$) *	0.017	0.757
STAI state/scale	Cannabinoid dependence (CD); n = 214	6.57 ± 2.15	5.71 ± 2.41	6.08 ± 2.62	Intercept	$F_{1,507} = 430.42$ ($p < 0.0001$)	0.459	1.000
					CD/control	$F_{1,507} = 12.60$ ($p < 0.001$)	0.024	0.943
					DRD2	$F_{2,507} = 0.04$ ($p = 0.962$)	0.0001	0.056
	C: Control; n = 301	3.75 ± 1.50	4.75 ± 2.18	4.50 ± 2.02	CD/control × DRD2	$F_{2,507} = 1.48$ ($p = 0.228$)	0.006	0.317
Neuroticism/scale	Cannabinoid dependence (CD); n = 214	6.85 ± 1.77	6.61 ± 2.19	6.98 ± 2.50	Intercept	$F_{1,507} = 546.67$ ($p < 0.0001$)	0.519	1.000
					CD/control	$F_{1,507} = 32.57$ ($p < 0.0001$)	0.060	0.999
					DRD2	$F_{2,507} = 0.45$ ($p = 0.637$)	0.002	0.123
	Control; n = 301	3.25 ± 2.06	4.76 ± 2.01	4.41 ± 2.02	CD/control × DRD2	$F_{2,507} = 1.90$ ($p = 0.151$)	0.007	0.395
Extraversion/scale	Cannabinoid dependence (CD); n = 214	4.28 ± 2.43	5.65 ± 2.17	5.87 ± 2.03	Intercept	$F_{1,507} = 717.55$ ($p < 0.0001$)	0.586	1.000
					CD/control	$F_{1,507} = 12.53$ ($p = 0.0004$)	0.024	0.942
					DRD2	$F_{2,507} = 0.59$ ($p = 0.553$)	0.002	0.148
	Control; n = 301	7.75 ± 0.50	6.30 ± 1.98	6.57 ± 1.98	CD/control × DRD2	$F_{2,507} = 2.34$ ($p = 0.097$)	0.009	0.474
Openness/scale	Cannabinoid dependence (CD); n = 214	4.57 ± 2.23	4.95 ± 2.02	5.37 ± 1.91	Intercept	$F_{1,507} = 565.02$ ($p < 0.0001$)	0.527	1.000
					CD/control	$F_{1,507} = 1.87$ ($p = 0.171$)	0.004	0.276
					DRD2	$F_{2,507} = 0.62$ ($p = 0.535$)	0.002	0.154
	Control; n = 301	4.25 ± 2.99	4.55 ± 1.59	4.48 ± 1.61	CD/control × DRD2	$F_{2,507} = 0.77$ ($p = 0.465$)	0.003	0.180
Agreeability/scale	Cannabinoid dependence (CD); n = 214	5.00 ± 2.23	4.30 ± 2.04	4.17 ± 1.69	Intercept	$F_{1,507} = 583.61$ ($p < 0.0001$)	0.535	1.000
					CD/control	$F_{1,507} = 17.50$ ($p < 0.0001$)	0.033	0.987
					DRD2	$F_{2,507} = 4.33$ ($p = 0.013$) *	0.017	0.751
	Control; n = 301	8.25 ± 2.36	5.64 ± 2.11	5.21 ± 1.85	CD/control × DRD2	$F_{2,507} = 1.39$ ($p = 0.249$)	0.005	0.299
Conscientiousness/scale	Cannabinoid dependence (CD); n = 214	6.14 ± 1.34	5.45 ± 2.32	5.54 ± 2.13	Intercept	$F_{1,507} = 629.99$ ($p < 0.0001$)	0.554	1.000
					CD/control	$F_{1,507} = 2.61$ ($p = 0.107$)	0.005	0.364
					DRD2	$F_{2,507} = 1.04$ ($p = 0.351$)	0.004	0.233
	Control; n = 301	7.25 ± 2.99	6.02 ± 2.11	6.21 ± 2.25	CD/control × DRD2	$F_{2,507} = 0.09$ ($p = 0.917$)	0.0003	0.063

*—significant result; CD—cannabinoid dependence; M ± SD—mean ± standard deviation.

A significant statistical impact of cannabis dependence or absence and *DRD2* genotype rs1799732 was demonstrated for flux as a feature and score of the NEO-FFI agreeableness scale.

There was a statistically significant effect of *DRD2* genotype interaction rs1799732 and addiction to cannabis or its absence (control group) on the trait anxiety scale score ($F_{2,507} = 4.39$; $p = 0.013$; $\eta^2 = 0.017$; Figure 1). The potency observed for this factor was 76%, and the polymorphism of the *DRD2* gene explained approximately 2% of rs1799732 and cannabis dependence or lack thereof on trait anxiety score variance. There was also a statistically significant effect of addiction to cannabis or its absence on the trait anxiety scale score ($F_{1,507} = 27.02$; $p < 0.0001$; $\eta^2 = 0.051$). The potency observed for this factor was over 99% and approximately 5% was explained by cannabis dependence or lack thereof on the variance in the trait anxiety score. Table 5 shows the results of the post-hoc test.

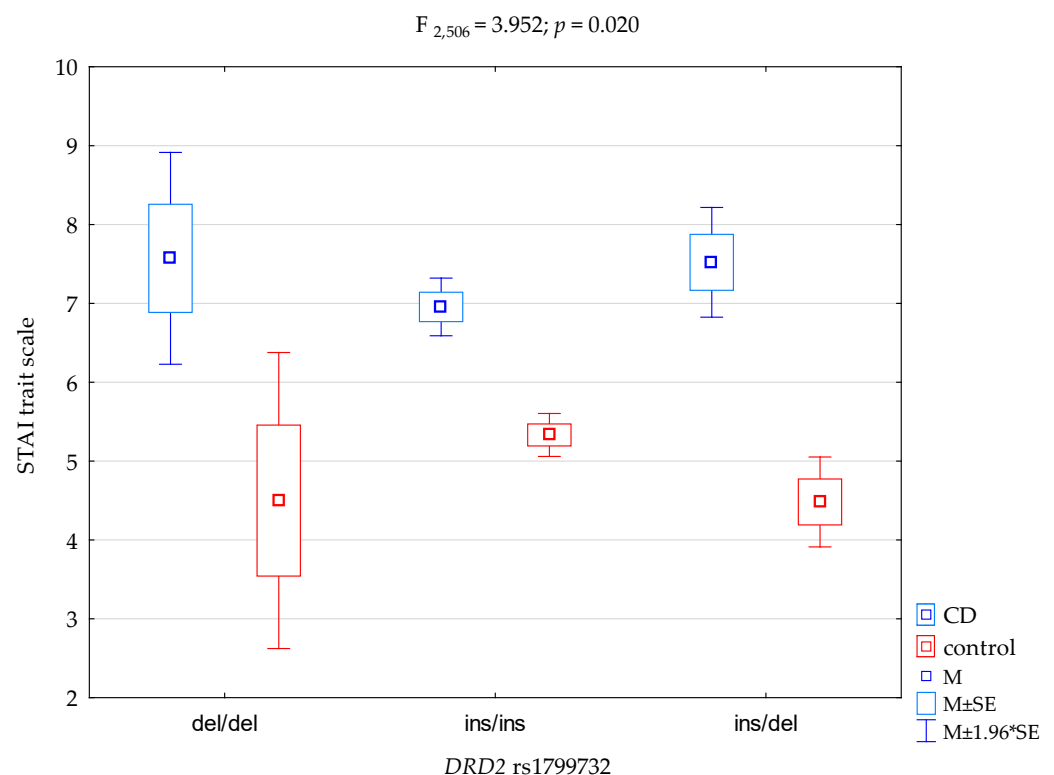


Figure 1. Interaction between the patients diagnosed with polysubstance use disorder comorbid with cannabinoid dependence (CD)/control and the *DRD2* gene rs1799732 and STAI trait scale.

Table 5. Post-hoc test (Bonferroni) analysis of interactions between the patients diagnosed with polysubstance use disorder comorbid with cannabinoid dependence/control and the *DRD2* gene rs1799732 and STAI trait scale.

DRD2 Gene rs1799732 and STAI Trait Scale						
	{1} M = 7.57	{2} M = 6.96	{3} M = 7.52	{4} M = 4.50	{5} M = 5.33	{6} M = 4.48
Cannabinoid dependence del/del {1}		1.0000	1.0000	0.4344	0.1396	0.0093 *
Cannabinoid dependence ins/ins {2}			1.0000	0.4604	0.0000 *	0.0000 *
Cannabinoid dependence ins/del {3}				0.1462	0.0000 *	0.0000 *
Control del/del {4}					1.0000	1.0000
Control ins/ins {5}						0.1611
Control ins/del {6}						

*—significant statistical differences; M—mean.

A statistically significant influence of the *DRD2* genotype was demonstrated: rs1799732 on the NEO-FFI agreeableness scale score ($F_{2,507} = 4.33$; $p = 0.013$; $\eta^2 = 0.017$). The po-

tency observed for this factor was set at 75%, and approximately 2% was explained by the polymorphism of the *DRD2* gene rs1799732 variances of the NEO-FFI Agreeableness Scale Score. There was also a statistically significant effect of addiction to cannabis or its absence on the NEO-FFI agreeableness scale score ($F_{1,507} = 17.50$; $p < 0.0001$; $\eta^2 = 0.033$). The potency observed for this factor was estimated to be approximately 99%, and approximately 3% was explained by cannabis dependence or lack thereof by variations in the NEO-FFI agreeableness score (Table 4).

4. Discussion

Addiction and abuse of illegal psychoactive substances are major problems in public health [42]. To develop a more effective approach to prevention and treatment, it is necessary to better understand the source of individual differences in risk. Extensive research suggests that genetic factors play an essential role in developing substance use disorder [42,43].

We aim to examine the combination of personality traits measured by two inventories—NEO-FFI and STAI—and genetic factors in the contextual occurrence of addiction.

We found many important correlations regarding the factors mentioned above. In addicts, the results of neuroticism and openness were higher, and the results of extraversion, agreeableness, and conscientiousness were lower than in the control group. Compared to the control group, the subjects addicted to cannabis had significantly higher scores on the assessment of anxiety (STAI) as a state and trait scale, neuroticism, openness, and lower scores on the extraversion, agreeableness, and conscientiousness scales. Additionally, the analysis of the results of the NEO-FFI inventory shows a significant effect of addiction to cannabis or its absence on the NEO-FFI agreeableness scale score. Our observations are congruent with the latest data that neuroticism, agreeableness, and conscientiousness are associated with drug use. It was stated that high neuroticism, high openness to experience, and low agreeableness may also be somewhat due to typical familiar effects not only as a result of the individual personality traits [44]. By these authors, it was found that high openness to experience was connected with cannabis use, high neuroticism was related to wrong drug prescription, while both high extraversion and low agreeableness concerned cocaine/crack and stimulant use [44].

There was no statistically significant difference in the frequency of *DRD2* rs1799732 genotypes in the tested cannabis addicts compared to the control group. However, we found statistically significant differences in the frequency of *DRD2* rs1799732 gene alleles between cannabis-dependent subjects and the control group.

Multi-factor ANOVA of addicted subjects and control subjects and the *DRD2* rs1799732 variant interaction approximated the statistical significance for the STAI trait and agreeableness scale.

As it has been shown in other data, neuroticism is thought to modulate the genetic risk to cannabis dependence and this range is estimated to be about 15.5–19.5% (9-fold increase). The SNPs (single nucleotide polymorphisms) of the *DRD2* and *PENK* (proenkephalin) genes seem to be candidates playing a significant role in this process [45]. These gathered data let us assume that low agreeableness together with high neuroticism might be the significant traits for cannabis addiction.

In patients with addiction to psychoactive substances, anxiety disorders often coexist and are more common in families with the problem of using psychoactive substances [46]. The anxiety–impulsive personality traits in people affected by substance use disorders and their families reach higher values than in the control group. Anxiety–impulsive personality traits are a potential endophenotype risk of developing cocaine or amphetamine addiction [47]. People with higher levels of anxiety are more prone to substance addiction. Research confirms the relationship between the anxiety traits measured by STAI and dependence [48]. Addicted patients obtained a higher score on the STAI inventory and the depression scale and lower on the tolerance scale (stress tolerance). Dealing with stress and negative mood states is a common theme of substance use among heavy addicts [49].

Research shows that personality traits play a leading role in problematic substance use. Substance abusers and non-drug abusers have higher measures of stress sensitivity than controls, suggesting that neuroticism may be an endophenotype in substance use disorders. A study by Terracciano et al. [50] shows that low conscientiousness scores and high neuroticism scores indicate an association with many psychoactive substances such as tobacco, heroin, and cocaine. Cannabis users score low on the conscientiousness scale but average on the neuroticism scale and high on the openness scale, which is the hallmark of cannabis users.

This observation shows that there are two extremes of the personality characteristics which may be involved in CUD—on one side is the high neurotic predisposition and the other is schizothymic construct. Soler et al. [51] proved that the cannabis-addicted patients with the genetic variant of *ZNF804* (rs1344706) were characterized by their significant relationship with schizotypal personality traits and psychosis proneness. Furthermore, the schizotypy scores were positively correlated with the cannabis use pattern (dose and frequency) in these subjects. Although, a large meta-analysis performed in 24 studies with 6075 cases and 6643 controls involved with the rs 1799732 *DRD2* variant indicated no association of this locus with schizophrenia [52]. The data collected by means of functional magnetic resonance gave evidence for the role of the *DRD2* rs 1799732 polymorphism in response inhibition and the self-monitoring process in impulsive behavior as is seen alcohol abuse disease [53].

According to literature reports, personality traits may become a predisposing factor to addiction. The most widely described trait is impulsivity, which Barrat defines as “acting under the pressure of the moment”. Experimenting with different substances and behaviors that can lead to addiction is the decision for addicted patients. There is a clear connection between this trait with various addiction profiles. Compared to alcohol addicts, drug addicts are more impulsive [54].

Dopaminergic transmission is related to novelty seeking, a feature related to addiction and relapse [55–59]. Additionally, extraversion is a personality trait associated with the dopaminergic system. Studies of twins reveal that genetics have a different effect on each trait—from 25% to 61% [60].

Dopaminergic conductivity plays a key role in shaping the reward phenomenon in response to psychoactive substances. Despite the use of various methods and different groups of patients, the research results indicate a certain role of *DRD2* gene polymorphisms in addiction [61].

5. Conclusions

Compared to the control group, the case group obtained significantly higher scores on the STAI State, STAI Trait, Neuroticism, and Openness scales and lower scores on the Extraversion, Agreeableness, and Conscientiousness scales. There was no statistically significant difference between addicts and the control group in the frequency of genotypes, but there was a statistically significant difference between addicts and the control group in the frequency of the *DRD2* allele rs1799732.

The multivariate ANOVA analysis showed a statistically significant influence of the *DRD2* rs1799732 genotype on the NEO-FFI agreeableness scale and a statistically significant effect of addiction to cannabis or its absence on the NEO-FFI agreeableness scale score.

The multi-factor ANOVA of addicted subjects and control subjects and the *DRD2* variant interaction approximated the statistical significance for the STAI trait.

We are careful in our conclusions because we still know too little about the biological determinants of addiction. Studying homogeneous subgroups—as in our study—seems reasonable, particularly when combined with genetic determinants and psychological traits. In multigenic and multifactorial entities, such a strategy has a future.

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References

- Center for Behavioral Health Statistics and Quality. *Results from the 2010 National Survey on Drug Use and Health: Summary of National Findings*; Center for Behavioral Health Statistics and Quality: Rockville, MD, USA, 2011.
- EMCDDA. *2009 Annual Report on the State of the Drugs Problem in Europe*; EMCfDaDA: Lisbon, Portugal, 2009.
- Adlaf, E.M.; Begin, P.; Sawka, E.; Canadian Addiction Survey (CAS). *A National Survey of Canadians' Use of Alcohol and Other Drugs: Prevalence of Use and Related Harms: Detailed Report*; Canadian Addiction Survey: Ottawa, ON, Canada, 2005.
- Grzywacz, A.; Barczak, W.; Chmielowiec, J.; Chmielowiec, K.; Suchanecka, A.; Trybek, G.; Masiak, J.; Jagielski, P.; Grocholewicz, K.; Rubiś, B. Contribution of Dopamine Transporter Gene Methylation Status to Cannabis Dependency. *Brain Sci.* **2020**, *10*, 400. [CrossRef] [PubMed]
- United Nations. *World Drug Report 2020*; United Nations: New York, NY, USA, 2020.
- Connor, J.P.; Stjepanović, D.; le Foll, B.; Hoch, E.; Budney, A.J.; Hall, W.D. Cannabis Use and Cannabis Use Disorder. *Nat. Rev. Dis. Primers* **2021**, *7*, 16. [CrossRef] [PubMed]
- World Health Organization. ICD-11 for Mortality and Morbidity Statistics 11th Revision) (WHO, Version 09/2020). Available online: <https://icd.who.int/browse11/l-m/en> (accessed on 5 April 2022).
- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*; American Psychiatric Association: Washington, DC, USA, 2013; ISBN 0890425558.
- Degenhardt, L.; Charlson, F.; Ferrari, A.; Santomauro, D.; Erskine, H.; Mantilla-Herrera, A.; Whiteford, H.; Leung, J.; Naghavi, M.; Griswold, M.; et al. The Global Burden of Disease Attributable to Alcohol and Drug Use in 195 Countries and Territories, 1990–2016: A Systematic Analysis for the Global Burden of Disease Study 2016. *Lancet Psychiatry* **2018**, *5*, 987. [CrossRef]
- SAMHSA. *Results from the 2010 National Survey on Drug Use and Health: Detailed Tables*; SAMHSA: Rockville, MD, USA, 2011.
- World Health Organization (WHO). *The Health and Social Effects of Nonmedical Cannabis Use*; World Health Organization: Geneva, Switzerland, 2016.
- Ridenour, T.A.; Maldonado-Molina, M.; Compton, W.M.; Spitznagel, E.L.; Cottler, L.B. Factors Associated with the Transition from Abuse to Dependence among Substance Abusers: Implications for a Measure of Addictive Liability. *Drug Alcohol Depend.* **2005**, *80*, 1. [CrossRef] [PubMed]
- Bossong, M.G.; van Berckel, B.N.M.; Boellaard, R.; Zuurman, L.; Schuit, R.C.; Windhorst, A.D.; van Gerven, J.M.A.; Ramsey, N.F.; Lammertsma, A.A.; Kahn, R.S. Δ^9 -tetrahydrocannabinol induces dopamine release in the human striatum. *Neuropsychopharmacology* **2009**, *34*, 759–766. [CrossRef]
- Thiruchselvam, T.; Malik, S.; Le Foll, B. A review of positron emission tomography studies exploring the dopaminergic system in substance use with a focus on tobacco as a co-variate. *Am. J. Drug Alcohol Abuse* **2017**, *43*, 197–214. [CrossRef]
- Urban, N.B.; Slifstein, M.; Thompson, J.L.; Xu, X.; Girgis, R.R.; Raheja, S.; Haney, M.; Abi-Dargham, A. Dopamine release in chronic cannabis users: A [11 C]raclopride positron emission tomography study. *Biol. Psychiatry* **2012**, *71*, 677–683. [CrossRef]
- van de Giessen, E.; Weinstein, J.J.; Cassidy, C.M.; Haney, M.; Dong, Z.; Ghazzaoui, R.; Ojeil, N.; Kegeles, L.S.; Xu, X.; Vadhan, N.P.; et al. Deficits in striatal dopamine release in cannabis dependence. *Mol. Psychiatry* **2017**, *22*, 68–75. [CrossRef]
- Volkow, N.D.; Wang, G.J.; Telang, F.; Fowler, J.S.; Alexoff, D.; Logan, J.; Jayne, M.; Wong, C.; Tomasi, D. Decreased dopamine brain reactivity in marijuana abusers is associated with negative emotionality and addiction severity. *Proc. Natl. Acad. Sci. USA* **2014**, *111*, E3149–E3156. [CrossRef]
- Bloomfield, M.A.; Morgan, C.J.A.; Egerton, A.; Kapur, S.; Curran, H.V.; Howes, O.D. Dopaminergic function in cannabis users and its relationship to cannabis-induced psychotic symptoms. *Biol. Psychiatry* **2014**, *75*, 470–478. [CrossRef]
- Bloomfield, M.A.; Morgan, C.J.; Kapur, S.; Curran, H.V.; Howes, O.D. The link between dopamine function and apathy in cannabis users: An [18 F]-DOPA PET imaging study. *Psychopharmacology* **2014**, *231*, 2251–2259. [CrossRef] [PubMed]
- Ferland, J.M.N.; Hurd, Y.L. Deconstructing the neurobiology of cannabis use disorder. *Nat. Neurosci.* **2020**, *23*, 600–610. [CrossRef] [PubMed]

21. Masiak, J.; Chmielowiec, J.; Chmielowiec, K.; Grzywacz, A. DRD4, DRD2, DAT1, and ANKK1 Genes Polymorphisms in Patients with Dual Diagnosis of Polysubstance Addictions. *J. Clin. Med.* **2020**, *9*, 3593. [CrossRef]
22. Calabria, B.; Degenhardt, L.; Briegleb, C.; Vos, T.; Hall, W.; Lynskey, M.; Callaghan, B.; Rana, U.; McLaren, J. Systematic Review of Prospective Studies Investigating “Remission” from Amphetamine, Cannabis, Cocaine or Opioid Dependence. *Addict. Behav.* **2010**, *35*, 741–749. [CrossRef] [PubMed]
23. Freeman, T.P.; Winstock, A.R. Examining the Profile of High-Potency Cannabis and Its Association with Severity of Cannabis Dependence. *Psychol. Med.* **2015**, *45*, 3181. [CrossRef]
24. Agrawal, A.; Lynskey, M.T.; Bucholz, K.K.; Martin, N.G.; Madden, P.A.F.; Heath, A.C. Contrasting Models of Genetic Co-Morbidity for Cannabis and Other Illicit Drugs in Adult Australian Twins. *Psychol. Med.* **2007**, *37*, 49–60. [CrossRef]
25. von Sydow, K.; Lieb, R.; Pfister, H.; Höfler, M.; Wittchen, H.U. What Predicts Incident Use of Cannabis and Progression to Abuse and Dependence? A 4-Year Prospective Examination of Risk Factors in a Community Sample of Adolescents and Young Adults. *Drug Alcohol Depend.* **2002**, *68*, 49–64. [CrossRef]
26. DRD2 Gene-GeneCards | DRD2 Protein | DRD2 Antibody. Available online: <https://www.genecards.org/cgi-bin/carddisp.pl?gene=DRD2&keywords=DRD2> (accessed on 11 April 2022).
27. Chmielowiec, J.; Chmielowiec, K.; Suchanecka, A.; Trybek, G.; Mroczek, B.; Małecka, I.; Grzywacz, A. Associations Between the Dopamine D4 Receptor and DAT1 Dopamine Transporter Genes Polymorphisms and Personality Traits in Addicted Patients. *Int. J. Environ. Res. Public Health* **2018**, *15*, 2076. [CrossRef]
28. Arinami, T.; Gao, M.; Hamaguchi, H.; Toru, M. A functional polymorphism in the promoter region of the dopamine D2 receptor gene is associated with schizophrenia. *Hum. Mol. Genet.* **1997**, *6*, 577–582. [CrossRef]
29. Jönsson, E.G.; Nöthen, M.M.; Grünhage, F.; Farde, L.; Nakashima, Y.; Propping, P.; Sedvall, G.C. Polymorphisms in the dopamine D2 receptor gene and their relationships to striatal dopamine receptor density of healthy volunteers. *Mol. Psychiatry* **1999**, *4*, 290–296. [CrossRef]
30. Voisey, J.; Swagell, C.D.; Hughes, I.P.; van Daal, A.; Noble, E.P.; Lawford, B.R.; Young, R.M.; Morris, C.P. A DRD2 and ANKK1 haplotype is associated with nicotine dependence. *Psychiatry Res.* **2012**, *196*, 285–289. [CrossRef] [PubMed]
31. Grzywacz, A.; Jasiewicz, A.; Małecka, I.; Suchanecka, A.; Grochans, E.; Karakiewicz, B.; Samochowiec, A.; Bieńkowski, P.; Samochowiec, J. Influence of DRD2 and ANKK1 polymorphisms on the manifestation of withdrawal syndrome symptoms in alcohol addiction. *Pharmacol. Rep.* **2012**, *64*, 1126–1134. [CrossRef]
32. Jabłoński, M.; Jasiewicz, A.; Kucharska-Mazur, J.; Samochowiec, J.; Bienkowski, P.; Mierzejewski, P.; Samochowiec, A. The effect of selected polymorphisms of the dopamine receptor gene DRD2 and the ANKK-1 on the preference of concentrations of sucrose solutions in men with alcohol dependence. *Psychiatr. Danub.* **2013**, *25*, 371–378. [PubMed]
33. Samochowiec, J.; Kucharska-Mazur, J.; Grzywacz, A.; Jabłoński, M.; Rommelspacher, H.; Samochowiec, A.; Szabowicz, M.; Horodnicki, J.; Sagan, L.; Pełka-Wysiecka, J. Family-based and case-control study of DRD2, DAT, 5HTT, COMT genes polymorphisms in alcohol dependence. *Neurosci. Lett.* **2006**, *410*, 1–5. [CrossRef] [PubMed]
34. Suchanecka, A.; Chmielowiec, J.; Chmielowiec, K.; Masiak, J.; Sipak-Szmigiel, O.; Szabowicz, M.; Czarny, W.; Michałowska-Sawczyn, M.; Trybek, G.; Grzywacz, A. Dopamine Receptor DRD2 Gene rs1076560, Personality Traits and Anxiety in the Polysubstance Use Disorder. *Brain Sci.* **2020**, *10*, 262. [CrossRef]
35. Chen, D.; Liu, F.; Shang, Q.; Song, X.; Miao, X.; Wang, Z. Association between polymorphisms of DRD2 and DRD4 and opioid dependence: Evidence from the current studies. *Am. J. Med. Genet B Neuropsychiatr. Genet.* **2011**, *156B*, 661–670. [CrossRef]
36. Sutin, A.R.; Terracciano, A.; Deiana, B.; Uda, M.; Schlessinger, D.; Lakatta, E.G.; Costa, P.T. Cholesterol, Triglycerides, and the Five-Factor Model of Personality. *Biol. Psychol.* **2010**, *84*, 186. [CrossRef]
37. Terracciano, A.; Esko, T.; Sutin, A.R.; de Moor, M.H.M.; Meirelles, O.; Zhu, G.; Tanaka, T.; Giegling, I.; Nütle, T.; Realo, A.; et al. Meta-Analysis of Genome-Wide Association Studies Identifies Common Variants in CTNNA2 Associated with Excitement-Seeking. *Transl. Psychiatry* **2011**, *1*, e49. [CrossRef]
38. Costa, P.T.; McCrae, R.R. The Revised NEO Personality Inventory (NEO-PI-R). In *The SAGE Handbook of Personality Theory and Assessment: Volume 2-Personality Measurement and Testing*; Sage Publications, Inc.: Thousand Oaks, CA, USA, 2008; pp. 179–198. [CrossRef]
39. DeYoung, C.G.; Hirsh, J.B.; Shane, M.S.; Papademetris, X.; Rajeevan, N.; Gray, J.R. Testing Predictions From Personality Neuroscience: Brain Structure and the Big Five. *Psychol. Sci.* **2010**, *21*, 820. [CrossRef]
40. Chmielowiec, J.; Chmielowiec, K.; Masiak, J.; Pawłowski, T.; Larysz, D.; Grzywacz, A. Analysis of Relationships between DAT1 Polymorphism Variants, Personality Dimensions, and Anxiety in New Psychoactive Substance (Designer Drug) (NPS) Users. *Genes* **2021**, *12*, 1977. [CrossRef]
41. Grzywacz, A.; Suchanecka, A.; Chmielowiec, J.; Chmielowiec, K.; Szumilas, K.; Masiak, J.; Balwicki, L.; Michałowska-Sawczyn, M.; Trybek, G. Personality Traits or Genetic Determinants—Which Strongly Influences E-Cigarette Users? *Int. J. Environ. Res. Public Health* **2020**, *17*, 365. [CrossRef] [PubMed]
42. Kendler, K.S.; Karkowski, L.M.; Neale, M.C.; Prescott, C.A. Illicit Psychoactive Substance Use, Heavy Use, Abuse, and Dependence in a US Population-Based Sample of Male Twins. *Arch. Gen. Psychiatry* **2000**, *57*, 261–269. [CrossRef] [PubMed]
43. Grove, W.M.; Eckert, E.D.; Heston, L.; Bouchard, T.J.; Segal, N.; Lykken, D.T. Heritability of Substance Abuse and Antisocial Behavior: A Study of Monozygotic Twins Reared Apart. *Biol. Psychiatry* **1990**, *27*, 1293–1304. [CrossRef]

44. Dash, G.F.; Martin, N.G.; Slutske, W.S. Big Five personality traits and illicit drug use: Specificity in trait- drug associations. *Psychol Addict Behav.* **2021**, *11*, adb0000793. [[CrossRef](#)] [[PubMed](#)]
45. Jutras-Aswad, D.; Jacobs, M.M.; Yiannoulos, G.; Roussos, P.; Bitsios, P.; Nomura, Y.; Liu, X.; Hurd, Y.L. Cannabis- dependence risk relates to synergism between neuroticism proenkephalin SNOs associated with amygdala gene expression: Case control study. *PLoS ONE* **2012**, *7*, e39243. [[CrossRef](#)] [[PubMed](#)]
46. Merikangas, K.R.; Swendsen, J.D.; Preisig, M.A.; Chazan, R.Z. Psychopathology and Temperament in Parents and Offspring: Results of a Family Study. *J. Affect Disord.* **1998**, *51*, 63–74. [[CrossRef](#)]
47. Ersche, K.D.; Turton, A.J.; Chamberlain, S.R.; Müller, U.; Bullmore, E.T.; Robbins, T.W. Cognitive Dysfunction and Anxious-Impulsive Personality Traits Are Endophenotypes for Drug Dependence. *Am. J. Psychiatry* **2012**, *169*, 926. [[CrossRef](#)]
48. Pietras, T.; Witusik, A.; Panek, M.; Szemraj, J.; Górski, P. Anxiety, Depression and Methods of Stress Coping in Patients with Nicotine Dependence Syndrome. *Med. Sci. Monit.* **2011**, *17*, CR272. [[CrossRef](#)]
49. Hyman, S.M.; Sinha, R. Stress-Related Factors in Cannabis Use and Misuse: Implications for Prevention and Treatment. *J. Subst. Abuse Treat.* **2009**, *36*, 400. [[CrossRef](#)]
50. Terracciano, A.; Löckenhoff, C.E.; Crum, R.M.; Bienvenu, O.J.; Costa, P.T. Five-Factor Model Personality Profiles of Drug Users. *BMC Psychiatry* **2008**, *8*, 22. [[CrossRef](#)]
51. Soler, J.; Arias, B.; Moya, J.; Ilbaniez, M.I.; Ortet, G.; Fananas, L.; Fatjo-Vilas, M. The interaction between the ZNF804A gene and cannabis use on the risk of psychosis in a non-clinical sample. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **2019**, *89*, 174–180. [[CrossRef](#)]
52. Yao, J.; Pan, Y.; Ding, M.; Pang, H.; Wang, B. Association between DRD2 (rs1799732 and rs1801028) and ANKK1 (rs1800497) polymorphisms and schizophrenia: A meta- analysis. *Am. J. Med. Genet B Neuropsychiatr. Genet.* **2015**, *168B*, 1–13. [[CrossRef](#)]
53. Filbey, F.M.; Claus, E.D.; Morgan, M.; Forester, G.R.; Hutchison, K. Dopaminergic genes modulate response inhibition in alcohol abusing adults. *Addict Biol.* **2012**, *17*, 1046–1056. [[CrossRef](#)]
54. le Bon, O.; Basiaux, P.; Streel, E.; Tecco, J.; Hanak, C.; Hansenne, M.; Ansseau, M.; Pelc, I.; Verbanck, P.; Dupont, S. Personality Profile and Drug of Choice; a Multivariate Analysis Using Cloninger's TCI on Heroin Addicts, Alcoholics, and a Random Population Group. *Drug Alcohol Depend.* **2004**, *73*, 175–182. [[CrossRef](#)]
55. Cloninger, C.R.; Svrakic, D.M.; Przybeck, T.R. A Psychobiological Model of Temperament and Character. *Arch. Gen. Psychiatry* **1993**, *50*, 975–990. [[CrossRef](#)]
56. 3Einstein, R.P.; Novick, O.; Umansky, R.; Priel, B.; Osher, Y.; Blaine, D.; Bennett, E.R.; Nemanov, L.; Katz, M.; Belmaker, R.H. Dopamine D4 Receptor (D4DR) Exon III Polymorphism Associated with the Human Personality Trait of Novelty Seeking. *Nat. Genet* **1996**, *12*, 78–80. [[CrossRef](#)]
57. Koob, G.F. Neurobiology of Addiction. Toward the Development of New Therapies. *Ann. N. Y. Acad. Sci.* **2000**, *909*, 170–185. [[CrossRef](#)]
58. Mahoney, J.J.; Thompson-Lake, D.G.Y.; Cooper, K.; Verrico, C.D.; Newton, T.F.; de La Garza, R. A Comparison of Impulsivity, Depressive Symptoms, Lifetime Stress and Sensation Seeking in Healthy Controls versus Participants with Cocaine or Methamphetamine Use Disorders. *J. Psychopharmacol.* **2015**, *29*, 50–56. [[CrossRef](#)] [[PubMed](#)]
59. 3Ismael, F.; Baltieri, D.A. Role of Personality Traits in Cocaine Craving throughout an Outpatient Psychosocial Treatment Program. *Rev. Bras. Psiquiatr.* **2014**, *36*, 24–31. [[CrossRef](#)]
60. Jang, K.L.; Livesley, W.J.; Vernon, P.A. Heritability of the Big Five Personality Dimensions and Their Facets: A Twin Study. *J. Pers.* **1996**, *64*, 577–592. [[CrossRef](#)]
61. Gorwood, P.; le Strat, Y.; Ramoz, N.; Dubertret, C.; Moalic, J.M.; Simonneau, M. Genetics of Dopamine Receptors and Drug Addiction. *Hum. Genet.* **2012**, *131*, 803–822. [[CrossRef](#)] [[PubMed](#)]