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Additive Effects of Former Methylenedioxymethamphetamine and Cannabis Use on Subclinical Psychotic Symptoms

Geçmişte Kannabis ve MDMA Birlikte Kullanımının Subklinik Psikotik Semptomlar Üzerindeki Ek Etkisi

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ABSTRACT

Introduction: Methylenedioxymethamphetamine (MDMA) is an amphetamine-derived psychostimulant, usually known as "ecstasy." The long-term neuropsychological effects of MDMA are examined in several studies with conflicting results. The most common findings reported are depression, anxiety, and memory and attention deficits. In addition to acute psychotic reactions observed after MDMA use, serotonergic and dopaminergic toxicities may increase the psychosis risk in the long-term. Cannabis usage among MDMA users is very high. The aim of this study was, therefore, to examine the additive effects of cannabis and MDMA on subclinical psychotic symptoms (SPS).

Methods: Here, 131 healthy controls (hC), 54 former cannabis and MDMA users (C&M), and 46 former cannabis users (C) were evaluated for SPS. The definition of former user was based on the Munich Composite International Diagnostic Interview. The SPS scores were assessed by using the Schizotypal Personality Questionnaire (SPQ). The relationship between substance-free periods and total MDMA exposure with SPS was also examined.

Results: The C&M group had higher levels of SPS than both C and hC groups. This is true not only for the total SPQ scores but both positive and negative schizotypy scores as well as cognitive–perceptual, disorganized, and interpersonal schizotypy scores aligned hierarchically in the 3 study groups (C&M>C>hC). The total MDMA exposure was positively correlated and MDMA-free period was negatively correlated with the SPS score.

Conclusion: We found that the former use of cannabis and MDMA is associated with marked elevation in SPS. Moreover, the exposure amount of MDMA and MDMA-free periods are important determinants of SPS. The longer the cannabis and ecstasy free periods, the larger is the waning of SPS.

Keywords: Psychotic disorders, substance-related disorders, substance-induced psychosis

ÖZ

Amaç: Metilendioksimetamfetamin (MDMA), sıklıkla 'Ekstazi' olarak bilinen amfetamin türevi bir psikostimülandır. Uzun süre MDMA kullanımının nöropsikolojik etkileri çeşitli çalışmalarda incelenmişse de sonuçları çelişkilidir. En sık bildirilen bulgular depresyon, anksiyete, bellek ve dikkat kusurlarıdır. MDMA kullanımı sonrası bildirilen akut psikotik bulguların yanı sıra ortaya çıkan serotonerjik ve dopaminerjik toksisitenin geç dönem psikoz riskini arttırabileceği düşünülebilir. MDMA kullanıcılarında kannabis kullanım oranı çok yüksektir. Bu çalışmanın amacı, subklinik psikotik semptomlar (SPS) üzerinde MDMA ve kannabis birlikte kullanımının etkilerini değerlendirmektir.

Yöntem: 131 sağlıklı kontrol (SK), 54 eski kannabis ve MDMA kullanıcısı (K&M) ve 46 eski kannabis kullanıcısı (K) SPS yönünden değerlendirilmiştir. Geçmiş kullanıcı tanımı Munich Uluslararası Bileşik Tanı Görüşmesi temel alınarak yapılmıştır. SPS, Şizotipal Kişilik Ölçeği (ŞKÖ) ile ölçülmüştür. Ayrıca, maddeyi kullanımı sonlandıktan sonra geçen süre ve toplam maruziyetin SPS ile ilişkisi de incelenmiştir.

Bulgular: K&M grubunun SPS puanı her iki gruptan yüksektir. Yanı sıra pozitif ve negatif şizotipi, bilişsel-algısal, dezorganize ve kişilerarası şizotipi puanları açısından da üç grup hiyerarşik olarak sıralanmıştır (K&M>K>SK). SPS ile toplam MDMA maruziyeti pozitif yönde, MDMA kullanımını bıraktıktan sonra geçen süre de negatif yönde korelasyon göstermiştir.

Sonuç: Geçmiş kannabis ve MDMA kullanımı belirgin derecede SPS ile ilişkilidir. Ayrıca, toplam MDMA maruziyeti ile MDMA kullanımı bırakıldıktan sonra geçen süre de SPS açısından önemli belirleyicilerdir. Ekstazi ve esrardan uzak kalma süresi uzadıkça eşik altı psikoz belirtileri azalır.

Anahtar kelimeler: Psikotik bozukluklar, madde kullanımı, madde kullanımına bağlı psikotik bozukluk

INTRODUCTION

Methylenedioxymethamphetamine (MDMA) is an amphetamine-derived psychostimulant, usually known as "ecstasy" (1). After the 1980s, especially in the UK, the drug gained huge popularity through all-night dance parties (2). By increasing the questions about drugs' neurotoxicity, MDMA was classified as an illegal substance in the US. However, MDMA tablets are now synthesized and the drug has a widespread market in the world (3). According to the epidemiological data from Europe and USA, it is clear that MDMA has been tried at least once by 1%–5% of the young population (4). Moreover, a study conducted in Britain reported that of 13% university students have tried MDMA at least once (5). Therefore, MDMA usage has clearly become a public health problem throughout the world.

According to preclinical animal research, MDMA is a selective serotonergic neurotoxin: it abruptly decreases the levels of 5-hydroxytryptamine and 5-hydroxyindoleaceticacid (6,7). Structural damage to the serotonergic system has been reported in studies conducted on primates (8). Probably, MDMA-related damage is associated with oxidative stress, excitotoxicity, and mitochondrial dysfunction in serotonergic and

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dopaminergic systems (9,10). The long-term neuropsychological effects of MDMA were examined in several studies, but have yielded conflicting results. The most common findings reported are depression, anxiety, and memory and attention deficits (11). In addition to the acute psychotic reactions observed after MDMA use, serotonergic and dopaminergic toxicity related to chronic use may increase psychosis risk (12,13). It was reported that MDMA decreases prepulse inhibition—an indicator of psychosis proneness (14,15). Cases with chronic psychosis related to MDMA were also reported (1). However, a literature survey fails to identify a study that has examined the effects of former MDMA use on subclinical psychotic symptoms (SPS).

Cannabis use among MDMA users is very high (16). Studies from Europe reported that approximately of 75% MDMA users also use cannabis (4). The most important active ingredient of cannabis is delta-9 tetrahydrocannabinol (THC). Acute administration of THC reduces [^{11}C]raclopride binding in the ventral striatum and the dorsal putamen (when compared to the placebo), which is consistent with an increase in dopamine levels in these regions (17). Early cannabis use may increase the risk for psychotic symptoms and repeated exposure to cannabis may sensitize the individuals who are genetically prone to psychosis (18,19). Both animal research and studies on human subjects suggest that cannabis-induced dopamine dysregulation may give rise to psychotic symptoms (20). However, only a small proportion of cannabis users develop psychosis. This can be partly explained not only by the amount and duration of the consumption of cannabis but also by the age at which the individuals are first exposed to cannabis. Evidence suggests that the mechanisms of gene–environment interaction are likely to underlie the association between cannabis and psychosis (19).

The aim of this study was to examine the additive effects of cannabis and MDMA on SPS. Considering the high co-occurrence of cannabis use among MDMA users, we especially preferred to examine the additive effects of these substances by means of ecological validity. Since previous research suggests different biological pathways regarding the psychosis risk revealed by the use of cannabis and MDMA, it is plausible to assume that these two substances together may have additive effects on SPS. Furthermore, since acute toxic effects of both substances also resemble psychosis, we preferred to examine psychosis-like phenomena, particularly in former users who have been substance-free for at least a month. We hypothesized that former users of cannabis together with MDMA have higher SPS than former cannabis users alone and subjects without former substance use.

METHODS

Settings and Sample

The participants were male military conscripts boarding at the same military training school between January and March 2008 in Çanakkale, Turkey. Psychiatric and substance-use histories were obtained as part of a routine medical examination at the first month after recruitment, which enabled a washout period from exposure. As ascertained from the military records, all the participants were physically in good health without medical or psychiatric comorbid conditions. Based on the Munich Composite International Diagnostic Interview, our definition of former use stipulated exposure on at least 5 independent occasions with use of either a joint (alone or shared) or an ecstasy tablet alone at each event (21). Out of the total 190 eligible index subjects, 8 refused to participate and 68 were excluded (n=8, history of psychosis; n=11, antipsychotic use; n=15, psychotic disorder in a first-degree relative; n=11, cocaine, hallucinogen, or opiate abuse; n=23, not meeting former use criteria). To ensure the reliability of the participants' self-reports, the remaining 114 conscripts were further assessed using a semi-structured interview for a detailed history of cannabis and ecstasy abuse including age of first use (AoFU), methods and reasons for use, the frequency of use, intervals of regular use, and length of substance-free periods. The reports for 14 subjects were not found to be consistent with their reports at the study's inception. The remaining 100 subjects were evaluated for SPS. Among these 100 subjects, 54 were former users of both cannabis and MDMA (C&M group) and 46 were that of cannabis (C group). There was no former user with only MDMA use. The mean age and education levels (in years) are presented in Table 1.

The controls (n=131) were cannabis- and ecstasy-naive conscripts whose military numbers were less than former users. Here 29 of the 160 controls were excluded (n=4, history of prior psychotic disorder; n=3, antipsychotic use; n=18, psychotic disorder in a first-degree relative; and n=4, cocaine abuse). The remaining 131 healthy controls (hC group) were evaluated for SPS.

The SPS scores were assessed by the Turkish version of the Schizotypal Personality Questionnaire (SPQ), which is shown to be a reliable and valid measure for psychosis-like phenomena among young adults (22).

Table 1. Comparison of sociodemographic features and SPS among the 3 study groups

	C (n=46)	C&M (n=54)	hC (n=131)	
Age (mean±SD)	20.89±1.49	20.47±0.79	21.33±2.23	F=4.3* p=0.01 (hC>C>C&M)
Education (years) (mean±SD)	7.87±2.96	8±2.47	8.6±3.74	F=1.1* p=0.33
SPQ- total score (mean±SD)	33.27± 17	44.6±15.17	16.9±11.12	F=88.8* p<0.001 (C&M>C>hC)
Lifetime exposure to cannabis (months) (median, range)	48, 84	48, 110	-	Z=-1.5** p=0.132
Positive schizotypy score (mean±SD)	22.27±12.85	28.47±10.59	9.71±7.6	F=84.3* p<0.001 (C&M>C>hC)
Negative schizotypy score (mean±SD)	15.02±7.07	21.51±7.27	9.27±6.17	F=68* p<0.001 (C&M>C>hC)
Cognitive-perceptual schizotypy score (mean±SD)	15.31±8.44	18.49±6.92	6.94±5.47	F=71.9* p<0.001 (C&M>C>hC)
Disorganized schizotypy score (mean±SD)	6.96±4.59	9.98±4.28	2.77±2.91	F=81.9* p<0.001 (C&M>C>hC)

hC: control group; C: former cannabis exposure group; C&M: former cannabis and MDMA exposure group; SD: standard deviation; SPQ: schizotypal personality questionnaire

*1-way ANOVA and post-hoc LSD tests were used, **Mann–Whitney U-test was used.

Total MDMA exposure (TME) was determined by using 3 different variables established by the semi-structured interviews: *(i)* total duration of ecstasy exposure (Td) that was determined as the sum total (in months) of former MDMA use intervals; *(ii)* the amount of ecstasy tablets consumed during a routine event (AeT), and *(iii)* the mean frequency of abuse within a given month (FoU) (e.g., FoU is 7/30 for a subject who used MDMA 7 days a month). TME was calculated by using the following formula: (Td×AeT)/FoU. The duration of the last MDMA-free interval (dMFI) at the time of assessment was measured in months.

Ethics Approval

The study was approved by the university and military hospital ethics boards. All the participants provided written informed consents.

Measures

Information regarding the age, education, and psychiatric and medical disease histories as well as substance-use history was gathered by the sociodemographic questionnaire that was prepared by the authors. SPQ was used for the assessment of SPS. SPQ is a self-report questionnaire that consists of 74 items and was developed by Raine and colleagues (23). Cronbach's alpha coefficient for the overall Turkish version of the scale is 0.91 with coefficients for subscales ranging from 0.66 to 0.83 (22). Factor analysis of the SPQ reveals cognitive–perceptual and disorganized schizotypy factors that correspond to positive schizotypy and an interpersonal schizotypy factor (i.e., social anxiety, constricted effect, and lack of close friendships) that corresponds to negative schizotypy (24). SPQ has also been used for the identification of risk factors for proneness to psychosis and the severity of psychosis-like phenomena (25,26). Mean SPQ and subscale scores in the 3 study groups are presented in Table 1.

Statistical Analyses

Lifetime exposure to cannabis was defined as the total duration of use in months and compared between the 2 index groups by means of the Mann–Whitney U-Test. In order to compare the 3 groups by means of age, education, and SPQ scores, 1-way ANOVA tests were used. Post-hoc analyses were conducted by means of the least significant difference (LSD) test. The correlations between TME and dMFI with total SPQ and subscale scores were calculated by using the Spearman correlation analysis. In order to prevent type-1 errors resulting from multiple comparisons, we used the Bonferroni method.

RESULTS

The 3 groups were different in terms of age, but the effect size was small. This is probably due to the homogeneity of variances within the groups. The level of education was comparable between the study groups (Table 1). The amount of lifetime exposure to cannabis was comparable between former cannabis users and former users of both cannabis and MDMA (Table 1). The C&M group had higher levels of SPS than both the C and hC groups. This is true not only for the total SPQ scores but also for both the two-factor solution subscale scores (indicating positive and negative schizotypy). Similarly, the three-factor solution subscale scores corresponding to cognitive–perceptual, disorganized, and interpersonal dimensions of schizotypy aligned hierarchically among the 3 study groups (C&M>C>hC).

The mean TME was 61.45±11.04 months, and the mean dMFI was 4.12±0.47 months.

The Spearman correlations of MDMA-related parameters and SPS are presented in Table 2. TME was positively correlated with all the dimensions of SPS. However, TME and disorganized schizotypy correlation lost significance after the Bonferroni correction. Further, dMFI was negatively correlated with all the schizotypy dimensions. However, the significance regarding the correlation of negative schizotypy and disorganized schizotypy with dMFI also disappeared after the Bonferroni correction (Table 2).

The relationship between TME and dMFI with the total SPQ scores is shown in Figure 1, 2 respectively.

Table 2. Correlations of TME and dMFI with SPS dimensions (Spearman correlation test)

	TME	dMFI
SPQ- total score	r=0.38, p=0.005	r=-0.38, p=0.005
Positive schizotypy score	r=0.39, p=0.003	r=-0.41, p=0.003
Negative schizotypy score	r=0.36, p=0.007	r=-0.26, p=0.059*
Cognitive-perceptual schizotypy score	r=0.4, p=0.003	r=-0.43, p=0.002
Disorganized schizotypy score	r=0.33, p=0.016*	r=-0.34, p=0.015*

TME: total MDMA exposure; dMFI: duration of the last MDMA-free interval
*Not significant after Bonferroni correction.

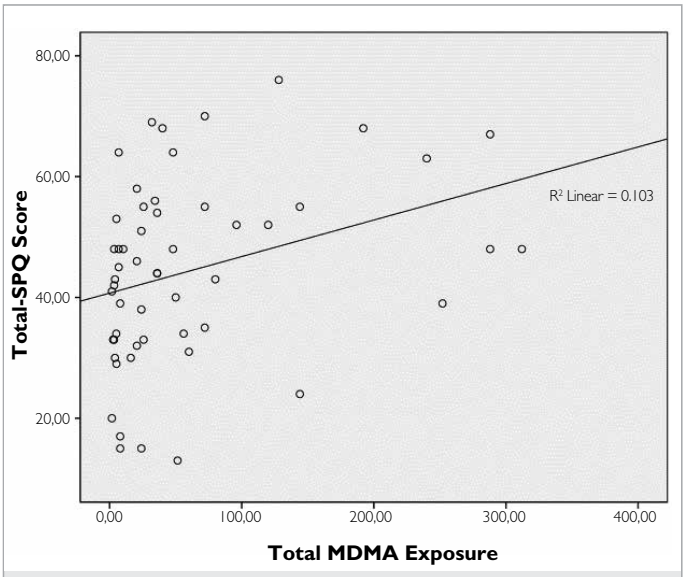

Figure 1. Relationship between TME and total SPQ score

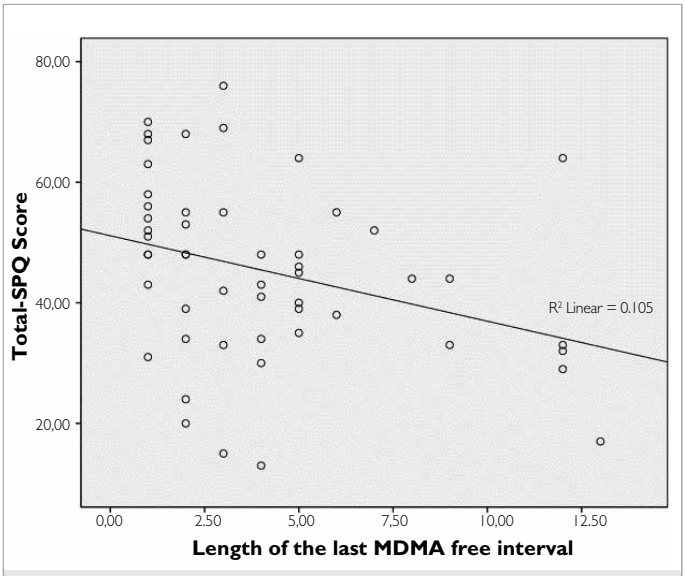

Figure 2. Relationship between dMFI and total SPQ score

DISCUSSION

In a cross-sectional design, we compared the former users of both MDMA and cannabis to former users of cannabis alone and control subjects without former substance-use history in terms of SPS. We found that former users of both cannabis and MDMA had markedly higher levels of SPS than both former cannabis users and healthy control subjects. Former cannabis users also had higher SPS than healthy controls. Lifetime exposure to cannabis (in months) was not different between the 2 index groups and, therefore, did not complicate the relationship between MDMA and SPS. Moreover, the amount of MDMA exposure was positively correlated and the time duration elapsed after last MDMA use was negatively correlated with SPS.

The relationship of former cannabis use and SPS was previously shown and dopamine sensitization was suggested as a possible mechanism (27, 28). On the other hand, the psychotic consequences of stimulant use are also well documented (29). The toxic effects of MDMA on serotonergic and dopaminergic neurotransmitter systems were suggested as possible mechanisms. Therefore, cannabis and MDMA may be expected to have additive effects on psychotic symptoms. Our results revealed by 1-way ANOVA support this view. However, previous observations (case reports and studies on the relationship of MDMA and psychosis) predominantly focus on the acute effects of MDMA use. To our knowledge, this is the first study that reports the effect of former MDMA use on SPS.

More importantly, we showed a dose–response relationship between the amount of MDMA exposure and SPS. Although the cross-sectional design does not permit to make a clear conclusion on causal mechanisms, a dose–response relationship may at least point out to a biological gradient between MDMA use and psychosis. Nevertheless, the negative correlation between dMFI and SPS is also an interesting finding and may either indicate an aftereffect (i.e., a transient neurotoxic effect) or this finding may be accepted as analogous to Hill's criterion on "reversibility" and may, therefore, support a causal effect (30). Notwithstanding, the decline observed by us in SPS after the cessation of MDMA is important in terms of the rehabilitation of subjects who abuse MDMA and it underscores the clinical importance of dMFI in these subjects. Professionals working in this field may note that the longer the subject stays free from MDMA, SPS will fade away. Additionally, since MDMA and cannabis abuse are predominantly comorbid conditions, investigating the effects of both these substances together is advantageous in terms of ecological validity.

Limitations

This study has prominent limitations. First and foremost, we did not quantitatively analyze the blood and/or urine substance levels and substance use was determined based on the participants' self-reports. Secondly, the sample consisted of young adults who recently joined military service, which may indeed interfere with the results. For the same reason, the external validity of the results is low (i.e., our results cannot be generalized to all healthy males and females). On the other hand, all the participants were inhabitants of a military school who shared the same environment; therefore, the setting of this study enabled us to control many environmental effects that may be associated with SPS. Finally, although an emerging body of research suggests an association between schizotypy and cannabis, the direction of this relationship is not fully clear. That is, subjects with incipient psychosis may use cannabis to self-medicate their SPS or, conversely, exposure to cannabis may be a risk factor for psychosis onset. The findings of our research suggest that there is a need to examine the relationship between cannabis and MDMA use and the development of SPS in well-designed, prospective, longitudinal cohort studies in order to make clear inferences.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Ankara University Ethics Committee.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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