Title: Comparing Mental Health across Distinct Groups of Users of Psychedelics, MDMA, Psychostimulants, and Cannabis.

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Abstract (200 words):

Differences in mental health (MH) of users of distinct psychoactive substances have been shown. Both substance use (SU) and MH in users is influenced by stressful life events. This study compared MH parameters in distinct groups of substance users and evaluated the impact of stress factors on these outcomes. Data stem from the longitudinal Swiss Cohort Study on Substance Use Risk Factors (C-SURF) involving 4,475 young adult men. Distinct groups were created for the past 12 months use of psychedelics, MDMA, psychostimulants, and cannabis. MH measurements (depressive symptoms, overall MH, perceived stress, life satisfaction) were used as outcome variables, while indicators of past family functioning and stressful life events served as covariates. The MH of psychedelics users was not significantly different from the no-drug use group, whereas poorer MH was found in the other SU groups. Observed effects were influenced by the tested stress factors. The absence of association between use of psychedelics and worsening of MH deserves further investigation in male and female samples. Stressful life experiences must be considered when assessing the MH of users of illicit substances. These findings suggest that some men practice SU as self-medication to cope with life adversity.

Keywords: psychedelics, MDMA, psychostimulants, cannabis, mental health, stress events.

Introduction

There is growing evidence that the effects of substances on mental health (MH) depend on many distinct factors. These factors can be divided into internal (genetic predisposition and life history of the individual), and external factors (pharmacological properties of the substance, attitudes of the social environment towards substance use [SU] practice) (Kendler et al. 2003). Whether a substance has deleterious effects on a person's life depends therefore on many aspects such as frequency and dosage of its use, biological and social consequences, or the presence of contextual stressors. The interplay between these factors contributes to the development, or not, of a habit formation called addiction (Heyne et al. 2000; Hyman 2005).

Whereas there is abundant literature about substance related effects in individuals presenting a substance use disorder (SUD), little is known about effects of substances in users within the general population, regardless of whether they have developed a SUD or not. It appears that not all persons who are experiencing psychotropic effects of a substance, even repeatedly, will develop an SUD (Anthony, Warner and Kessler 1994).

In recent years, there has been a surge in scientific interest in putative beneficial effects of some substances being classified as addictive drugs. These substances are entactogens such as 3,4-methylenedioxymethamphetamine (MDMA, also called ecstasy) and psychedelic substances such as psilocybin or lysergic acid diethylamide (LSD). When under investigation as potential treatments, MDMA and psychedelics are used in settings where a psychotherapeutic intervention is the basic element of treatment. Thus, the use of these substances is not considered as beneficial in itself, but rather as an adjunct ingredient within a psychotherapeutic process (MDMA- or LSD-assisted psychotherapy) (Jungaberle 2008; Mithoefer, Grob and Brewerton 2016). Following this concept, the interactions between the set (the individual), the substance (the pharmacological properties of the chosen agent), and the setting (the therapeutic framework and relationship) are considered to be of crucial importance. In such settings, beneficial effects of psychedelics on the mood and subjective experience of the persons under their influence have been shown (Studerus et al. 2011).

As with stimulants and opioids, MDMA and psychedelics are often used by people outside well-defined medical settings. This recreational use is generally associated with such varied motives as self-medication, self-exploration, or sensation seeking (Parks and Kennedy 2004). A recent study by our group revealed that about 5.5% of young men in Switzerland had used MDMA and 5.7% had used psychedelics during a 12-month observation period (Rougemont-Bücking et al. 2017). As these substances are illicit, their use occurs in unstructured settings, and this absence of clear settings is of interest when assessing the effects of substances on young men's health.

Young adults using MDMA have been found to present significantly higher rates of MH disorders and psychiatric comorbidity than non-users (Huizink et al. 2006; Lieb et al. 2002). However, these longitudinal studies also revealed that the use of MDMA was more likely to be a consequence of psychiatric suffering than the cause of it. The pharmacological effects of MDMA, which increases self-confidence and feelings of well-being and bonding with others, are thought to be the reason why many individuals who suffer from anxiety, low self-esteem, and social inhibition choose to take this drug in an attempt to self-medicate (Scott et al. 2013).

Regarding the link between the use of psychedelics and the occurrence of MH problems, there is some evidence of a reduced risk of suffering from psychological distress (Johansen and Krebs 2015; Krebs and Johansen 2013). The hypothesis that psychedelics are comparatively harmless substances was corroborated by the fact that the use of illicit substances, but not the use of psychedelics, was associated with an increased risk of presenting with severe MH problems such as suicidal tendencies (Hendricks et al. 2015).

Regarding cannabis, studies showed that its use is correlated with poor educational achievement and cognitive impairment in adolescents and young adults (Karila et al. 2014). Other related health outcomes are development of a cannabis addiction and of psychotic episodes (Degenhardt and Hall 2012; Marconi et al. 2016). Also, in the general population, anxiety disorders were shown to be associated with its use (Kedzior and Laeber 2014). Further, a study by our workgroup revealed that use of cannabis in young men is associated

with poor MH, as measured on depression ratings (Baggio et al. 2014). However, there continues to be a debate about whether these findings can also be attributable to shared causes and risk factors commonly found in the investigated populations (Hall 2015). In addition, more recently some emphasis was put on investigating possible positive effects of cannabis use on MH. Thus, it was shown, that cannabis use can decrease symptoms of stress and anxiety, whereas in users being depressed an exacerbation of depressive symptoms was observed (Cuttler, Spradlin and McLaughlin 2018).

Concerning psychostimulant drugs (methamphetamine, amphetamine, cocaine), there is evidence that their use is associated with the considerable burden on physical and MH of their users (Bao et al. 2013; Degenhardt and Hall 2012).

Other factors known to contribute to both the severity of SU and poor general health are the presence of stressful life events and problematic household function during childhood and adolescence (Bahr, Hoffmann and Yang 2005; Dube et al. 2003; Sinha 2008). Specifically, a gene-environment interaction was shown for the development for some substance related health outcomes such as developing alcohol abuse in the general population or presenting psychotic episodes in cannabis users. Having suffered from adverse experiences during childhood contributes to the development of these outcomes, but these effects are moderated by genetic predispositions (Alemany et al. 2014; Schellekens et al. 2013). In addition, protective effects of specific parenting styles have also been identified. SU among young MDMA, cannabis, and cocaine users was shown to be diminished if a warmly caring and controlling parenting style was employed in their families (Montgomery, Fisk and Craig 2008).

This study includes only young men. Male gender, more precisely masculine attitudes are known to play a preponderant role for individuals to engage in risky behavior, such as experiencing drug effects (Levant and Wimer 2014; Peralta et al. 2016). Furthermore, regarding the effects of early life stressors on SU, it was shown that the association between traumatic antecedents and subsequent development of a SUD is stronger in female samples than in male samples (Danielson et al. 2009). However, despite findings showing the

importance of accounting for the links between early life stress exposure, SU during young adulthood, and MH in men, there are only few studies having investigated the contribution of these factors simultaneously (Fothergill et al. 2016; Kogan et al. 2017). The rationale for our study was to assess the relationship between SU in young men, occurring within an unstructured, real-life setting, and indicators of their MH.

Methods

Study design

Data were drawn from the Swiss Cohort Study on Substance Use Risk Factors (C-SURF). C-SURF is a longitudinal study investigating SU patterns and socio-economic and psychopathological characteristics of young Swiss men. The study started with a baseline assessment in 2010, two follow-up assessments took place in 2012 and 2016. C-SURF procedures were approved by the IRB of the Canton de Vaud, Switzerland.

Participants were enrolled at three of Switzerland's six recruitment centers that conscript men for military service, but study participation was independent of the military. Attending military recruitment is mandatory for all Swiss men at around the age of 19. All the men attending recruitment were eligible for participation in our study, regardless of their eligibility for service. Enrolling participants at these locations provided C-SURF with a representative sample of young Swiss men. The present study used C-SURF data collected from the initial baseline assessment (socio-demographic characteristics, family functioning), the first (stressful life experiences), and the second follow-up assessment (SU and MH). Thus, this study combines longitudinal (family functioning, stressful life events) and cross-sectional (MH) aspects of SU.

Participants

An initial group of 7,556 conscripts consented to participate. Of these, 5,987 (79.2%) participated in the baseline assessment, when participants were around 20 years old. Of the baseline completers, 1193 (19.9%) were excluded because they did not completed the

follow-up questionnaires. A further 319 participants were excluded due to SU patterns not compatible with any specific group tested in this study. The final sample consisted of 4,475 participants (59.2 % of those consented, and 74.7% of baseline completers).

Use of substances

To obtain well-defined SU groups, we applied a strict exclusion of all non-compatible substances from any distinct user group, with the exception of cannabis and alcohol. Cannabis was used at least once a year by as many as 31.5 % of C-SURF participants, and alcohol was used by 93% of the sample (Rougemont-Bücking et al. 2017). So there was a high probability that most users of illicit substances also used cannabis and alcohol. Consequently, excluding cannabis and alcohol users from our distinct substance groups would have resulted in very low numbers of participants in each group, making any analysis impossible.

All participants in the wave 3 assessment were asked whether they had taken any illicit substances during the past 12 months. Possible answers were “used” (coded 1) or “not used” (coded 0). Examples of distinct pharmacological agents and their commonly employed street names were listed for each substance group. The psychedelics group included synthetic hallucinogens (e.g., LSD, 2-CB, DMT), and natural hallucinogens (e.g., psilocybin, salvia divinorum, ayahuasca, ibogaine). The MDMA group consisted solely of MDMA (ecstasy) users. The psychostimulants group included amphetamines, methamphetamines, and cocaine. Another group was created to include the use of any other illicit substances, such as khat, poppers, inhalants, opiates (e.g., morphine, heroin, methadone), ketamine, GHB, synthetic cannabinoids, and research chemicals. For this any-other-drug group the use of any of the substances included in the other three specific groups (psychedelics, MDMA, psychostimulants) was exclusive. Importantly, cannabis use was not an exclusion criterion for any of the four groups; individuals were included whether or not they had consumed cannabis in parallel to their distinct group substances. A fifth group was created for cannabis users who used this substance exclusively. A sixth group was created for all the individuals

who consumed no illicit drugs during the observation period. This no-drug group served as the reference group in the analysis. With regard to the frequency of cannabis use, participants were asked how frequently they used this substance during the evaluated period. Responses were coded in the following way: “never” (coded 0), “once a month or fewer” (coded 6), “two to four times a month” (coded 36), “two to three times a week” (coded 130), “four to five times a week or more often” (coded 234), and “every day or nearly every day” (coded 364). Frequency of cannabis use was then divided by 12 to get the number of days of cannabis use in a month.

A quantity-frequency measure was used to estimate weekly drinking volume (DV) of alcohol consumption. Participants were asked to report the usual frequency of drinking days per week and the usual quantity (number of standard drinks) per drinking day in the previous twelve months. Pictures of standard drinks containing approximately 10–12 grams of pure alcohol were provided. Weekly DV was obtained by multiplying frequency and quantity of alcohol consumption.

Mental health outcomes

All MH outcomes were used as continuous variables in the regression model. The Major Depression Inventory (MDI) was used to assess the presence of depressive symptoms among participants during the two weeks prior to assessment (Bech et al. 2001; Olsen et al. 2003). The MDI contains 12 questions assessing 10 criteria of depression (two criteria, describing restlessness or agitation, and heightened or decreased appetite, are described by two questions). A Likert scale from “1 = always” to “6 = never” was used to give a value range between 0 and 60; the means of the individuals’ score was used in the model.

Six questions investigating the effects of sadness, nervousness, and depression in daily life during the past month, taken from the Short Form Health Survey (SF-12), were used as indicators of general MH (Ware, Kosinski and Keller 1996). The total score, called the mental component summary score, was calculated, and linear transformations were

performed to obtain SF-12 norm-based scores (mean = 50; SD = 10, with lower scores reflecting poor MH).

Stress during the past month was assessed using the Perceived Stress Scale (Cohen, Kamarck and Mermelstein 1983). This questionnaire contains ten questions about general situations in life in which people typically experience stress. Answers were given on a Likert scale ranging from “0 = never” to “4 = always”. The means of the individuals’ scores were calculated and used in the model.

Finally, the Satisfaction With Life Scale (SWLS) was used to assess general contentment (Diener et al. 1985). This instrument consists of five questions about whether the participant is satisfied with his life in general. Each item is scored between “1 = do not agree” and “7 = totally agree), and the mean of the individuals’ scores were used in the model.

Stressful events and family functioning

Assessment of stressful events

Exposure to highly stressful incidents (e.g., traffic accidents, earthquakes, severe illness) was assessed using part 1 of the Post-traumatic Diagnostic Scale (PDS-enhanced; see Foa et al. 1997). This is a list of 12 stressful events, including one open question for any non-specified stressful events. This list was complemented with six events drawn from the Trauma History Questionnaire (THQ; see Hooper et al. 2011) and two from the Life Event Checklist (Gray et al. 2004). Lifetime prevalence of stressful events was assessed at wave 2, approximately 50 months before the wave 3 assessment when SU and MH outcomes were collected. Thus, all stressful events investigated in the present study preceded the outcomes by at least 50 months. The sum of stressful events accumulated by each participant was used as a continuous variable in the model.

Assessment of family functioning factors

Four family-related factors were measured during the baseline assessment which took place when participants were about 20 years old. First, the perceived quality of participants' relationships with their parents, before reaching the age of 18, was assessed using two questions from the European School Survey Project on Alcohol and Drugs (ESPAD; see Hibell et al. 2012). Responses were given on a five-point Likert scale scored from "1 = very satisfactory" to "5 = very unsatisfactory relationship". The means of these responses were used as a continuous variable in the model. Second, the presence of a MH disorder in a parent (including an SU disorder) was assessed using the family history section of the Addiction Severity Index (McLellan et al. 1980). This factor was coded in the final model with values between 0 and 6 according to whether the participant's mother or father had presented with either an alcohol-related disorder, a drug-related disorder, or any other psychiatric disorder (each disorder mentioned scored one point). To obtain third and fourth factors describing family functioning, the perceived quality of parenting during childhood was assessed using four questions from the ESPAD at baseline. Two items were related to parental monitoring, and two related to parental support (participants believed having been raised in an emotionally supportive family environment). This selection of items was in line with other studies that have used the ESPAD to test family influences on SU (Miller and Plant, 2003; Tornay et al., 2013). Responses were given on a five-point Likert scale from "1 = almost always" to "5 = almost never". The means for each factor were used as continuous variables describing either parental monitoring or support.

Socio-demographic variables

Perceived family income during the participant's childhood was used an adjustment variable. This measure corresponded to the subjective estimation of each participant who had to guess whether the income of his household was above, below, or equal to the average income in the households in the general population. Also, the participant's highest level of educational attainment (number of years of training at school or university) was used to adjust for socio-demographic differences.

Statistical analysis

Data were analyzed using the SPSS 23. Linear regression analyses were run with distinct SU groups (the no-drug group served as reference group), and MH variables as outcomes. Because the MDI and SWLS were not normally distributed, a log-transformation of their scores was carried out. Covariates describing stressful events, family functioning and weekly DV were added to the model. Since the number of participants was relatively small in several SU groups in the current study, meaningful differences may not reach the threshold of significance because of lack of power. Thus, we also computed Cohen's d, an index of effect size, according to the formula of Nakagawa and Cuthill (2007). A convention for quantifying the magnitude of Cohen's d is 0.01 = very small, 0.20 = small, 0.50 = medium, 0.80 = large (Sawilowsky, 2009).

As it was impossible to exclude cannabis users from the creation of the distinct SU groups, the differences observed between groups in the regression models may be attributable to differences in the frequency of cannabis use between the groups. However, since the participants in the no-drug group did not use cannabis at all, adjustment for the frequency of cannabis use in the regression models may bias the estimates. Accordingly, an analysis with and without adjustment for the frequency of cannabis use was conducted on the distinct groups of drug users. Here, the no-drug group was excluded from the model and the psychedelics group was set as the reference group.

Results

Mean participant age at wave 3 was 25.4 years (SD = 1.2 years). Table 1 shows the study sample's descriptive statistics; Table 2 the distribution of the continuous variables.

Table 3 shows the associations between the distinct substance groups and MH outcomes. Associations are adjusted for the socio-demographic covariates in the upper part (henceforth termed the partially adjusted model), adjusted for family factors and stressful life events and weekly DV in the lower part (henceforth termed the fully adjusted model).

In the partially adjusted model, log-transformed MDI scores were significantly and positively associated with all substance groups (high log-transformed MDI scores correspond to poor MH). When applying the full adjustment, the psychedelics group and the psychostimulants group were no longer significantly associated with MDI scores. Furthermore, cannabis showed the smallest and psychedelics showed the second smallest effect sizes. All covariates of the adjustment were significantly and positively correlated with that outcome, except for the fact of the parents having presented an MH problem.

Concerning the mental component summary scores in both models, three substance groups showed significant and negative associations (high MH component summary scores correspond to better MH): MDMA, psychostimulants, and cannabis. In both models, the psychedelics group showed the smallest effect size followed by the cannabis group. All covariates, except for the fact of the parents having presented an MH problem and weekly DV, were significantly and negatively correlated with the MH summary score.

With regard to the measurement of perceived stress, the MDMA and psychostimulants groups showed significant positive associations with MH in the partially adjusted model (high log-transformed perceived stress scores correspond to poor MH). When adding the covariates, none of the SU group associations reached significance. In both models, the cannabis and psychedelics users' groups showed the smallest effect sizes. Again, all covariates, except for parents having presented with an MH problem and weekly DV, were significantly and positively correlated with that outcome.

Regarding life satisfaction (the log-transformed SWLS), the partially adjusted model showed significant and positive associations with the psychostimulants and cannabis groups (high log-transformed SWLS scores correspond to poor MH). When the covariates were added, only one significant association remained with the psychostimulants group (p= .030). In this model, the psychedelics group had the smallest and the cannabis group the second lowest effect size. With regard to the covariates, only the good quality of relationships with parents and the perception of having been supported by them showed significant and positive associations with greater life satisfaction.

With regard to the effects of covariate adjustments on the coefficients of different distinct substance groups, observed effects were most pronounced for psychostimulants (B, *p* values, and Cohen's d were substantially reduced when the full adjustment was added).

Further analyses investigating whether adjustments for the frequency of cannabis use in the distinct groups of drug users altered the results are reported in table 4. In comparison to the model adjusted for socio-demographic variables, stressful events, family functioning, and weekly DV, the model with an additional adjustment for the frequency of cannabis use did not substantially reduce the coefficients calculated for the different groups of drug users. Rather, coefficients of associations were equal or higher, Cohen's d were larger, and p-values were lower than in the model without adjustment for the frequency of cannabis use. Moreover, the models adjusted for frequency of cannabis use only accounted for an additional 0.2% to 0.5% of the variance in MH outcomes. This supports the idea that the differences observed in the main analyses cannot be accounted for by differences in frequency of cannabis use between the different groups of drug users.

Discussion

The present study's results corroborate previous findings that the use of psychedelics is not associated with significant deterioration in MH (Hendricks et al. 2015; Krebs and Johansen 2013; Studerus et al. 2011). In all the outcomes and models tested, the psychedelics group was only significantly associated with one outcome (depressive symptoms in the partially adjusted model) and had the smallest or the second smallest (after cannabis group) effect sizes. All the other distinct substance groups tested showed several significant associations. In the fully adjusted model, the psychedelics group was the only one that showed no significant associations. In addition, with regard to the effect size of each SU groups on MH outcomes as measured by Cohen's d, the present study showed that the psychedelics group showed the smallest difference for MH component summary, life satisfaction and perceived stress (ex aequo with cannabis group), and the second smallest difference for MDI, in comparison with the other groups.

In the fully adjusted model the substance groups associated with the poorest MH outcomes were MDMA, with the largest effect sizes on three of the four outcomes, and psychostimulants with the largest effect size on one of the four outcomes and the second largest on the other three. For MDMA, these findings were in line with previous observations showing an increased prevalence of psychiatric comorbidities in MDMA users (Keyes, Martins and Hasin 2008). However, because MDMA generally has mood elevating properties (Patel and Titheradge 2015; Wardle and de Wit 2014) and it has been shown that its use is the result of psychic suffering rather than its cause (Lieb et al. 2002), the association between MDMA use and poor MH might best be explained by the users' attempts to self-medicate (Moonzwe, Schensul and Kostick 2011; Scott et al. 2013). However, as Parrot (2014) posited, using MDMA outside a supportive, therapeutic context - as typically done in self-medication - can bring out negative feelings while the user is under the effects of the drug. Additionally, the serotonin depletion syndrome following MDMA use is likely to contribute to a worsening of MH, especially when the drug is taken frequently. Our findings thus reconfirmed the ambiguous effects of MDMA use in unstructured settings and underlined the need to monitor the risks of self-medication with MDMA in recreational users.

With regard to psychostimulants, our findings were also in line with reported associations between poor MH and use of these substances (Baker and Dawe 2005; Haasen et al. 2005; Prinzleve et al. 2004). However, our analysis showed that psychostimulants' effects on MH were substantially reduced when family functioning and stressful events were added to the model. This observation is further evidence that these covariates have a strong influence on the overall MH effects of psychostimulants. It also underlines the need to take personal histories into account when assessing the overall contribution of psychostimulants on young adults' MH problems.

For the cannabis use group, the differences with the no drug group were relatively small on MH outcomes, as indicated by very small effect sizes. However, the differences were significant in two of the four outcomes. This particular finding might be explained by the fact that the cannabis group had a much higher number of observations than the other

distinct substance groups, and thus was associated with more statistical power. Increased depressive symptoms and lower scores on MH, as shown in our results, were in line with the abundant literature showing that cannabis use is associated with poor MH (Copeland, Rooke and Swift 2013; Fergusson and Boden 2008). However, the fact that cannabis users did not differ from non-users of drugs, with regard to measurements of life satisfaction and perceived stress when adjusted for covariates, might correspond with previous findings that the alterations in cannabis users' well-being might be attributable to concomitantly difficult situations in their lives and to genetic predispositions rather than to the effects of the substance itself (Alemany et al. 2014; Barnwell, Earleywine and Wilcox 2006).

The any-other-drug group showed only one significant association and the second largest effect size (to the MDI depression score) in the fully adjusted model. This result is likely best explained by the group's high heterogeneity and the fact that it only included substances which were not in the other distinct substance groups (except for cannabis). Thus, the low number of associated MH outcomes observed in the present study may reflect a rather atypical subpopulation of young Swiss men who have quite good overall MH despite their use of mainly marginal and rare substances.

With regard to the effects of stress exposure and family functioning during childhood and adolescence our study showed that these factors have significant impact on MH. In most models factors corresponding to high stress showed significant associations with poor MH. Also, the unstandardized coefficients and Cohen's d of the different SU groups were considerably reduced when adding these confounders. These findings are in line with previous studies showing that family factors, especially parental monitoring and the quality of family relationships, contributed directly or indirectly, via influences on the choice of and adherence to deviant peer groups, to SU during adolescence and early adulthood (Tornay et al. 2013; Van Ryzin, Fosco and Dishion 2012). With regard to the effects of accumulated stressful events in the past, our results confirmed previously established associations between various risk factors during childhood and youth, present SU, and a deterioration of MH in adults (Pries et al. 2018). This underlines the need to take such antecedents into

account when assessing the MH of drug users (Brady and Sinha 2005; Rao, Hammen and Poland 2009).

One study limitation was the fact that the distinct SU groups contained comparatively few users in comparison to the cannabis group or the reference group. It is possible that associations involving the cannabis group were based on a stronger statistical power and appeared to be significant at levels which could not be achieved in the analyses of the other distinct SU groups. Nevertheless, the unstandardized coefficients and effect sizes of the psychedelics group were lower compared with the other user groups or (except the cannabis only group in two cases), independent of whether they reached significance or not. The absence of more detailed measurements of the frequency of use of all the substances, except cannabis, is another limitation, as it proved impossible to distinguish between very low-frequency and high-frequency users. As a consequence, our results risk overestimating the effects of sporadic SU and underestimating the effects of excessive SU. Third, our model did not include other relevant life stressors, such as problems at work or in intimate personal relationships. Finally, the results presented here are only representative of Swiss young males and cannot be generalized to the male population as a whole, to female samples, or to people living in different socio-economic contexts.

In conclusion, this study showed that the recreational use of psychedelics by young Swiss men was not associated with a significant deterioration in their MH. Among the other SU groups tested, however, such associations were shown, with psychostimulants and MDMA use being most strongly associated with worsening MH. When covariates describing problematic family functioning and stressful life events were added to the statistical model, these associations weakened, suggesting that these stress factors must be taken into account when assessing the overall effects of SU on MH. The influence of these stress factors was most pronounced for the psychostimulants user group. These results offer insights into how the effects of distinct substances on MH interact with the stressful real-life experiences of young men. Whereas most individuals using illicit substances in unstructured

settings experience a worsening of their MH, the MH of psychedelics users was no different from that of their peers in the no-drug reference group. This absence of association between use of psychedelics and worsening of MH deserves further investigation in male and female samples. With regard to MDMA, our results underlined the need for an appropriate follow-up of individuals experiencing MDMA effects, as some of them might be tempted to self-medicate with that substance when trying to cope with past or present adverse events in their lives.

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Table 1: Description of study sample and sociodemographic covariates

	N (total = 4,475)	Percent
Substance use groups		
No illicit drugs, no cannabis (no-drug group)	3,230	72.2
Any drug, but no MDMA, no psychostimulants, no psychedelics	88	2.0
MDMA, no other drugs *	75	1.7
Psychedelics, no other drugs *	68	1.5
Psychostimulants, no other drugs *	72	1.6
Cannabis, no other drugs	942	21.1
Family income		
above average	1,997	44.6
average	1,874	41.9
below average	604	13.5
Education		
9 years	120	2.7
12 years	1,734	38.7
13 years and more	2,621	58.6

Note: * in this substance use group use of cannabis was not exclusive

Table 2. Description of the MH outcome variables and of the variables describing stressful events, family functioning, frequency of cannabis use per month, and weekly alcohol consumption

	Mean	Standard Deviation	Skewness	Kurtosis
MH outcomes				
MDI [b]	8.24	7.05	1.85	4.29
MDI [b] (log-transformed)	1.95	0.78	-0.49	0.42
Mental component summary score [c]	47.24	9.34	-0.94	0.75
Perceived stress scale [d]	13.13	5.91	0.31	0.18
Life satisfaction [e]	26.27	5.97	-1.05	0.91
Life satisfaction (log-transformed)[e]	2.07	0.70	-0.78	0.93
Stressful events and family functioning				
Stressful life events [a]	1.53	2.06	1.98	4.86
Relationship with parents [a]	1.76	0.81	1.10	1.20
Parents having MH problems [a]	0.13	0.45	4.94	35.28
Parental support [a]	1.54	0.75	1.63	2.74
Parental monitoring [a]	1.81	0.93	1.21	1.17
Frequency of cannabis use per month	1.33	5.2	4.82	22.82
Weekly drinking volume	6.44	8.11	2.91	15.17

Note: MH = mental health;

[a] Low scores equal: low number of stressful life events, high satisfaction of relationship with parents, low number of mental disorders in parents, having been highly supported by parents, and having been highly monitored by parents.

[b] Major depression index, normal scale: low scores equal better MH; log-transformed scores; low scores equal better MH

[c] Mental component summary score; low scores equal poor MH

[d] Perceived stress scale; low scores equal better MH

[e] Satisfaction of life scale, normal scale: low scores equal poor MH; log-transformed: low scores equal better MH

Table 3: Associations between substance use groups and MH outcomes

N = 4,475	MDI [b]				Mental component summary score [c]				Perceived stress scale [d]				Life satisfaction [e]			
	B	**SE**	***p***	***d***	**B**	**SE**	***p***	***d***	**B**	**SE**	**p**	***d***	**B**	**SE**	***p***	***d***
Adjusted for sociodemographics only																
Substance use groups																
Any drug, but no MDMA, psychostimulants, or psychedelics	0.24	0.08	.004	0.31	-1.84	1.00	.066	0.20	0.60	0.63	.340	0.10	0.12	0.07	.094	0.18
MDMA only *	0.27	0.09	.003	0.35	-3.99	1.08	<.001	0.43	1.52	0.69	.027	0.26	0.12	0.08	.150	0.17
Psychedelics only *	0.20	0.09	.038	0.25	-1.29	1.13	.255	0.14	0.47	0.72	.517	0.08	0.04	0.08	.660	0.05
Psychostimulants only *	0.33	0.09	<.001	0.42	-4.23	1.10	<.001	0.46	1.75	0.70	.012	0.30	0.28	0.08	<.001	0.40
Cannabis only	0.16	0.03	<.001	0.20	-1.65	0.34	<.001	0.18	0.27	0.22	.210	0.05	0.06	0.03	.011	0.09
Fully adjusted model																
Substance use groups																
Any drug, but no MDMA, psychostimulants, or psychedelics	0.17	0.08	.034	0.23	-1.30	0.98	.183	0.14	0.31	0.63	.617	0.05	0.09	0.07	.206	0.14
MDMA only *	0.20	0.09	.024	0.26	-3.57	1.07	<.001	0.39	1.19	0.68	.082	0.20	0.09	0.08	.261	0.13
Psychedelics only *	0.10	0.09	.270	0.14	-0.49	1.11	.659	0.05	<0.01	0.71	.998	<0.01	-0.01	0.08	.906	0.01
Psychostimulants only *	0.15	0.09	.099	0.20	-2.56	1.09	.019	0.28	0.82	0.70	.240	0.14	0.18	0.08	.030	0.26
Cannabis only	0.10	0.03	<.001	0.13	-1.16	0.34	<.001	0.13	<0.01	0.22	.970	<0.01	0.04	0.02	.133	0.05
Stressful events and family functioning covariates																
Stressful life events [a]	0.03	0.01	<.001	-	-0.29	0.07	<.001	-	0.16	0.04	<.001	-	<0.01	<0.01	.332	-
Relationship with parents [a]	0.15	0.02	<.001	-	-1.68	0.20	<.001	-	0.49	0.13	<.001	-	0.11	0.01	<.001	-
Parents having MH problems [a]	0.02	0.03	.365	-	-0.60	0.31	.056	-	0.22	0.20	.265	-	0.02	0.02	.391	-
Parental support [a]	0.06	0.02	.002	-	-0.54	0.22	.017	-	0.62	0.14	<.001	-	0.09	0.02	<.001	-
Parental monitoring [a]	0.04	0.01	.003	-	-0.37	0.16	.018	-	0.34	0.10	<.001	-	0.01	0.01	.298	-
Weekly drinking volume	<0.01	<0.01	.001	-	-0.02	0.02	.310	-	0.02	0.01	.095	-	<0.01	<0.01	.584	-

Note. The no-drug group was set as reference; MH = mental health; B = unstandardized coefficient; SE = Standard Error of B; p = p value; d = Cohen's d; sociodemographics: perceived family income and education applied (values not shown); Fully adjusted model: covariates for perceived family income and education applied (values not shown) and covariates of stressful life events, family functioning, and weekly drinking volume as shown.
* in this substance use group use of cannabis was not exclusive;
[a] Low scores equal: low number of stressful life events, high satisfaction of relationship with parents, low number of mental disorders in parents, having been highly supported by parents, and having been highly monitored by parents.
[b] Major depression index, log-transformed; low scores equal better MH
[c] Mental component summary score; low scores equal poor MH
[d] Perceived stress scale; low scores equal better MH
[e] Satisfaction with life scale, log-transformed; low scores equal better MH

Table 4: Associations between substance use groups and MH outcomes with and without frequency of cannabis use a covariate

N= 1,245	MDI [b]				Mental component summary score [c]				Perceived stress scale [d]				Life satisfaction [e]			
	B	**SE**	***p***	***d***	**B**	**SE**	***p***	***d***	**B**	**SE**	***p***	***d***	**B**	**SE**	***p***	***d***
Model without adjustment for frequency of cannabis use																
Substance use groups																
Any drug, but no MDMA, psychostimulants, or psychedelics	0.08	0.11	.484	0.15	-1.05	1.52	.489	0.15	0.39	0.97	.690	0.09	0.10	0.11	.334	0.21
MDMA only *	0.11	0.12	.363	0.21	-3.10	1.58	.051	0.46	1.22	1.01	.226	0.28	0.11	0.11	.339	0.22
Psychostimulants only *	0.05	0.12	.673	0.10	-2.20	1.60	.170	0.33	0.86	1.02	.398	0.20	0.19	0.11	.086	0.41
Cannabis only	-0.01	0.09	.993	<0.01	-0.87	1.19	.464	0.09	-0.01	0.75	.989	<0.01	0.06	0.08	.502	0.09
Stressful events and family functioning covariates																
Stressful life events [a]	0.02	0.01	.009	-	-0.14	0.13	.286	-	0.09	0.08	.262	-	<0.01	0.01	.635	-
Relationship with parents [a]	0.14	0.03	<.001	-	-1.90	0.39	<.001	-	0.55	0.25	.025	-	0.16	0.03	<.001	-
Parents having MH problems [a]	0.03	0.04	.518	-	-0.36	0.58	.533	-	0.20	0.37	.586	-	-0.01	0.04	.741	-
Parental support [a]	0.04	0.03	.205	-	-0.15	0.43	.728	-	0.38	0.28	.154	-	0.06	0.03	.041	-
Parental monitoring [a]	0.07	0.02	<.001	-	-0.96	0.29	.001	-	0.50	0.19	.007	-	-0.01	0.02	.723	-
Weekly drinking volume	<0.01	<0.01	.097	-	-0.05	0.03	.085	-	0.02	0.02	.355	-	<0.01	<0.01	.351	-

Table 4- continued

N= 1,245	MDI [b]				Mental component summary score [c]				Perceived stress scale [d]				Life satisfaction [e]			
	B	SE	*p*	*d*	B	SE	*p*	*d*	B	SE	*p*	*d*	B	SE	*p*	*d*
Model with adjustment for frequency of cannabis use																
Substance use groups																
Any drug, but no MDMA, psychostimulants, or psychedelics	0.11	0.11	.331	0.21	-1.46	1.53	.340	0.21	0.59	0.97	.545	0.13	0.12	0.11	.257	0.25
MDMA only *	0.11	0.12	.340	0.22	-3.16	1.58	.046	0.47	1.25	1.00	.213	0.29	0.11	0.11	.325	0.23
Psychostimulants only *	0.08	0.12	.531	0.15	-2.52	1.61	.117	0.37	1.02	1.02	.318	0.24	0.21	0.11	.066	0.44
Cannabis only	0.02	0.09	.830	0.03	-1.13	1.19	.344	0.12	0.12	0.76	.876	0.02	0.07	0.08	.419	0.10
Stressful events and family functioning covariates																
Stressful life events [a]	0.02	0.01	.018	-	-0.11	0.13	.406	-	0.08	0.08	.350	-	-0.01	0.01	.533	-
Relationship with parents [a]	0.14	0.03	<.001	-	-1.85	0.39	<.001	-	0.53	0.25	.032	-	0.15	0.03	<.001	-
Parents having MH problems [a]	0.02	0.04	.569	-	-0.32	0.58	.582	-	0.18	0.37	.627	-	-0.02	0.04	.705	-
Parental support [a]	0.04	0.03	.171	-	-0.19	0.43	.656	-	0.40	0.28	.142	-	0.06	0.03	.035	-
Parental monitoring [a]	0.07	0.02	.001	-	-0.91	0.29	.002	-	0.49	0.19	.010	-	-0.01	0.02	.656	-
Weekly drinking volume	<0.01	<0.01	.066	-	-0.05	0.03	.058	-	0.02	0.02	.289	-	<0.01	<0.01	.297	-

Frequency of cannabis use	0.01	<0.01	.012	-	-0.07	0.03	.015	-	0.04	0.02	.057	-	<0.01	<0.01	.116	-

Notes: The psychedelics group was set as reference; MH = mental health. B = unstandardized coefficient; SE = Standard Error of B; p = p value; d = Cohen's d.

* In this substance use group use of cannabis was not exclusive;

[a] Low scores equal: low number of stressful life events, high satisfaction of relationship with parents, low number of mental disorders in parents, having been highly supported by parents, and having been highly monitored by parents.

[b] Major depression index, log-transformed; low scores equal better MH

[c] Mental component summary score; low scores equal poor MH

[d] Perceived stress scale; low scores equal better MH

[e] Satisfaction with life scale, log-transformed; low scores equal better MH