medical sciences forum

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Proceeding Paper

Exploring Genetic Variations and Psychological Factors in Alcohol and Drug Consumption in a Portuguese Female Sample †

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† Presented at the 6th International Congress of CiiEM—Immediate and Future Challenges to Foster One Health, Almada, Portugal, 5–7 July 2023.

Abstract: While in some countries, the possession of psychoactive substances leads to prison sentences or execution, other countries, like Portugal, follow an avenue leading to a drug-tolerant culture. However, there is a lack of empirical data on Portuguese populations to measure the drug-use trend. The present study uses multidisciplinary approaches to explore the prevalence of alcohol and drug consumption on a Portuguese student population (N = 81, ages ranged from 17 to 40 years), associating it with psychological and genetic factors. The results show a prevalence of cannabis consumption higher than what is reported by the EMCDDA, and suggests that carriers of the minor allele of 5-HTTLPR have a higher propensity for addiction.

Keywords: genetic variations; psychological factors; consumptions; drugs; alcohol

Citation: Couceiro, J.; Oliveira, S.; Godinho, C.; Alves, I.; Fonte, J.; Baúto, R.; Silva, A.M.e.; Almeida, I.; Soeiro, C.; Quintas, A. Exploring Genetic Variations and Psychological Factors in Alcohol and Drug Consumption in a Portuguese Female Sample. *Med. Sci. Forum* **2023**, *22*, 34. https://doi.org/10.3390/msf2023022034

Academic Editors: José Brito, Nuno Taveira and Ana I. Fernandes

Published: 16 August 2023

1. Introduction

Drug abuse is a ubiquitous historical phenomenon that largely depends on the cultural and political environment. In Portugal, the primary drug law is Decree-Law 15/93, which frames the legal regime applicable to drug trafficking and consumption of psychoactive substances. Decree-Law 130-A/2001 changed the 1993 framework by decriminalizing the consumption, acquisition and possession of drugs for personal consumption. Notwithstanding this, people possessing substances of abuse quantities below the amounts stated on the current drug Decree-Law and not under suspicion of drug trafficking are evaluated by the local Commission for Dissuasion of Drug Addiction. In extreme cases, punitive sanctions can be applied, but the main purpose is to promote addiction treatment. The Portuguese case for drug control frequently receives focus due to the encouraging results regarding drug use prevalence, which remains reasonably low compared to other European countries. However, the statistics compiled by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) indicate that between 2001 and 2007, lifetime prevalence rates for cannabis, cocaine, amphetamines, ecstasy, and LSD use rose for the Portuguese general population (ages 15–64) and for the 15–34 age group [1].

The Portuguese government's investment in drug safety, which involves assessment, drug checking, and wastewater analysis, among other analytical tools to monitor the drug consumption trend, is the lowest in Europe, with a value of 0.003% of GDP [2], since most of the drug-related public budget is expended on the health consequences of drug abuse. Consequently, the lack of empirical data is a significant problem that may bias the

reports' numbers. The latest report by the EMCDDA indicates a lifetime prevalence of 8% of cannabis use among the Portuguese population aged 15–34. However, the survey used on this report was from 2016. The figures for the abuse of other drugs are much lower, with a lifetime prevalence of 0.3% for cocaine and 0.2% for MDMA. Finally, among individuals seeking treatment, 33.9% use cannabis and 39.4% use opioids [1].

Independently of the success or lack of success of public policies, psychoactive substance use must be studied and debated based on its very foundations without any prejudice. Literature data on psychoactive substance use suggest evolutionary, environmental, neurobiological, personality [3], and genetic causes for drug addiction. However, multi- and transdisciplinary approaches are scarce. Thus, a holistic approach for drug addiction is needed. This assumes a higher relevance on cannabis and alcohol use due to their consumption prevalence and people enrolling in treatment programs.

Factors such as the progression of consumption patterns, the initiation age, the substances used, the routes of administration, concurrent substance consumption, relapse circumstances, previous cessation attempts, and drug-related health problems are significant in comprehending the psychosocial aspects and the accompanying psychopathological impact of drug use [4]. From a biological perspective, some studies suggest that hereditary influences may contribute to a predisposition for substance use; however, these effects can be mitigated by the presence of adequate parental monitoring and supervision, further underscoring the impact of psychosocial development [5]. Several genes have been identified and associated with addiction, including the serotonin transporter gene (*SLC6A4*). Serotonin (5-HT) is a neurotransmitter that, after release, is taken up again from synaptic spaces by SLC6A4, localized in presynaptic neuronal membranes, terminating the synaptic actions of 5-HTT and recycling it into the neurotransmitter pool. The *SLC6A4* is a 31 kb gene on chromosome 17 (17q11.2) (OMIM-182138). *5-HTTLPR*, its most common polymorphism, is a 44-bp indel at the promotor region modifying SLC6A4 activity. It has two major alleles: the long (L) and the short (S) form [6]. The S form is associated with lower basal transcriptional efficiency of the *SLC6A4* gene promotor, resulting in lower serotonin uptake activity comparing with the L form [7]. Several case–control and family-based association studies try to link variants in *SLC6A4* with alcohol or drug dependence. The results are contradictory, as some of these studies reported positive findings, while many others found no evidence of association. A 2013 meta-analysis based on 55 studies supports the associations of *5-HTTLPR* with alcohol, heroin, cocaine, and methamphetamine dependence and abuse [7]. However, the authors suggest that further studies are needed. According to several studies *SLC6A4/5-HTTPLR* is one of the four genes associated with addiction, particularly in the European population [8]. The present research aims to explore the intricate interplay between genetic factors and the psychosocial development of individuals with a history of substance abuse.

2. Materials and Methods

This pilot study examined a sample of 81 female university students with ages ranging from 17 to 40 years, with an average age of 21.04 years (*SD* = 3.16). DNA was obtained from a buccal swab and the psychological variables were collected through three self-report instruments assessing substance consumption, adverse childhood experiences, aggression and personality. For the analysis of the polymorphism *SLC6A4/5-HTTLPR*, DNA was obtained from the buccal swab. DNA extraction was performed with the QIAamp DNA investigator Kit® (QIAGEN), according to the manufacturer's instructions. *5-HTTLPR* genotyping was performed via PCR, using the following primers: 5′ GGCGTTGCCGCTCTGAATGC 3′ (forward) and 5′ GAGGGACTGAGCTGGACAACCAC 3′ (reverse). In this process, 25 µL PCR mix reactions were used, containing approximately 50 ng of genomic DNA, 1X Horse-Power™ Taq DNA polymerase MasterMix® (Canvax), 5 pmol of each primer, and 2% DMSO. Reactions were carried out with the following program: 94 °C for 2 min, followed by 35 cycles at 94 °C for 10 s, 61 °C for 30 s, and 68 °C for 30 s. The amplification products were analyzed on a 2.5% (*w/v*) agarose gel; random products were

confirmed via Sanger sequencing. Regarding psychological variables and substance consumption, The Adverse Childhood Experiences Questionnaire (ACE; Felitti & Anda, 1998; Portuguese Version: Maia & Silva, 2007), The Reactive-Proactive Aggression Questionnaire (RPQ; Raine et al., 2006; Portuguese Version: Pechorro et al., 2017) and the NEO Five-Factor Inventory (NEO-FFI, McCrae and Costa in 2004) were used to collect data.

3. Results

The results indicate that 11.1% (n = 9) of the subjects reported never consuming alcoholic beverages. The remaining 88.9% was divided between "sometimes" consuming alcohol, accounting for 49.4% (n = 40), and "frequent" consumption, representing 39.5% (n = 32). Regarding cannabinoid consumption, 61.7% (n = 50) reported never consuming cannabinoids, 28.4% (n = 23) reported consuming cannabinoids "sometimes", and the remaining 9.9% (n = 8) reported consuming them frequently. As for heavier drug consumption, including ecstasy, cocaine, or heroin, 91.4% (n = 74) reported never consuming these drugs, while 3.7% (n = 3) reported consuming them "sometimes", and 4.9% (n = 4) reported consuming them "frequently", meaning that nearly 9% of all subjects were engaged in hard drug use. Regarding the Five Factor Model (Personality), we also found a weak positive correlation between neuroticism and alcohol consumption, which we identified as the most relevant (Spearman) correlation (r = 0.22, $p < 0.01$). This result provides a linkage that suggests that genetic factors can influence the regulation of neurotransmitters and neural pathways associated with reward and stress response, making individuals with higher neuroticism scores more vulnerable to developing problematic alcohol consumption patterns. Concerning *SLC6A4/5-HTTLPR*, the subjects were separated only between consumers and non-consumers. *5-HTTLPR* allele distribution was consistent with the Hardy–Weinberg equilibrium. The major allele frequency was L = 91(56.2%), which was consistent with the values observed in previous studies for the European population (48–71%). The genotype frequencies were analyzed, and there was no evidence of a significant association between *5-HTTLPR* and consumption for all substances under analysis (alcohol, cannabinoids, and ecstasy, cocaine, and heroin). For alcohol abuse, 18.1% of the 'consumption' group had the SS-genotype, while in the 'no consumption' group, no one with the same genotype was found. The frequency of the LL-genotype was 27.8% and 33.3% for the 'consumption' and 'no consumption' groups, respectively. The heterozygous genotype was present in 54.2% of the consumers and in 66.7% of the non-consumers. For cannabinoid consumption analysis, the genotype distribution in the consumers was 54.8%, 22.6%, and 22.6% for the LS-, LL-, and SS-genotype, respectively. In the 'no consumption' group, the distribution was 56%, 32%, and 12%, respectively. Finally, for ecstasy, cocaine and heroin abuse, this trend is even higher. The frequency of homozygous individuals in the 'consumption' group was 28.6% for the S allele and 14.3% for the L allele. On the contrary, in non-consumers, this distribution was 14.9% for the SS-genotype and 29.7% for the LL-genotype. The heterozygous individuals were evenly distributed between the two groups (57.1% and 55.4%, correspondingly). Although the results only show trends, without statistical significance, they are in line with what is described in the literature. The *5-HTTLPR* S-allele results in a less efficient transporting function, leading serotonin to remain longer in the synapse, reducing its recycling period, thus resulting in a reduction in circulating serotonin [8]. This is the reason why *5-HTTLPR* has been linked to higher levels of anxiety and a negative mood in healthy individuals, and consequent consumption/addiction.

4. Discussion

Based on the presented research, deepening the studies on genetic variability and psychological variables is of utmost importance for developing a better understanding of substance use. Exploring these factors contributes to a more personalized approach to treating and preventing addiction, considering individual differences and specific intervention responses. Furthermore, analyzing the female gender in this context is crucial, as women have biological, psychosocial, and cultural particularities that influence alcohol and drug

consumption. The inclusion of studies focused on the female gender fills significant gaps and provides a solid foundation for the implementation of health policies and appropriate interventions. Therefore, continuing research in this area is encouraged, aiming to understand the risk factors, consumption patterns, and specific needs of women to promote effective and comprehensive interventions in addressing alcohol and drug consumption.

Author Contributions: Conceptualization, A.Q. and C.S.; methodology, J.C., A.Q and C.S.; software, J.C., C.S., S.O., C.G., I.A. (Inês Alves) and J.F.; validation, C.S. and A.Q.; formal analysis, C.S., J.C., A.M.e.S. and A.Q.; investigation, J.C., C.S., S.O., C.G., I.A. (Inês Alves) and J.F.; resources, A.Q. and C.S.; data curation, C.S., R.B. and J.C.; writing—original draft preparation, J.C. and R.B.; writing—review and editing, A.Q.; supervision, A.Q., C.S. and J.C.; project administration, I.A. (Iris Almeida); funding acquisition, I.A. (Iris Almeida), R.B. and A.M.e.S. All authors have read and agreed to the published version of the manuscript.

Funding: Research funding by CiiEM Investiga 2018 (CEI/24/2018) by Egas Moniz Center for Interdisciplinary Research (CiiEM).

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of Egas Moniz School of Health and Science for studies involving humans.

Informed Consent Statement: We rigorously adhered to the highest ethical standards, including the principles outlined in the Helsinki Declaration. Furthermore, we obtained informed consent from all participants, ensuring their autonomy and well-being throughout the scientific study.

Data Availability Statement: Not applicable.

Acknowledgments: The authors acknowledge Egas Moniz Center for Interdisciplinary Research (CiiEM) from Egas Moniz School of Health and Science for the financial support to CiiEM Investiga 2018 (CEI/24/2018).

Conflicts of Interest: The authors declare no conflict of interest.

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