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Associations between experimental substance use, FAAH-gene variations, impulsivity and sensation seeking

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Abstract

Background: Experimental substance use among young people is related to individual factors including personality traits such as impulsivity and sensation seeking, and genetic variations such as single nucleotide polymorphisms (SNPs) in the fatty acid amide hydrolase (FAAH) gene. The objective of this study is to analyze the relationship between these three sets of variables. **Methods:** Volunteer undergraduate students (N = 861, 76% female, M = 20.7 years) completed an ad hoc questionnaire on variables related to their consumption of alcohol, tobacco, cannabis, synthetic drugs and cocaine. In addition, 591 of them completed the Barratt Impulsiveness Scale-11 (BIS-11) and the Sensation Seeking Scale-V (SSS-V). All participants were genotyped in FAAH C385A SNP and its proxy variant rs12075550. **Results:** Consistent with previous data, both impulsivity and sensation seeking were associated with most of the variables related to experimental substance use. In addition, we found the first evidence of an association between the rs12075550 SNP and some of these consumption phenotypes. However, no significant association was found between either of the two SNPs and impulsivity or sensation seeking. **Conclusions:** The results highlight the importance of considering both personality and genetic differences, together with contextual factors, in the analysis of substance use.

Keywords: Experimental substance use, impulsivity, sensation seeking, rs12075550, FAAH C385A.

Resumen

Asociaciones entre el uso experimental de sustancias, variaciones del gen FAAH, impulsividad y búsqueda de sensaciones. **Antecedentes:** el uso experimental de sustancias en los jóvenes está relacionada con factores individuales que incluyen rasgos de personalidad, como impulsividad o búsqueda de sensaciones, y variaciones genéticas, como polimorfismos de un solo nucleótido (SNPs) del gen amida hidrolasa de ácidos grasos (FAAH). El objetivo de este estudio es analizar la relación entre estos tres conjuntos de variables. **Método:** estudiantes universitarios voluntarios (N = 861, 76% mujeres, M = 20,7 años) rellenaron un cuestionario ad hoc de variables relacionadas con el consumo de alcohol, tabaco, cannabis, drogas sintéticas y cocaína. Además, 591 de ellos rellenaron las escalas BIS-11 y SSS-V. Se genotipó a todos ellos en SNP FAAH C385A y su variante proxy rs12075550. **Resultados:** como se esperaba, la impulsividad y la búsqueda de sensaciones estuvieron asociadas con la mayor parte de las variables relativas al uso experimental de sustancias. Además, encontramos por primera vez evidencia de una asociación entre rs12075550 y algunos de estos fenotipos de consumo. Sin embargo, no encontramos asociaciones significativas entre SNPs e impulsividad o búsqueda de sensaciones. **Conclusiones:** los resultados resaltan la importancia de tener en cuenta las diferencias genéticas y las de personalidad, junto con los factores contextuales, al analizar el uso de sustancias.

Palabras clave: uso experimental de sustancias, impulsividad, búsqueda de sensaciones, rs12075550, FAAH C385A.

Substance use disorders are common, complex disorders, characterized by compulsive substance seeking and use despite harmful consequences. The initiation of substance use takes place mainly during adolescence (Plan Nacional sobre Drogas, 2018). An early onset of substance use is associated with a significantly greater risk of later developing a substance use disorder (Chen, Storr, & Anthony, 2009).

Various risk factors for substance use initiation have been identified, including multiple contextual and individual variables (e.g. Blanco, Flórez-Salamanca, Secades-Villa, Wang, & Hasin, 2018), and both prevention and treatment strategies must take into account all these factors (Becoña, 2018). Among individual variables, personality traits like impulsivity and sensation seeking seem to be particularly relevant. Impulsivity is a multidimensional construct that can be broadly defined as a tendency toward rapid and unplanned reactions without regard to the consequences of these reactions (Stanford et al., 2009). Evidence indicates that impulsivity acts as a determinant factor for substance use initiation (e.g. Fernie et al., 2013; Mitchell & Potenza, 2014; Rømer-Thomsen et al., 2018; Verges, Littlefield, Arriaza, & Alvarado, 2019) and that, in turn, substance use increases subsequent impulsive behaviors (de Wit, 2009). Sensation seeking can be defined as the tendency of the individual to seek out varied, novel and intense experiences and the willingness to take risks for the sake of such experiences (Zuckerman, 1994). Several studies have linked sensation seeking with substance use disorders and have even indicated that it is one of its most powerful predictors (e.g. Ames, Zogg, & Stacy,

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2002; Evans-Polce, Schuler, Schulenberg, & Patrick, 2018; Jaffe & Archer, 1987; Malmberg et al., 2012; Martínez-Loredo et al., 2018). Nevertheless, other studies suggest that abnormal sensation seeking values are more likely to be a consequence of substance use than a preexisting vulnerability factor (Ersche, Turton, Pradhan, Bullmore, & Robbins, 2010).

Beyond personality and related to it, genetic characteristics play an important role in the development of substance use disorders. Data indicate that there are a number of genes, each with a small influence, that interact with each other and with environmental factors, affecting substance use and the likelihood of developing a substance use disorder (e.g. Gray & Squeglia, 2018; Meyers & Dick, 2010). The influence of genetic factors on substance use appears to increase considerably from early adolescence to young adulthood (Rose, Dick, Viken, & Kaprio, 2001). Among genetic variations related to substance use, single nucleotide polymorphisms (SNPs) in the endocannabinoid system may play a relevant role (see Bühler et al., 2015 for a review). The endocannabinoid system is implicated in a variety of cognitive and physiological processes including modulation of learning and memory, as well as brain reward signaling, influencing therefore vulnerability to substance use disorders (Parsons & Hurd, 2015). Among the different components of the endocannabinoid system, the fatty acid amide hydrolase enzyme (FAAH) has received special attention. This enzyme is responsible for the degradation of endocannabinoids and is encoded by its homonym gene *FAAH* which presents a missense SNP (rs324420/C385A) that reduces the expression and the activity of that enzyme, resulting in increased anandamide levels (Chiang, Gerber, Sipe, & Cravatt, 2004; Dincheva et al., 2015). Several studies have shown an association between *FAAH* C385A and different phenotypes related to substance use (e.g. Bühler et al., 2014; Sloan et al., 2018; Sipe, Chiang, Gerber, Beutler, & Cravatt, 2002), although the studies as a whole have shown heterogeneous results (Bühler et al., 2015).

The effects of FAAH C385A can depend on its interaction with other SNPs. In this line, Flanagan, Gerber, Cadet, Beutler, and Sipe (2006) revealed a haplotype which included FAAH C385A and its proxy variant rs12075550 –D' = 1, r = 0.1875 in Caucasian individuals– (Michiela & Chanock, 2015). Rs12075550 is approximately 37 Kb from the C385A locus, in a non-coding region near the *FAAH* gene, which is likely to affect activator protein binding and expression of this gene (Boyle et al., 2012; Veyrieras et al., 2008). However, there is a deep lack of information about the influence of rs12075550 on human phenotypes, including those related to substance use.

In addition to different consumption phenotypes, FAAH C385A has been previously associated with impulsivity (Hariri et al., 2009). However, Bidwell et al. (2013) did not find a significant interaction of impulsivity and *FAAH*-gene variations (including C385A but not rs12075550) to predict marijuana-related problems. On the other hand, Helfand, Olsen, and Hillard (2017) found that FAAH knockout mice exhibited increased active responses in an operant sensation seeking task. Also, numerous studies have demonstrated a positive correlation between impulsivity and sensation seeking, suggesting a common biological mechanism underlying this association (Hur & Bouchard, 1997). It is reasonable, then, to ask whether impulsivity and sensation seeking operate as endophenotypes between FAAH C385A or rs12075550 and experimental substance use, understanding as such the exploratory behavior during early stages of substance use (Schindler et al., 2005).

In summary, the objective of this study is to analyze the associations between three sets of variables: phenotypes of experimental substance use, genotypes in two variations involved in the activity of the endocannabinoid system (rs12075550 and C385A SNPs), and two personality traits and potential endophenotypes (impulsivity and sensation seeking).

Method

Participants

We recruited 929 undergraduate students from the Complutense University of Madrid. All of them participated voluntarily and a part received credits for their participation. To reduce the risk of population stratification, only the data of the 861 participants of self-reported European ancestry (76.00% female) were analyzed. Their age ranged from 18 to 40 (M = 20.66, SD = 3.28). They all filled a consumption questionnaire and donated a saliva sample. In addition, 591 of them (77.30% female, mean age = 20.09, SD = 2.78) completed the personality tests. The rest of participants (n = 270, 73.00 % female, mean age = 21.91, SD = 3.88) did not fill these tests, because their application was mistakenly omitted.

Instruments

Three different self-report questionnaires were used. An ad hoc questionnaire on substance use asked the participant, among other things, whether or not he/she had ever tried alcohol, tobacco, cannabis, cocaine or synthetic drugs (*ever tried*), the age of first use of each of these substances (*age of first use*), and which of them he/she had consumed in the past 30 days (*currently use*).

To assess impulsivity, the Spanish version of the *Barrat Impulsiveness Scale-11A*, translated and adapted by Oquendo et al. (2001), was administered. The BIS-11 is a self-report questionnaire widely used (Stanford et al., 2009) that contains 30 items, measured on a four-point Likert-type scale. Since the Spanish version of Oquendo et al. (2001) was based on an initial version of BIS-11 [BIS-11A] (Barrat, 1994) and with the aim of making the data comparable to those of studies carried out with the much more used final version [BIS-11] (Patton, Stanford, & Barrat, 1995), only the 24 items common to the two versions have been taken into account (International Society for Research on Impulsivity, 2013). However, the total scores were transformed to the usual scale of 30 to 120 points of this final version by multiplying each of them by 1.25. In this study, Cronbach's alpha coefficient for the questionnaire was 0.75.

To assess sensation-seeking, the Spanish version of the *Sensation-Seeking Scale Form V* (SSS-V) (Zuckerman, Eysenck, & Eysenck, 1978), translated and adapted by Perez and Torrubia (Pérez & Torrubia, 1986), was used. The SSS contains 40 yes-no items. The items 10, 11, 14, 23 and 39 were not counted, because they directly ask about the consumption of substances, which would increase the association of sensation seeking with consumption, but the total scores were transformed to the usual scale of 0 to 40 points by multiplying each of them by 1.143. In this study, Cronbach's alpha coefficient for the questionnaire was 0.73. The correlation between SSS-V and BIS-11 total scores was r = .314 (p <.001).

Procedure

Participants first signed two informed consents, one for the collection and use of the data from the questionnaires, and another for the genetic study. They then completed the questionnaires and subsequently donated a saliva sample. The Research Ethics Committee of the Complutense University of Madrid (Faculty of Psychology) approved all procedures.

DNA from saliva was genotyped as previously described by Bühler et al. (2014) and Huertas, Bühler, Echeverry-Alzate, Giménez, and López-Moreno (2012). Briefly, DNA was collected using Oragene DNA Self-Collection kit (DNA Genotek, Ottawa, Ontario, Canada) and purified from 250-μl aliquots using the ethanol precipitation protocol as described by the manufacturer. TaqMan genotyping was performed using pre-designed and validated TaqMan SNP genotyping assays (Assay ID: rs324420 and rs1275550) for humans from Applied Biosystems (Foster City, CA94404, USA). These genotyping assays were performed with a LightCycler 480II-machine (Roche Diagnostics, Barcelona, Spain) with endpoint genotyping method. Color fluorescence measures after amplification were analyzed with LightCycler 480 endpoint genotyping software version 1.5 (Roche Diagnostics, Barcelona, Spain).

Data analysis

Data regarding the current use of cocaine and synthetic drugs were excluded from the analysis because the number of participants who had consumed these substances in the last 30 days was small (10 and 12 respectively). Consequently, some n per group were too small when analyzing differences in personality or differences in genotypes between participants who have consumed the substances and those who did not. In the same way, the age at which these two substances were first used was also excluded because the number of participants who had ever tried them was small (51 and 59 respectively) and also because this number was very unbalanced between genotypes. This resulted in some n per cell too small when comparing ages in function of genotypes.

Consistent with previous studies (i.e. Bühler et al., 2014) and after a preliminary data inspection, analysis were performed under a dominant genetic model for the C allele of rs12075550 (CC/CT vs. TT), and for the A allele of FAAH C385A (AA/AC vs. CC).

Statistical analysis was performed using the Statistical Package for the Social Sciences of International Business Machines (IBM SPSS Statistics 22 for Windows, SPSS Inc., Chicago, IL). To test the association between each of these SNPs with the *ever tried* and *currently used* variables, we used Pearson's chi-square (χ^2) with exact significance and the odds ratio (OR, 95%IC), controlling the gender effect by means of the Mantel-Haenszel method. Survival analysis, estimated by the Kaplan-Meier method, was used to assess the association of each SNP with age of first use, and the curves of the genotypes were compared using the Breslow (Generalized Wilcoxon) test.

To assess the association between *ever tried* / *currently used* of each substance, as well as each SNP, with the BIS-11 / SSS-V total scores, univariate ANOVAs were used, adding gender as an additional factor (see e.g. Baker & Yardley, 2002). The Pearson's correlation test (*r*) was applied to measure the strength of the associations between *age of first use* and the BIS-11 / SSS-V total scores.

We applied the Benjamini-Hochberg correction for multiple tests (Benjamini & Hochberg, 1995), with a false discovery rate of .05.

Results

Genetic data

Genotype distribution data of both SNPs are shown in Table 1.

The genotype distributions of both SNPs did not deviate from Hardy-Weinberg equilibrium (FAAH C385A $\chi^2 = 0.32$, $p = 0.57$, rs12075550 $\chi^2 = 1.96$, $p = 0.16$) neither were there significant differences between genotypes in the gender distribution (C385A $\chi^2 = 2.96$, $p = 0.23$, rs12075550 $\chi^2 = 0.12$, $p = 0.94$). Allele frequency distributions of C385A and rs12075550 were consistent with the NIH LDlink data for European population, where the minor allele frequencies were A (21%) and C (41,3%) respectively (Michiela & Chanock, 2015). In the same way, the distribution of C385A-rs12075550 haplotype frequency, also shown in Table 1, was consistent with NIH LDlink data for European population.

The *p*-values of associations between consumption, genotypes and personality traits are summarized in Table 2.

Table 1
FAAH C385A and rs12075550 SNPs genotype distribution

	Male	Female	Total	Male	Female	Total	Male	Female	Total	
C385A										
	AA			AC			CC			TOTAL
n	12	23	35	57	207	264	138	424	562	861
%	1,39	2,67	4,07	6,62	24,04	30,66	16.03	49,25	65,27	100
rs12075550										
	CC			CT			TT			TOTAL
n	43	130	173	95	308	403	69	216	285	861
%	4.99	15,10	20,1	11.03	35.77	46,81	8,01	25.09	33.10	100

Note: Minor allele frequency: 385A = .19; rs12075550 C = .44. Haplotype distribution (C385A - rs12075550): A-C = 0 (0.0%); A-T = 334 (19.4%); C-C = 749 (43.5%); C-T = 639 (37.1%)

Table 2
P-value of significant associations between experimental substance use, personality traits and SNPs, after Benjamini-Hochberg correction for multiple tests

	Questionnaires		SNPs	
	SSS-V	BIS-11	C385A	rs12075550
Substance use				
Ever tried:				
alcohol	< .001	–	–	–
tobacco	< .001	< .001	–	–
cannabis	< .001	.001	–	.023
synthetic drugs	< .001	-	–	.015
cocaine	–	.019	–	–
Age of first use:				
alcohol	<.001	<.001	–	–
tobacco	–	–	–	–
cannabis	<.001	.002	–	.017
Current use:				
alcohol	< .001	< .001	–	–
tobacco	.001	< .001	–	.011
cannabis	< .001	< .001	–	–
SNPs:				
C385A	–	–	< .001	< .001
rs12075550	–	–		
Questionnaires:				
SSS-V	<.001	<.001	–	–
BIS-11			–	–

Note: The results of the specific statistical analyses for each association can be found in the *Results* section. *Current use* indicates whether or not the participant has consumed the substance in the last 30 days

Association consumption - impulsivity/sensation seeking

- *BIS-11 questionnaire*. BIS-11 total scores were higher in participants who have ever tried tobacco (*dif* = 4.20, $F(1, 585) = 16.516$, $p < .001$, *partial* $\eta^2 = .027$), cannabis (*dif* = 3.79, $F(1, 585) = 10.302$, $p = .001$, *partial* $\eta^2 = .017$) or cocaine (*dif* = 5.10, $F(1, 585) = 5.521$, $p = .019$, *partial* $\eta^2 = .009$). BIS-11 total scores were also higher in participants with a current use of alcohol (*dif* = 4.81, $F(1, 585) = 14.657$, $p < .001$, *partial* $\eta^2 = .024$), tobacco (*dif* = 4.48, $F(1,585) = 15.323$, $p < .001$, *partial* $\eta^2 = .026$) or cannabis (*dif* = 4.66, $F(1, 585) = 18.087$, $p < .001$, *partial* $\eta^2 = .030$). In addition, a negative correlation was found between the BIS-11 total scores and age of first use of alcohol ($r = -.135$, $p = .002$) or cannabis ($r = -.158$, $p = .002$).
- *SSS-V questionnaire*. As expected, SSS-V total scores were higher in participants who have ever tried alcohol (*dif* = 5.37, $F(1, 587) = 16.365$, $p < .001$, *partial* $\eta^2 = .027$), tobacco (*dif* = 2.04, $F(1, 587) = 12.777$, $p < .001$, *partial* $\eta^2 = .021$), cannabis (*dif* = 2.96, $F(1, 587) = 26.778$, $p < .001$, *partial* $\eta^2 = .044$) or synthetic drugs (*dif* = 3.93, $F(1, 587) = 13.299$, $p < .001$, *partial* $\eta^2 = .022$). SSS-V total scores were also higher in those participants who currently use alcohol (*dif* = 2.67, $F(1, 587) = 16.165$, $p < .001$, *partial* $\eta^2 = .027$), tobacco (*dif* = 1.78, $F(1, 587) = 12.107$, $p = .001$, *partial* $\eta^2 = .020$) or cannabis (*dif* = 3.24, $F(1, 586) = 31.162$, $p < .001$, *partial* $\eta^2 = .050$). We also found a negative correlation between SSS-V total scores and age of first use of alcohol ($r = -.208$, $p < .001$) or cannabis ($r = -.178$, $p < .001$).

Association genotypes - consumption

- *SNP rs12075550*. The percentage of participants who had tried each of the substances was lower among T-homozygotes than among C-allele carriers, but this difference reached statistical significance only in the case of cannabis (50.18 % vs 57.64 %, $\chi^2 = 4.294$, $p = .023$, odds ratio = 1. 359, $p = .036$, 95% CI [1.020-1.811]) and synthetic drugs (4.56 % vs 8.85 %, $\chi^2 = 5.106$, $p = .015$, odds ratio = 2.046, $p = .025$, 95% CI [1.094-3.829]), after applying the Benjamini-Hochberg correction for multiple tests. The T homozygotes were also significantly older when they first used cannabis (16.6 years vs 16.2 years, Breslow $\chi^2 = 5.667$, $p = .017$) and were less likely to be current tobacco users (26.32 % vs 34.90 %, $\chi^2 = 6.444$, $p = .011$, odds ratio = 1.501, $p = .011$, 95% CI [1.096-2.055]).
- *SNP FAAH C385A*. No consumption phenotype was significantly associated with this SNP after applying the Benjamini-Hochberg correction for multiple tests.

Association genotypes - impulsivity/sensation seeking

No significant differences were found between genotypes of FAAH *C385A* or *rs12075550* in impulsivity or sensation-seeking.

Discussion

In this study, we found for the first time an association of experimental substance use with the rs12075550 SNP, but we could not find that same association with the C385A SNP. We also found an association of experimental substance use with impulsivity and sensation seeking. However, we failed to found an association between any of these genetic variations and any of those personality traits.

The rs12075550 is a genetic variation practically unknown in terms of its biochemical background or its phenotypic effects. To our knowledge, only three studies have included it. In one of them, Flanagan et al. (2006) found that the A allele of FAAH C385A was associated with the T allele of rs12075550 in up to 92.6% of Caucasian individuals and in 75.2% of African-American subjects using multiple substances. They proposed a haplotype that contains both SNPs. Given this finding, it could be thought that in our case the association of rs12075550 with experimental substance use might simply be a result of its association with C385A, since this SNP has been related to different phenotypes of substance use (e.g. Bühler et al., 2014; Sipe et al., 2002). However, in the present study the A allele of FAAH C385A was associated with the T allele of rs12075550 in 100% of cases, as correspond to the sample of participants from European ancestry, but also the C allele of C385A was associated with the T allele of rs12075550 in 46% of cases. This is consistent with the LD haplotype calculation for the Iberian population in Spain (Machiela & Chanock, 2015). These results, together with the lack of association between FAAH C385A and the consumption variables analyzed in this study, seem to indicate that the association between rs12075550 and experimental substance use would not be a consequence of its linkage disequilibrium with FAAH C385A.

In a second study involving rs12075550, Bühler et al. (2014) failed to found an association between this SNP and intensity of alcohol, tobacco or cannabis consumption. However, the results

of the present study indicate that it may be associated with having ever tried some substances, with the age at which they were first used and with having used them in the last 30 days. That is, the TT genotype of this SNP could confer a protective effect against experimental substance use. Since this type of use and risk consumption are partially independent (e.g. Swendsen et al., 2012), this SNP may be related to the first type of use, but not necessary to the second.

To our knowledge, only one study has so far explored the biochemical implications of rs12075550, demonstrating that it is likely to affect protein binding and FAAH gene expression, as demonstrated in lymphoblastoid cell lines (Veyrieras et al., 2008). However, any functional explanation of the association we have found between this SNP and phenotypes related to experimental substance use would be scarcely justified at the current level of knowledge.

With respect to FAAH C385A, its behavioral consequences in human substance use are still under research (Bühler et al., 2015). The results obtained in this work have not shown a statistically significant association between FAAH C385A and the phenotypes under study, so the effect of this SNP could be more directly related to substance use disorders, which is what has usually been explored, than to experimental substance use.

Extensive empirical evidence indicates that impulsivity and sensation seeking are personality traits associated with substance consumption, particularly in earlier stages of substance use (e.g. Meil et al., 2016; Michell & Potenza, 2014; Moreno et al., 2012). Some studies indicate that substance use increases impulsivity and sensation seeking (e. g. de Wit, 2009; Ersche et al., 2010). However, other studies with both humans (e.g. Farley & Kim-Spoom, 2015; Fernández-Atarmendi, Martínez-Loredo, Grande-Gosende, Simpson, & Fernández-Hermida, 2018) and animals (e.g. Belin, Mar, Dalley, Robbins, & Everitt, 2008; Diergaarde et al., 2008) also indicate that impulsivity and sensation seeking increase substance use. Since impulsivity and sensation seeking have been related to the endocannabinoid system (e.g. Helfandet al., 2017; Moreira, Jupp, Belin, & Dalley, 2015; Ucha et al., 2019) they were suitable candidates as endophenotypes between the FAAH gene variations and the phenotypes of experimental substance use analyzed in this study. To our knowledge, there are no previously published data on the association between rs1275550 and impulsivity or sensation seeking, but with respect to the association of C385A with impulsivity, previous studies have obtained contradictory results (Bidwell et al., 2013; Hariri et al., 2009). In the present study we failed to found a significant association between either of the two SNPs and neither of the two personality variables, although our data show an association between these personality variables and experimental substance use on the one hand, and between rs1275550 and some phenotypes of that experimental use on the other. Therefore, it does not seem that impulsivity or sensation seeking, closely related to each other according to our and previous results, operate as endophenotypes between any of the two SNPs and the phenotypes of substance use that we have analyzed.

One limitation of the present study is its exploratory nature. For this reason, three variables related to the experimental use of each of five substances, two personality traits and two SNPs related to the FAAH gene were included. And for this same reason the Benjamini-Hochberg correction for multiple tests was applied. Another limitation is that participants constitute a convenience sample, composed of university students of European ancestry, mostly female. Therefore, the data are not directly generalizable to other populations. Particularly important is that participants were not recruited on the basis of their substance use. Consequently, any generalization to this type of patients should be done with caution. A last limitation is related to the fact that the impulsivity and sensation seeking questionnaires were applied to only 591 of the 861 participants, as indicated in the *Participant*s section, so the conclusions regarding these variables should be interpreted according to that smaller number. The results obtained here will therefore have to be replicated through further studies before drawing definitive conclusions.

In conclusion, we provide first evidence for an association between SNP rs12075550 and phenotypes of experimental substance use. On the other hand, consistently with previous evidence, we found that impulsivity and sensation seeking are associated with these same phenotypes in our sample of young people of European ancestry, although our data do not permit to establish causal relationships. Nevertheless we failed to found a significant association of rs12075550 or *FAAH* C385A SNPs with one or another personality trait. In any case, these results show the importance that genetic and personality differences have in the experimental substance use and in the probability of developing a substance use disorder as a consequence of that use. They also highlight the importance of taking into account these individual differences, together with contextual factors, when designing prevention policies.

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