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Interactions between specific parameters of MDMA use and cognitive and psychopathological measures ☆

Daniel Wagner, Sophia Adolph, Philip Koester, Benjamin Becker, Euphrosyne Gouzoulis-Mayfrank, Joerg Daumann *

Department of Psychiatry and Psychotherapy, University of Cologne, Kerpener Strasse 62, Cologne 50924, Germany

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ABSTRACT

The aim of the present study was to investigate the relevance of different parameters of 3,4-methylenedioxymethamphetamine (MDMA) use, including age of first use, cumulative lifetime dose and highest daily dose for predicting cognitive performance and self-reported psychopathology. Moreover, interactions between those parameters were examined. Ninety-six new MDMA users were interviewed to assess their drug use, and they completed a battery of cognitive tests concerning attention and information processing speed, episodic memory and executive functioning and self-reported psychopathology. Subjects participated again after 1 year to provide follow-up data. Significant associations between age of first use and cumulative lifetime dose have been found for attention and information processing speed. Furthermore, the results showed a significant effect of age of first use on the recognition performance of the episodic memory. The findings of the current study provide a first estimation of the interactions between different MDMA use parameters. Future research should focus upon additional parameters of drug use and concentrate on consequent follow-up effects.

1. Introduction

Even though the recreational use of the illegal drug 3,4-methylenedioxymethamphetamine (MDMA), commonly referred to as "ecstasy," has declined over the past years (World Drug Report, 2014, 2014), MDMA remains popular among young adults, especially in the electronic dance-music scene. National estimates of ecstasy use among young adults in Europe range from 0.1% to 3.1% (European Drug Report 2014: Trends and developments, 2014). The annual prevalence of ecstasy users in North America is 0.9% (World Drug Report 2014, 2014).

The drug, which usually comes in the form of a pill, is generally taken orally (Gouzoulis-Mayfrank and Daumann, 2009). The main pharmacological effect of MDMA is to bind to the serotonin transporter, causing a rapid release of serotonin and inhibition of its re-uptake (Gouzoulis-Mayfrank and Daumann, 2009). Changes in the serotonergic system can have diverse effects on the CNS, including disturbances in mental health and cognition. Several studies have found an association between MDMA use and psychiatric and cognitive syndromes (Gouzoulis-Mayfrank and Daumann, 2009; McGuire, 2000).

Cognitive symptoms found in ecstasy users mostly concern learning and memory processes (Gouzoulis-Mayfrank and Daumann, 2009). Most of these memory deficits include impaired retrospective and prospective memory (Parrott, 2013). In addition to learning and memory deficits, higher cognitive functions have also been found to be impaired in MDMA users (Parrott, 2013). Psychiatric symptoms associated with MDMA usage include depression, anxiety, phobias, psychotic symptoms, somatization, aggression, hostility, impulsiveness and sensation-seeking behavior (Karlsen et al., 2008). Furthermore, a study that used the Symptom-Checklist-90 (SCL-90) (Derogatis et al., 1973), a scale to measure self-reported psychopathology, and two other questionnaires in a non-clinical sample of young but heavy recreational users of ecstasy showed significantly higher scores on nine SCL-90 factors than the control group did (Parrott et al., 2000), indicating an increased self-reported psychopathology. Light ecstasy users had significantly higher scores than controls on only two factors. Medina and Shear (2007) found symptoms of anxiety, depression and executive dysfunction in a group of ecstasy users. However, these effects were not dose-dependent but associated with higher polydrug use.

The utilization of different means to measure ecstasy use may lead to inconsistent findings for psychopathological and cognitive symptoms in

Abbreviations: MDMA, 3,4-Methylenedioxymethamphetamine; SCL-90, Symptom-Checklist-90; RAVLT, *Auditiv-Verbaler Lerntest*; LGT, *Lern- und Gedächtnistest*; HAWIE-R, *Hamburg-Wechsler-Intelligenztest*; Mini-DIPS, *Diagnostisches Kurz-interview bei psychischen Störungen*; MANCOVA, multivariate analyses of covariance

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* Corresponding author. Tel.: +49 221 478 87113; fax: +49 221 478 97543.
E-mail address: joerg.daumann@uk-koeln.de (J. Daumann).

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the literature. It is possible that the study of the highest daily dose indicates a different association between the drug and these symptoms than the age of first use of MDMA, for example. To the best of the authors' knowledge, this has not been studied before. However, Wagner and colleagues used a similar approach to compare different measures of cannabis use (Wagner et al., 2010). They discovered significant associations between verbal memory and frequency of use, cumulative lifetime dose and duration of regular use.

Klomp et al. (2012) have shown that the developing brain is more vulnerable to MDMA than the matured brain. This finding indicates that the age of first use of MDMA might be relevant in explaining cognitive and psychopathological symptoms after the use of this drug. Another important factor is the cumulative lifetime dose of MDMA. A higher cumulative lifetime dose is associated with poorer performance on several cognitive tests, including learning and memory (Zakzanis et al., 2007). As far as the authors know, there are no studies that have investigated and compared the associations between different means of measuring MDMA use and cognitive functions. Therefore, the purpose of this study is to examine the relevance of different parameters of MDMA use.

Most studies that investigate psychopathological and cognitive symptoms are beset with methodological shortcomings, as for example polydrug use and the lack of a baseline measurement of psychopathology and cognition of MDMA novices. These shortcomings may cause inconsistencies in findings and complicate the interpretation of results. For this reason, the current study aims to explore the importance of different parameters of ecstasy use while at the same time accounting for the methodological problems.

To answer the question of whether or not different parameters of MDMA usage lead to different cognitive deficits and psychopathological alterations, new MDMA users were interviewed to assess their usage of the drug. They were asked to do a battery of tests measuring different cognitive functions (declarative memory, figural visual recognition, a working memory task, an information processing test, a cognitive interference test and a test to measure mental flexibility) and filled in the SCL-90 at the beginning of the experiment and again after 1 year. MDMA use was measured with the following variables: age of first use, cumulative lifetime dose and highest daily dose. Earlier use of the drug is expected to lead to worse performance on the tests, based on the results of Klomp et al. (2012). A higher total number of pills taken is expected to be related to lower cognitive abilities, as Zakzanis et al. (2007) have found. Cuyas et al. (2011) discovered a negative correlation between greater lifetime use of MDMA and performance on a visuospatial memory task as well as on an attention and perceptual speed test. In addition to that, when comparing MDMA users with controls, heavy lifetime MDMA use interacted with genetic polymorphisms in performance on cognitive tasks. Gallagher et al. (2014) studied prospective memory deficiency in ecstasy users and their relation with the average long-term typical dose of the drug. They discovered a link between a higher average dose and worse performance on the memory tasks. The average dose of MDMA seems to play a crucial role in predicting memory deficits; however, to the best of the authors' knowledge, the highest daily dose has not been studied before, a fact which emphasizes the need to investigate the relationship between this factor and cognitive and psychopathological symptoms as well. A higher single dose may lead to a more severe toxic effect of the drug, as is the case with other drugs, such as alcohol (de la Monte and Kril, 2014). The hypothesis is that an increased highest daily dose leads to more symptoms in cognitive and mental health. MDMA use is expected to have a greater effect upon the results of the tests measuring memory and learning abilities than the other cognitive tests do, as earlier research has suggested (Gouzoulis-Mayfrank and Daumann, 2009). Furthermore, it is hypothesized that greater ecstasy use is associated with higher SCL-90 scores, as Parrott et al. (2000) have found in their study.

The current study focuses on the combined effect of two factors. For example, early onset and heavy use of MDMA might cause more severe symptoms than both factors alone, which is the reason why this study does not only investigate the association between different MDMA parameters and cognitive and mental health deficits individually, but also their interactions. Differences between early and late onset of MDMA use are expected to be more extreme when participants also show a high cumulative lifetime dose. A similar hypothesis concerns the age of first use and highest daily dose. Subjects who both started taking the drug early in life and used an increased highest daily dose are expected to perform worse than those who used a lower highest daily dose or who began MDMA consumption later in life. Finally, a high cumulative lifetime dose in combination with an increased highest daily dose is assumed to be associated with poorer performance on the tests than a lower highest daily dose or the ingestion of a small cumulative amount of pills.

2. Methods

2.1. Participants

The data of 96 new ecstasy users, which were part of a larger study, were analyzed in this study. The subjects had no current physical, neurological or psychiatric disorders; they had not used any illegal drugs besides cannabis more than five times; they were not alcohol dependent; and none of them took any medications on a regular basis aside from contraceptives. To ensure that none of the participants fulfilled any of these exclusion criteria, a standardized short-interview for psychiatric disorders, the mini-DIPS, was used (Margraf, 1994), and all subjects underwent a structured interview during which they were asked about their physical health. An abstinence from cannabis of longer than 1 day does not seem realistic, since most MDMA users also use cannabis (Parrott et al., 2007). Moreover, cannabis remains detectable in drug screenings for many days or weeks after consumption, which complicates the determination of the length of abstinence. All participants had some experience with MDMA but had not taken more than five pills when the study began. Participants were obtained through advertisements in magazines and newspapers and through notifications on campus. The subjects had to abstain from cannabis on the days of the experiment to rule out any acute intoxication effects of this drug; for any other illegal drug, the required minimal length of abstinence was 7 days. Of the 96 participants, 63 were male and 33 were female. The average age ranged from 18 to 41 years.

3. Materials

The variables, age of first use, cumulative lifetime dose and highest daily dose, were measured by a structured interview. To measure verbal declarative memory, a German version of the Rey Auditory Verbal Learning Test (Rey, 1964), namely, the *Auditiv-Verbaler Lerntest* (RAVLT) (Heubrock, 1992), was used. The performance was measured by six variables: immediate recall, total acquisition performance, delayed recall, loss through interference, recognition and repetitions needed for learning. Figural visual recognition was measured by a paired associates learning task, the *Lern- und Gedächtnistest* (LGT) (Bäumler, 1974). This task had two measurements, the immediate recall and the one-hour delayed recall. The working memory task used in this experiment was the Digit-Span-Test, which is part of the German version of the Wechsler Intelligence Test (Wechsler, 2008), the *Hamburg-Wechsler-Intelligenztest* (HAWIE-R) (Tewes, 1994). Working memory was measured in correctly recalled sequences of digits in reverse order. Another test, also taken from the HAWIE-R (Tewes, 1994), was the digit symbol test, which detected information processing. Information processing was measured in points acquired while transforming digits to symbols. In order to measure cognitive interference, the German version of the Stroop task (*Farb-Wort-Interferenztest*) (Bäumler, 1985; Stroop, 1935) was used. The trail-making test (Reitan, 1992) measured mental flexibility by measuring the time used in the

first part to connect the numbers and the time used in the second part to connect numbers and letters in the correct order. A detailed description of the cognitive test battery used in this study can be found in the article by Wagner et al. (2013). Self-reported psychopathology was assessed by the SCL-90 (Derogatis et al., 1973), employing the following list of symptoms: somatization, obsessive–compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism. Moreover, the global severity, the number of symptoms identified and the intensity of the answers on the SCL-90 were obtained as well.

Demographic data, such as gender, age and years of education, were collected in order to be able to account for possible confounding variables. To be able to give an indication of the possible influences of cannabis use, its use at the baseline and within follow-up as well as days passed since last cannabis use were also investigated.

4. Procedure

After having given informed consent, participants were interviewed to assess drug use. To rule out any drug use on the day of examination, the subjects were asked to give urine samples, and one-third were additionally required to give hair samples for further drug investigation. Afterwards, the participants filled in a health behavior questionnaire, which was part of the larger study, and gave demographic data. Next, participants were tested with the neuropsychological test battery described above. In the end, subjects filled in the SCL-90. Roughly a year later, this procedure was repeated to deliver the first follow-up measure in addition to the baseline.

5. Analysis

The data were analyzed by using 4 multivariate analyses of covariance (MANCOVA). Each analysis has age of first use, total number of pills taken and highest daily dose as fixed factors. For each of the three factors, a median split was conducted in order to divide the sample into two groups for analysis. Age of first use was divided into participants having used MDMA for the first time at an early age (19 years old or younger) and at a later age (20 years old or older). Cumulative lifetime dose was split into a low dose group (subjects having used 1.5 pills or fewer) and a high dose group (subjects having taken 2 or more pills). The third variable, highest daily dose, consisted of a low dose group (0.75 pills or fewer) and a high dose group (1 or more pills). The first MANCOVA concerned attention and information processing speed. The dependent factors were the first part of the trail-making test, the color-naming and reading condition of the Stroop task and the digit symbol test. The variables used in the second MANCOVA, which addresses episodic memory, were the six AVLT measures and immediate and delayed recall of the LGT. Executive functioning was investigated with the third MANCOVA, containing the second part of the trail-making test, the interference conditions of the Stroop task and the digit span score as variables. The dependent variables of the fourth MANCOVA were all SCL-90 measures. To control for pre-existing differences, change scores for the cognitive and psychopathological variables were created. To investigate which covariates needed to be included in the analyses, the aforementioned demographic data and pattern of cannabis use were examined for possible group differences on the independent variables. All analyses were performed with the IBM SPSS statistical software program version 21 (Chicago, IL, USA).

6. Results

To control for possible confounding variables, gender distribution, mean age, cannabis use at baseline and within follow-up, days since last cannabis use and mean years of education were investigated for both groups of all three independent variables. The results are given in Tables 1-3.

Table 1
Group characteristics of age of first use.

	19 or younger	20 or older	*T*-value	*P*-value
Female/male	20/26	13/37	3.24	.087[a]
Age	20.87 ± 2.75	24.94 ± 4.98	−5.02	**.000**[b]
Cannabis use at baseline	45.57 ± 45.4	43.58 ± 41.84	.22	.823[b]
Cannabis use within follow-up	10.8 ± 18.25	9.34 ± 19.49	.38	.705[b]
Days since last cannabis use	10.47 ± 46.05	60.2 ± 233.49	−1.22	.226[b]
Years of education	13.55 ± 2.17	15.98 ± 2.56	.4.99	**.000**[b]

Frequency of gender, mean age, mean duration of cannabis use in months at baseline and within follow-up, days since last cannabis use and mean years of education for both groups. Standard deviations are given in parenthesis.
[a] Computed by means of χ^2test.
[b] Computed by means of independent samples *t*-tests.

The groups did not differ significantly with respect to gender distribution and cannabis use, but age and years of education differ significantly between the two groups of the variable age of first use and cannabis use within follow-up differs significantly between the two groups of the variable cumulative lifetime dose. That is why mean age, cannabis use within follow-up and years of education have been included as covariates in the analyses.

The first MANCOVA, concerning attention and information processing speed, showed no significant main effect of group for the variables, age of first use ($F(83,4) = .91$, $p = .462$), cumulative lifetime dose ($F(83,4) = .48$, $p = .75$) and highest daily dose ($F(83,4) = 1.14$, $p = .346$); but a significant main interaction effect of age of first use and cumulative lifetime dose ($F(83,4) = 2.55$, $p = .045$) was found. Significant, but weak interaction effects on the corresponding between-subjects effects were found for the first part of the trail-making test ($F(1,85) = 5.1$, $p = .026$, $\eta^2 = .056$) and the digit symbol test ($F(1,85) = 5.42$, $p = .022$, $\eta^2 = .059$), but not for the two Stroop variables. The difference in time needed to complete the trail-making test A of subjects with a higher and lower cumulative lifetime dose was greater for subjects who were 19 years old or younger than for subjects who were 20 years old or younger. Means and standard errors are given in Fig. 1. Moreover, an early onset of use of MDMA is connected to a larger discrepancy between higher and lower cumulative lifetime dose of scores reached on the digit symbol test, than a later start of consumption of the drug is. Means and standard errors are given in Fig. 2. In contrast to the main interaction effect of age of first use and cumulative lifetime dose, the interaction between age of first use and highest daily dose ($F(82,4) = 2.18$, $p = .079$) and the interaction between cumulative lifetime dose and maximum-one-time dose ($F(82,4) = 2.05$, $p = .095$) did not prove to be significant.

The MANCOVA addressing episodic memory revealed a significant main effect of age of first use ($F(79,8) = 2,71$, $p = .011$). The referring test of between-subject effects delivered significant results for the recognition performance of the RAVLT ($F(1,86) = 11.07$, $p = .001$) This effect was medium-sized ($\eta^2 = .114$). On average, the early-start-of-MDMA-usage group achieved a higher recognition score

Table 2
Group characteristics of cumulative lifetime dose.

	1.5 pills or fewer	2 pills or more	*T*-value	*P*-value
Female/male	15/31	18/32	.12	.831[a]
Age	22.85 ± 3.77	23.12 ± 5.17	−.29	.77[b]
Cannabis use at baseline	40.97 ± 35.15	47.82 ± 49.88	−.77	.442[b]
Cannabis use within follow-up	6 ± 5.66	13.76 ± 25.06	−2.13	**.038**[b]
Days since last cannabis use	68.43 ± 251.61	9.46 ± 25.58	1.38	.176[b]
Years of education	15.02 ± 2.59	14.63 ± 2.75	.73	.469[b]

Frequency of gender, mean age, mean duration of cannabis use in months at baseline and within follow-up, days since last cannabis use and mean years of education for both groups. Standard deviations are given in parenthesis.
[a] Computed by means of χ^2test.
[b] Computed by means of independent samples *t*-tests.

Table 3
Group characteristics of highest daily dose.

	.75 pill or fewer	1 pill or more	*T*-value	*P*-value
Female/male	16/28	17/35	.14	.83[a]
Age	22.98 ± 3.76	23 ± 5.13	−.02	.981[b]
Cannabis use at baseline	36.83 ± 5.29	48.68 ± 6.75	−1.62	.11[b]
Cannabis use within follow-up	6 ± 5.64	13.46 ± 24.64	−1.97	.052[b]
Days since last cannabis use	69.97 ± 255.23	9.63 ± 25.24	1.37	.179[b]
Years of education	15.1 ± 2.59	14.57 ± 2.73	.971	.334[b]

Frequency of gender, mean age, mean duration of cannabis use in months at baseline and within follow-up, days since last cannabis use and mean years of education for both groups. Standard deviations are given in parenthesis.
[a] Computed by means of χ^2test.
[b] Computed by means of independent samples *t*-tests.

($M = .19$, $SE = .36$) on the RAVLT than the late group ($M = -1.45$, $SE = .38$). Apart from that, age of first use did not prove to have a significant effect upon any of the other RAVLT variables or upon the two variables of the LGT. Furthermore, the analysis neither revealed any significant main effect of cumulative lifetime dose ($F(79,8) = 1.64$, $p = .127$) or highest daily dose ($F(79,8) = 1.31$, $p = .25$), nor did it show any main interaction effect for the interactions of age of first use and cumulative lifetime dose ($F(79,8) = 2.05$, $p = .051$), age of first use and highest daily dose ($F(79,8) = 2.01$, $p = .056$) and cumulative lifetime dose and highest daily dose ($F(79,8) = 1.82$, $p = .086$).

The third MANCOVA pertains to frontal and executive functioning. Neither age of first use ($F(84,3) = .25$, $p = .861$), nor cumulative lifetime dose ($F(84,3) = .88$, $p = .455$), nor highest daily dose ($F(84,3) = .37$, $p = .778$) had a significant effect on frontal/executive functioning. Furthermore, the analysis revealed no significant interaction effects between age of first use and cumulative lifetime dose ($F(84,3) = .7$, $p = .556$), age of first use and highest daily dose ($F(84,3) = .27$, $p = .849$) or cumulative lifetime dose and highest daily dose ($F(84,3) = 1.05$, $p = .377$) on frontal/executive functioning.

The last analysis concerned self-reported psychopathology. None of the three independent variables, age of first use ($F(75,12) = 1.03$, $p = .43$), cumulative lifetime dose ($F(75,12) = .69$, $p = .752$) and highest daily dose ($F(75,12) = .54$, $p = .883$), proved to be relevant for predicting the SCL-90 scores. Furthermore, there was no significant interaction between age of first use and cumulative lifetime dose ($F(75,12) = .86$, $p = .592$), age of first use and highest daily dose ($F(75,12) = .93$, $p = .522$) or cumulative lifetime dose and highest daily dose ($F(75,12) = .4$, $p = .961$) on self-reported psychopathology.

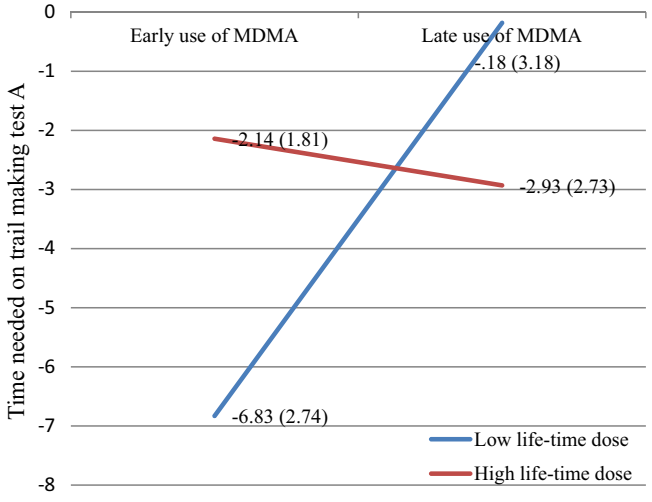

Fig. 1. Significant interaction between age of first use and cumulative lifetime dose upon the trail-making test A. Means of the change score for the groups are given in the figure; standard errors are given in parentheses.

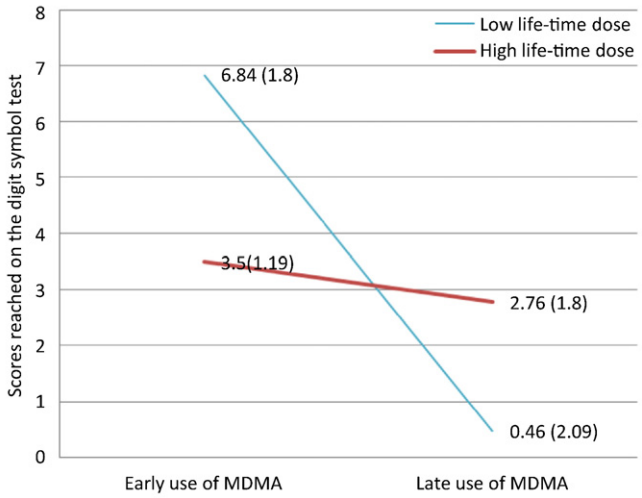

Fig. 2. Significant interaction between age of first use and cumulative lifetime dose upon the digit symbol test. Means of the change scores for the groups are given in the figure; standard errors are given in parentheses.

7. Discussion

The aim of the current study was to investigate the association between different parameters of MDMA use and cognitive as well as psychopathological symptoms. In addition, the interaction between those parameters was studied. This investigation was carried out by assessing ecstasy use patterns, including age of first use, cumulative lifetime dose and highest daily dose in a large sample of new MDMA users. Subjects completed a test battery, consisting of tests measuring attention and information processing speed, episodic memory and executive functioning and a questionnaire investigating self-reported psychopathology. Since age, years of education and cannabis use within follow-up proved to be relevant confounders, these variables were included in the investigation as well.

None of the three parameters of ecstasy use examined in this study appears to be a relevant factor in itself in predicting attention and information processing speed, but age of first drug consumption and cumulative lifetime dose combined can explain differences in this cognitive domain. All participants improved their performance during the follow-up, which can be explained as a training effect. But the current results also showed that participants who had started taking MDMA at an early age and had consumed a smaller total number of pills in their lives performed better on the first part of the trail-making test and the digit symbol test than those who had taken a higher cumulative lifetime dose of MDMA or those who had started consumption of the drug later in life. Subjects with a low age of first use only performed much better on both tasks when they showed a low cumulative lifetime dose. Moreover, high or low cumulative lifetime dose differences relative to scores reached on these tests are larger in the early age of ecstasy use group than in the late age of first use group. In contrast to what was expected, early age of first MDMA use combined with a high cumulative lifetime dose did not result in the poorest performance. The analyses that explored possible confounders revealed that age and years of education differed for the two groups of age of first use. The subjects were recruited at the onset of their MDMA use; therefore, subjects with an early age of first use were also younger when they participated in this study. Consequently, younger participants had received fewer years of education than the older subjects since many of the younger subjects were possibly still students. MDMA users who had started consuming the drug early possibly showed better attention and information processing speed because they were still in school. These subjects could have been used to this kind of cognitive testing because they received similar tasks at school. Combined with a lower cumulative lifetime dose of

MDMA, these participants scored better on the tasks. Older participants who were no longer in school might have had an occupation that demanded fewer skills in attention and information processing speed, resulting in an unfamiliarity with these tasks. Moreover, subjects who still attend school might be more accustomed to test situations, whereas participants who have already finished school could also perform worse due to nervousness, for example. This is one way to interpret these unexpected results, but further research is necessary to clarify this issue.

Age of first use is the only parameter that proved to have a specific effect on episodic memory, in contrast to what was hypothesized. MDMA users with an early age of first use performed better on the recognition task of the RAVLT than the late age of first use group did. This outcome could again be explained by the fact that in this study, MDMA users with an early age of first use are younger and probably still in school, compared to those with a later age of first use. Participants who are still in school are perhaps better prepared to do tasks that address recognition abilities of the episodic memory than older subjects who might use fewer of these skills in daily life. Again, future studies should concentrate on examining the differences between early and late onset MDMA users to be able to draw definitive conclusions.

Another way to explain the differences discovered in this study between participants with an early and late age of first use in episodic memory might be by considering specific character distinctions. The early onset of ecstasy use is associated with sensation seeking (Wu et al., 2010). This trait is predictive of an early age of first use of MDMA. In addition, there is a relation between openness to experience and general cognitive ability (Vinkhuyzen et al., 2012). Subjects who show more experience-seeking behavior have better general cognitive abilities. This could help MDMA users with an early age of first use compensate for deficits in episodic memory, which might be the reason for better performance on the RAVLT. Singer et al. (2004) compared older adolescent MDMA users (aged 18-30) with non-MDMA users at high risk of drug usage. MDMA users were more prone to polydrug use than non-MDMA users and reported having achieved lower academic grades; had more family, social and peer problems; experienced more childhood trauma, psychological distress, obsessive–compulsive symptoms, psychoticism and depression. This is a possible explanation for the fact that subjects with a higher age of first use of MDMA performed worse on the episodic memory task since earlier studies have shown that traumatic stress predicts episodic memory deficits (Guez et al., 2011), that obsessive–compulsive disorder is associated with verbal memory (Shin et al., 2014), and that depression is linked to memory deficits, including verbal recall and recognition (Bearden et al., 2006). Nevertheless, considering the current study is the first one that explores and compares the association between different parameters of ecstasy use, the results should be interpreted cautiously, and more research on this topic is indispensable.

No differences between groups of age of first use, cumulative lifetime dose and highest daily dose on executive functioning and self-reported psychopathology were found. These results are not in line with some of those of earlier studies. Executive deficits associated with MDMA use have been reported before, for example, by Reay et al. (2006), but in general, the results are inconsistent in the literature (Gouzoulis-Mayfrank et al., 2002). Hanson and Luciana (2004) investigated neurocognitive function of MDMA users. About half of their subjects met the diagnostic criteria for MDMA abuse or dependence. The two groups differed in their performance: The subjects whose MDMA use was clinically dysfunctional performed worse on verbal memory, verbal fluency, fine motor dexterity and a letter cancelation task, than the subjects with recreational MDMA use. These results prove that clinically significant patterns of use are important for detecting differences in cognitive impairment. The current study investigated neither whether subjects met the criteria for an MDMA-related diagnosis nor the severity of a possible diagnosis. Therefore, it is possible that the ecstasy users in this sample did not possess the clinical relevance needed for detecting cognitive dysfunction.

Several studies have found associations between MDMA use and self-reported psychopathology, for example, Parrott et al. (2000) and Schifano et al. (1998); but their design lacked a control for polydrug use. After avoiding poly-drug use influences and controlling for several other possible confounders, which most of the studies in the literature did not do, this study failed to replicate the results of earlier studies that lacked a prospective methodological approach. These results are in line with Medina and Shear (2007), who also used a design in which they controlled for the use of other drugs apart from MDMA. In that study, ecstasy users showed higher levels of anxiety, depression and executive dysfunction, but ecstasy use failed to predict these symptoms. Moreover, they found an association between higher usage of other drugs and the symptoms described.

This study was conducted to rule out polydrug use effects and to obtain an estimation of pre-onset cognitive functioning and self-reported psychopathology. This was done by controlling the influence of several relevant covariates in the analyses. However, there are still some limitations to be considered. The results of this study are very counter-intuitive. One possible explanation for these outcomes could be that the sample size was too small to be explored for complex interactions. Future research should concentrate on acquiring larger samples. Furthermore, this study focused on age of first MDMA use, cumulative lifetime consumption and highest daily dose but did not report other parameters, such as frequency of use or average use. Since those MDMA use measures have not been investigated so far, the possibility of those factors having an important role in predicting cognitive and mental health symptoms cannot be rejected. Moreover, no control group was used in this design, which is why the generalization of the conclusions is limited. To compare the discovered effects with the performance of non-users, future studies with a design including a control group are required. The current study concentrated on cognitive and psychopathological symptoms 1 year after ecstasy use onset. Consequent follow-up studies could shed light on later consequences of MDMA use. In addition to that, it is impossible to rule out any supposable expectation effects on the performance since participants were aware of the fact that this study addressed MDMA use. Finally, the lack of an experimental design does not allow the presumption of a causal relationship between early onset of MDMA use and episodic memory or the interaction between age of first use and cumulative lifetime dose on attention and information processing speed.

In conclusion, age of first use and the cumulative lifetime dose of MDMA use can help explain differences in attention and information processing. Age of first MDMA use also proves to be an important factor in predicting recognition of the episodic memory. A later onset of ecstasy use may be more critical to the episodic memory than an earlier one. However, we draw these conclusions with caution, for further studies with a similar design are needed to confirm the findings. This could help to broaden our understanding of ecstasy use patterns and their association with cognitive and mental health symptoms.

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