

Research Article

The Influence of Expectation on Verbal Memory Performance in Ecstasy Users

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Abstract

Research on potential long-term consequences of ecstasy use suggests alterations in psychological well-being and cognitive performance. Due to methodological difficulties, it is still unclear whether this effect may be attributed to ecstasy itself or to other confounding factors, such as negative expectations. This study is aimed at discerning the effect of identifying with a negative stereotype upon performance on a battery of cognitive tests. Ecstasy users with self-reported decline were categorized by their subjective deterioration, attributed either to ecstasy use or to other reasons. Subjects were compared by their performance on frontal/executive functioning, episodic memory and information and processing speed. No effect has been observed for frontal/executive functioning and information and processing speed. However, the groups differed on total acquisition and recognition performance of the Auditive-Verbale Lerntest (AVLT). Verbal memory tasks seem to be susceptible to worries and fears generated by negative expectations in ecstasy users. This aspect should be taken into account while measuring cognitive decline in ecstasy users.

Keywords

- N-Methyl-3,4-methylenedioxymphetamine (MDMA)
- Ecstasy
- Cognition
- Expectation
- Verbal memory

ABBREVIATIONS

MDMA: N-Methyl-3, 4-Methylenedioxymphetamine; SD: Standard Deviation; T1: Follow-Up Measurement 1; T2: Follow-Up Measurement 2; AVLT: *Auditiv-Verbale Lerntest* (A German Version Of The Rey Verbal Learning Test); LGT: *Lern- Und Gedächnistest* (Figural Visual Recognition Test); TRAIL: Trail-Making Test; STROOP: Stroop Test; DS Test: Digit Symbol Test

INTRODUCTION

The main psychoactive ingredient of the recreational drug "ecstasy" is MDMA (N-Methyl-3,4-methylenedioxymphetamine). It is an amphetamine-based stimulant, which induces an acute increase in levels of the neurotransmitters serotonin and dopamine. Since the long-term effects regarding the abuse of said substance are not fully understood, a growing number of studies has emerged as a consequence. Repeated administration of MDMA to non-human animals results in neurotoxic degeneration of serotonergic axon terminals followed by a decrease of 5-HT concentration in brain tissue and this effect persists even after several years [1]. In contrast to animal studies, where structural brain changes have been observed, a number of studies with human subjects associate the regular use of MDMA with an increase in psychopathological symptoms such as anxiety, depression and psychosis as well as with a decrease in cognitive

performance, apparent in executive dysfunction, impulse control disturbance and memory decline [2-4].

In addition to structural brain changes and psychopathological symptoms linked to drug abuse, there might be psychological mechanisms working as an intermediary effect on actual functioning. One such psychological mechanism is the placebo effect. People's expectations concerning the effectiveness of their medication and treatments have a great impact on their actual usefulness [5]. Expectations about one's own cognitive functioning might also influence actual cognitive performance, as has been observed in patients treated for depression. In a different study, negative expectation of subjects' functioning was associated with lower cognitive performance on neuropsychological tests [4,6]. In addition, the awareness of a negative stereotype about a social group in a particular domain produces suboptimal performance by members of this group [7]. The influence of stereotype threat on cognitive performance has been extensively investigated in the past with respect to several stereotypes (e.g., women and math performance). It has been argued that task-related fears might interfere with working memory capacity. Its effective utilization is central for successful performance on complex cognitive tasks, and failures in working memory have been suggested as responsible for performance decrements. In these studies, participants were asked to solve math problems while

keeping a set of words in memory. Later recollection of the words was used as an index of working memory capacity. These studies suggest that stereotype threat can disrupt the ability to maintain proper focus on task-relevant information [8].

The same might be true for ecstasy users. As a result of the wide media coverage of studies purporting to show cognitive deficits in ecstasy users, people belonging to this group might also be affected by stereotype threat. The effect of stereotype threat in ecstasy users has been investigated by comparing users and non-users with respect to working memory capacity, executive functioning and verbal memory capacity after they had been exposed to priming. The priming procedure consisted of exposing the subjects to information about the long-term effects of ecstasy, which either stated that ecstasy does or does not cause memory loss. Users who were informed that MDMA has no detrimental effects on memory performed better on the delayed portion of the prose task of the Rivermead Behavioural Memory Test battery than users having been negatively primed and even non-users [9]. These results suggest that, expectations due to a negative stereotype may have a greater influence on actual verbal memory test performance than the consumption of MDMA itself. The authors suggest that ecstasy users believe what they are told about the detrimental effects of ecstasy use on memory, but do not experience these problems themselves. However, in this study cognitive performance was directly affected by priming. It still remains unclear whether general subjective feelings of decline in physical and psychological well-being attributed to drug consumption have an effect on performance outcomes. Psychological mechanisms like self-evaluative threats might have a direct impact on tests intended to measure cognitive decline in drug users. This would be an important aspect to take into account for further meaningful research in the field of long-term effects of MDMA.

Thus the aim of this study was to assess whether such psychological mechanisms might play a role in mediating the cognitive performance of MDMA users; this was done by looking at the influence of their subjective feelings of cognitive and psychological decline on cognitive performance, especially in people attributing their deterioration to MDMA consumption.

MATERIALS AND METHODS

Participants

The current study is based on data assembled with the help of 96 subjects at baseline (t_0) [age range at t_0 : 18-35 years; mean: 23.42 years; standard deviation (SD): 4.76] in a project with two follow-up measurements (t_1 and t_2). These follow-up measurements occurred one year and two years after the baseline measurement, respectively. Subjects were comprised of new ecstasy users with first but limited experience at t_0 and no current or previous history of neurological or psychiatric disorders (Axes I and II according to DSM-IV criteria). Another exclusion criterion was the ingestion of any other illicit psychotropic substances on more than five occasions before the day of the first examination. This study was part of a bigger longitudinal project investigating the potential long-term effects of consumption in novice MDMA-users. For more detailed information, the researchers kindly refer the reader to the publications of the initial studies [4,10-15].

Materials

The following questionnaires and tests were used to assemble the data that will be incorporated into the present study: First, a structured interview concerning the use of illicit psychotropic substances, gathering information such as the age of first use, number of days since the last use, estimated cumulative lifetime dose (relevant for the present study) as well as the highest dose ever used and the duration of regular use measured in months. Second, a questionnaire containing questions about the subjective evaluation of a possible deterioration with regard to the participants' physical and psychological well-being. Furthermore, this questionnaire assessed the supposed reasons (e.g., MDMA consumption) participants ascribed to their self-perceived decline on a 5-point Likert scale (1 = not likely, 5 = very likely). Third, a comprehensive neuropsychological test battery assessing the function domain episodic memory, frontal executive functioning and attention and information processing speed. The episodic memory was measured using the *Auditiv-verbale Lerntest (AVLT)* and *Lern- und Gedächnistest (LGT)*. The *AVLT* is a German version of the Rey Verbal Learning test (*RAVLT*), and was used in order to assess verbal declarative memory performance by means of the variables, immediate recall, total acquisition performance, delayed recall after interference, loss after interference and recognition after a delay of 30 minutes. A subtest of the *LGT* was used to measure immediate and figural visual recognition. This instrument is a classical paired association-learning task containing 20 different logos, each composed of a central figure and surrounded by a frame. During immediate and delayed assessment the subjects were asked to find the correct frame associated with the central figures. Frontal executive functioning was assessed by means of the digit span test, the Stroop task and the Trail-Making Test. The digit span test is a component of the German version of the Wechsler Intelligence Test (WAIS), the *Hamburger-Wechsler-Intelligenztest für Erwachsene (HAWIE-R)*, which is used for assessing working memory. The subjects listen to a sequence of digits and are asked to recall them immediately in reverse order. The cognitive interference was assessed with a German pencil-and-paper version of the Stroop task. The participants are instructed under different conditions to either read out the names of the colors or the name of the ink in which the name of the colors is presented. The recording times as well as the corrected and uncorrected errors represent relevant criteria. The Trail-Making Test measures mental flexibility and consists of two different parts. In the first part the subjects have to connect, in ascending order, numbers in circles (1-25) on a sheet of paper as quickly as possible. In the second part the subjects are presented with numbers (1-13) and additional letters (A-L), and have to connect the numbers and letters alternately in correct ascending order (i.e., 1-A-2-B-3-C). The response time is recorded during each measurement. Attention and information processing speed are measured by the Digit Symbol Test, the Stroop Task and the Trail-Making Test. The Digit Symbol Test, which is also part of the WAIS, consists of nine digit-symbol pairs. After having acquired these pairs correctly, the subjects have 90 seconds to transform a list of 93 digits as quickly as possible into the associated symbols. The selection of tests is based on the results of previous cross-sectional and longitudinal studies of ecstasy users [4].

Procedure

Preceding the actual experiment, written informed consent was given to all participants. It provided information about the nature of the experiment, i.e. possible long-term effects of ecstasy use. Further it provided information of neurotoxic findings in animal studies by very high doses of MDMA. All of the aforementioned questionnaires, structured interviews and tests were administered at every time measurement point during the longitudinal study. In the present study, participants were subdivided into groups according to their subjective deterioration attributed to MDMA on questionnaire number 2: Subjects with high ratings (≥ 3) on MDMA as reason for their deterioration and low ratings (< 3) on the remaining possible reasons for their deterioration were classified in one group (*MDMA*), while subjects with low ratings on MDMA and high scores on any of the other reasons were placed in the second group (*non-MDMA*). Subjects from each group were paired, when possible, with a match-partner according to their respective amounts of ecstasy consumption, in order to correct for consumption. The resulting variable served as a group factor. When no fitting match-partner could be found, the subject was not included in the analysis. Thus, of the initial 96 subjects by t_0 , 22 remained for the t_1 assessment and 14 subjects for the t_2 follow-up.

Statistical analyses

At first, change scores of the results of the participants' neuropsychological tests of participants included in the analysis were computed by subtracting the scores of t_1 and t_2 from t_0 taking into account performance at baseline level, yielding

variables T_1 and T_2 . Multivariate analyses of variance (MANOVA) were conducted with group factor (*MDMA* vs. *non-MDMA*) and change scores per function domain (episodic memory, frontal executive functioning and information and processing speed) and measurement point (T_1 and T_2) as dependent variables. All analyses were performed with IBM SPSS statistical software program version 21 (Chicago, IL, USA).

RESULTS AND DISCUSSION

Group characteristics

After matching members of each group based on the amount of consumption, 22 participants remained for the group T_1 and 14 participants for the group of T_2 . For each group, gender distribution, mean age, years of education, and mean cumulative use of MDMA as well as the corresponding standard deviations are given in Table (1). The groups did not differ significantly with respect to any of the variables.

Performance effects

The MANOVA addressing episodic memory for T_1 revealed no significant main effect of group (*MDMA* versus *non-MDMA*) ($F_{(9,3)} = 1.00$, $p = .49$, $\chi^2 = .45$). The analyses for T_2 revealed a significant main effect of group ($F_{(9,3)} = 22.83$, $p = .01$, $\chi^2 = .99$). The corresponding tests of between-subject effects revealed significant effects of total acquisition ($F_{(1,11)} = 5.40$, $p = .04$, $\chi^2 = .33$) and recognition performance ($F_{(1,11)} = 7.28$, $p = .02$, $\chi^2 = .40$) of the verbal declarative memory performance test but not for any other variable. Mean test scores for both groups as well as significant levels of the corresponding tests of between-subject

Table 1: Group characteristics.

	Female/Male	Age	Years of education	Cumulative MDMA use*
MDMA	1/6	24.14 (± 2.27)	13.43 (± 1.81)	11.86 (± 21.40)
Non-MDMA	3/4	23.14 (± 5.87)	15.29 (± 1.38)	11.86 (± 21.40)

*at t_2

Abbreviations: MDMA: N-Methyl-3, 4-methylenedioxyamphetamine

Table 2: Mean test change scores - episodic memory.

	MDMA		non-MDMA		p	
	MEAN (SD)		MEAN (SD)			
	T ₁	T ₂	T ₁	T ₂	T ₁	T ₂
AVLT A	0.09 (3.17)	-7.57 (20.70)	-1.18 (3.12)	-1.29 (1.89)	.39	.48
AVLT B	-1.55 (3.53)	-0.57 (2.15)	1.00 (2.53)	2.00 (1.53)	.07	.04*
AVLT C	-0.36 (3.59)	0.71 (2.23)	-0.55 (3.30)	0.86 (2.12)	.61	.90
AVLT D	-1.55 (2.50)	-1.29 (2.87)	0.36 (1.96)	-0.14 (1.21)	.53	.08
AVLT E	0.45 (1.97)	0.57 (1.51)	-4.5 (1.97)	1.57 (2.37)	.20	.02*
AVLT F	0.91 (1.87)	0.14 (0.90)	0.9 (1.87)	-0.43 (1.90)	.49	.19
LGT A	1.18 (2.68)	-1.00 (6.11)	1.55 (5.43)	-2.43 (6.50)	.62	.86
LGT B	0.55 (4.89)	-3.14 (6.01)	-0.36 (5.94)	-2.79 (6.18)	.98	.40

*sig

Abbreviations: MDMA: N-Methyl-3, 4-methylenedioxyamphetamine; SD: standard deviation; T1: follow-up measurement 1; T2: follow-up measurement 2; AVLT: *Auditiv-verbale Lerntest* (a German version of the Rey Verbal Learning test), A: immediate recall, B: total acquisition, C: recall after interference, D: loss after interference, E: recognition performance, F: repetitions required for learning; LGT: *Lern- und Gedächnistest* (figural visual recognition test)

effects are given in Table (2). Additionally, for each group, means and standard deviations of both variables of the AVL T are given in Figure (1). The MANOVA addressing attention and information processing speed for T_1 revealed no significant main effect of group ($F_{(4,16)} = 1.75, p = .19, \chi^2 = .30$). The same was true for T_2 ($F_{(4,8)} = 1.88, p = .20, \chi^2 = .49$). Mean test scores for both groups as well as significant levels of the corresponding tests of between-subject effects are given in Table (3). The MANOVA addressing frontal executive functioning for T_1 revealed no significant main effect of group ($F_{(3,17)} = 1.16, p = .36, \chi^2 = .17$). The same was true for T_2 ($F_{(3,9)} = 2.29, p = .15, \chi^2 = .43$). Mean test scores for both groups as well as significant levels of the corresponding tests of between-subject effects are given in Table (4).

DISCUSSION

The aim of this study was to assess whether psychological mechanisms like self-evaluative threat might play a role in mediating the cognitive performance of ecstasy users. This was done by looking at the influence of their subjective feelings of cognitive and psychological decline on cognitive performance, especially in people attributing their deterioration to MDMA consumption. Therefore, subjects were categorized by their subjective deterioration attributed either to MDMA or to other reasons. After matching all participants according to their respective amounts of ecstasy consumption, 22 of the initial 96 subjects remained for the first follow-up assessment and 14

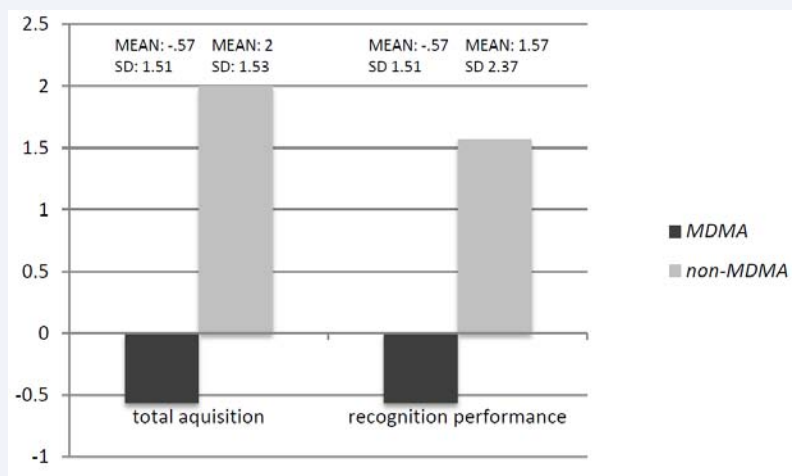


Figure 1 Means and standard deviations of significant AVL T change scores (T_2).

MDMA: subjects with high ratings on ecstasy as reason for their deterioration and low ratings on the remaining reasons, non-MDMA: subjects with low ratings on ecstasy and high scores on any of the other reasons.

Table 3: Mean test change scores - attention and information processing speed.

	MDMA		non-MDMA		<i>p</i>	
	MEAN (SD)		MEAN (SD)			
	T ₁	T ₂	T ₁	T ₂	T ₁	T ₂
Trail A	4.94 (7.10)	3.50 (5.52)	7.41 (8.91)	3.60 (10.38)	.33	0.16
Stroop A	9.25 (9.65)	7.39 (4.95)	1.98 (5.25)	.31 (4.20)	.07	.01*
Stroop B	7.88 (11.49)	1.58 (12.66)	5.78 (8.51)	5.53 (6.82)	.74	.28
DS Test	68.18 (11.47)	-13.57 (18.20)	67.91 (15.35)	7.57 (14.06)	.87	.42

*sig
Abbreviations: MDMA: N-Methyl-3, 4-methylenedioxyamphetamine; SD: standard deviation; T1: follow-up measurement 1; T2: follow-up measurement 2; TRAIL: Trail-Making Test; STROOP: Stroop Test; DS Test: Digit Symbol Test

Table 4: Mean test change scores - frontal executive functioning.

	MDMA		non-MDMA		<i>p</i>	
	MEAN (SD)		MEAN (SD)			
	T ₁	T ₂	T ₁	T ₂	T ₁	T ₂
Stroop C	12.57 (15.16)	10.10 (21.60)	9.21 (13.14)	14.83 (22.12)	.51	.53
DS back	-0.45 (3.62)	-0.43 (2.76)	2.00 (2.41)	0.14 (3.02)	.09	.72
Trail B	18.50 (15.88)	26.49 (24.33)	15.91 (24.76)	7.97 (34.92)	.88	.20

Abbreviations: MDMA: N-Methyl-3, 4-methylenedioxyamphetamine; SD: standard deviation; T1: follow-up measurement 1; T2: follow-up measurement 2; STROOP: Stroop Test; DS Test: Digit Symbol Test; TRAIL: Trail-Making Test

subjects for the second follow-up. Both groups were compared by their performance on cognitive tests originally intended to measure cognitive performance in MDMA users across the domains, episodic memory, information and processing speed, as well as frontal executive functioning. The groups did not differ with respect to the domains, frontal executive functioning and information and processing speed. However, significant group differences were found at the second measurement point for the domain of episodic memory especially regarding total acquisition and recognition performance of the verbal declarative memory performance test, but not for any other variable. Subjects not ascribing their subjective decline to MDMA performed better on these two tests compared to subjects ascribing their subjective decline to the use of the drug. Thus, negative effects of self-evaluation were not confirmed either for information and processing speed or for frontal executive functioning, but seemed to affect episodic memory performance of the participants ascribing their decline to MDMA consumption.

Effects of self-evaluative threat (e.g., stereotype threat) on memory performance have been described previously [8]. Particular verbal memory seems to be susceptible to task-related anxiety and worries, which interfere with phonological aspects of working memory and is therefore susceptible to negative performance expectations [7]. This is in line with the study where priming of a stereotype (MDMA causes memory loss vs. MDMA causes no memory loss) affected verbal memory performance of ecstasy users but not working memory and executive functioning performance [9]. The current findings support this theory and provide an alternative explanation for memory deficits observed in a number of studies concerning the long-term effects of MDMA. The present study is based on a longitudinal study which showed no difference on the AVL T test between ecstasy users and non-users [4]. In the present study, participants showed differences on the AVL T test according to their self-attributed reasons for deterioration. While some studies have found decreases in memory performance in ecstasy users, other studies could not confirm these results [16]. Cognitively more complex memory tasks (e.g., the California Verbal Learning Test (CVLT), which is similar to the AVL T) seem to increase the likelihood of potential ecstasy-related behavioral deficits in long-term verbal memory [17]. On the other hand, highly complex tasks require more working memory capacity and are therefore more susceptible to task-irrelevant aspects like performance worries [8]. Inconsistencies in results may arise because performance expectations have a greater influence on actual verbal memory test performance than the impact of MDMA itself. Therefore, studies on performance decrements of ecstasy users relative to non-users should be interpreted carefully.

The relation between ecstasy use and memory deficits is widely reported in the media, creating a stereotype with respect to ecstasy users. In the study by [9], ecstasy users believed what they were told about detrimental effects of ecstasy use on memory (priming), but did not experience these problems themselves. The awareness of a negative stereotype might not be enough to evoke negative performance expectations. Therefore, the present study

compared subjects according to their subjective self-evaluations of experiencing detriments and according to their reasons for deterioration. Self-reported problems attributed to ecstasy seem to reflect actual decline in well-being. As has been shown, subjects who perceived themselves as problematic ecstasy users indeed showed evidence of a range of symptoms. The same was true for subjects defining themselves as non-problematic, who showed no symptoms [18]. In the present study, both groups experienced cognitive and psychological decline and therefore might both suffer from fears. Nevertheless, participants attributing their decline to reasons other than MDMA showed better verbal memory performances on the AVL T. Since all participants were aware, due to informed consent, that the study was aimed at testing potential long-term effects of drug consumption, subjects attributing their deterioration to MDMA consumption may suffer from worries concerning their performance. On the other hand, subjects not attributing their deteriorations to MDMA use may not suffer from fears and subsequently perform better. This modulation effect has been observed in cannabis users. While men performed worse on a memory task under negative stereotype priming, female users were not affected and performed even better than female users who were not primed at all. The authors suggest that this surprising gender effect originates in differences in identification with the stereotype invented by priming procedure. Since men seem to identify more with the stereotype of a typical cannabis user, they may be more susceptible to the negative impact of stereotype threat. Women not identifying with the stereotype of a cannabis-user might experience stereotype lift and consequently improve their performance. Therefore stereotype threat might even work in opposite ways: the awareness of a negative stereotype, while not identifying with it, may lead the subject to extra task involvement and thus to higher performance [16]. Furthermore, a fMRI study showed altered brain activation during semantic processing in ecstasy users relative to non-users, but they performed equivalently on cognitive performance tests. The authors concluded that ecstasy users might rely on compensatory mechanisms establishing the same cognitive performance as non-users [19]. In this case, drug-related decrements due to MDMA consumption would not be reflected in cognitive test performance. Thus, differences in cognitive performance may account for more variability within the group of ecstasy users than between ecstasy users and non-users.

As a consequence, it is suggested that future research concerning potential long-term effects of MDMA on cognitive performance should strive to minimize the possible influence of negative expectations on test scores. How could this be accomplished? First of all, subjects should preferably remain naïve to the purpose of the study in which they are participating. However, concerning research on illicit substances, this may be impossible to achieve, since participants recruited for their experience with certain drugs will probably realize the connection between their substance use and the types of cognitive performance tests conducted. In this case, a number of interventions aimed at reducing stereotype threat might prove more useful. For example, the negative effects of stereotype threat

on performance in a math task could be completely reversed by having subjects perform a brief mindfulness exercise. According to the authors, mindfulness can be utilized to alleviate working-memory load, thereby freeing up the very resource drained by anxiety resulting from stereotype threat [20]. Another study suggests that priming positive feelings about him/ herself might be equally beneficial with respect to decreasing the impact of stereotype threat. Women who were primed to feel powerful did not show reductions in working memory capacity or math performance in response to threatening stereotypes [21]. Hence, implementing a short mindfulness exercise or priming a positive self-image before taking cognitive tests may increase the accuracy of results in studies on MDMA and cognitive performance.

Although the results of the current study partly support previous findings concerning the impact of negative expectation on verbal memory performance, it should be noted that the number of participants in this study was quite small. Of the original 96 subjects, only 22 participants remained for the first follow-up and 14 for the second follow-up measurement. The small number of participants resulted in a weak power of the study. In order to obtain more meaningful results, it is therefore advisable to conduct a study with more subjects. Furthermore, this study had no experimental design; subjects were selected by their subjective feelings of physical and psychological decline, and groups were formed based on their ratings on proposed reasons. Therefore, the present findings should be interpreted carefully, and causal relationships between verbal memory performance and negative expectations should be pondered critically. Another limitation of the present study is that the drug history of the participants was based on their self-reported consumption behavior. The reliability of such statements should be considered carefully.

CONCLUSION

Despite these methodological problems, there is growing evidence that observed memory deficits in MDMA research cannot be attributed with certainty to direct effects of the drug alone. In conclusion, researchers are advised to take precautionary steps to alleviate the influence of negative expectations on cognitive test results and to be cautious about presenting their findings to the media. Otherwise, the public stereotype about the detrimental effects of ecstasy use might be aggravated, thus further interfering with effective research on the potential long-term effects of MDMA.

CONFLICT OF INTEREST

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