Apparent Transient Effects of Recent ''Ecstasy'' Use on Cognitive Performance and Extrapyramidal Signs in Human Subjects

Ryan M. Smith, BA, Madalina Tivarus, PhD, Heather L. Campbell, BS, Ashleigh Hillier, PhD, and David Q. Beversdorf, MD

Objectives: Our purpose is to investigate cognitive performance and extrapyramidal function early after ecstasy use.

Background: Ecstasy, containing 3,4 methylenedioxymethamphetamine, has shown evidence of causing cognitive deficits and parkinsonian signs. Previous research has examined cognitive performance after a period of prolonged abstinence, but research assessing the early effects of ecstasy after recent use is limited despite temporal neurochemical differences demonstrated in nonhuman models.

Methods: This study compared task performance between 13 ecstasy users (10 to 15 h postdrug use) and a control group on a battery of neuropsychologic assessments while matching for education level, sleep deprivation, and premorbid IQ. The groups were also compared on measures relating to parkinsonian signs.

Results: The ecstasy subjects showed impairments on measures of executive function as evaluated by Raven's Standard Progressive Matrices (SPM) and the Wisconsin Card Sorting Task (WCST). Short-delay free recall memory was also impaired in ecstasy subjects on the California Verbal Learning Test (CVLT-II). No extrapyramidal motor impairments were detected.

Conclusions: These deficits resemble deficits previously reported in chronic ecstasy use but also seem to reveal transient impairments in executive function. Future research is needed to better understand the neurologic and neuropsychologic implications of ecstasy use across time and extent of use.

Key Words: ecstasy, MDMA, cognition, executive function, frontal lobe, memory

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The street drug ''ecstasy'' has become a popular drug for a select group of users, such as those who attend all night dance parties known as ''raves.'' An estimated 4.5% of twelfth graders used ecstasy in 2003, with 8.3% of twelfth graders using it at some point during their lifetime.[1] The principal active substance in ecstasy, 3,4 methylenedioxymethamphetamine (MDMA), is a structured amphetamine with stimulant and hallucinogenic properties that has both reported negative consequences and positive reinforcing effects related to its use.[2,3] Previous research has examined the effects of MDMA on humans, with most research attributing observed changes to the long-term effects the drug has on cognitive performance or physiologic effects in the brain. However, the transient effects the drug has on cognitive performance are relatively unknown despite evidence showing temporal variation in neurochemical changes observed in animal studies.[3] Therefore, the time course of the effects attributed to MDMA in humans must be better understood.

To date, research examining the transient effects of ecstasy or MDMA on cognition is limited to a few studies. Curran and Travill,[4] and Parrot and Lasky[5] studied the effects attributed to apparent MDMA use in subjects who self-administered ecstasy. Kuypers and Ramaekers[6] experimentally administered MDMA. All of these studies examined aspects of verbal memory and subjective effects of the drug, whereas 2 of them also examined aspects of working memory.[4,6] On-drug examinations revealed a significant effect on verbal memory in 2 of the studies, with MDMA users performing significantly worse than control subjects on recall tasks.[5,6] Subsequent immediate recall memory impairments were found by Parrot and Lasky[5] 2 and 7 days postdrug use, while Curran and Travill[4] reported a trend toward poorer overall performance on measures of immediate recall in the days after ecstasy use when compared with controls. Kuypers and Ramaekers[6] did not find subsequent verbal memory impairments 24.5 to 25.5 hours after MDMA administration despite impairments at an earlier time after use. These studies also demonstrated lower mood, greater fatigue, or greater depression in the days after MDMA consumption. Impairments in working memory were limited to a single study which showed that ecstasy users performed worse the day after drug use, although the precise period of abstention from the drug is not clear.[4] It was noted, however, that this finding may be attributable to lack of sleep in ecstasy users. Also, the findings by Curran and Travill,[4] and Parrot and Lasky[5]

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From the Department of Neurology, The Ohio State University, 1654 Upham Drive, Rm. 461, Columbus, OH.
Reprints: David Q. Beversdorf, MD, Department of Neurology, The Ohio State University, 1654 Upham Drive, Rm. 461, Columbus, OH 43210 (e-mail: david.beversdorf@osumc.edu).

may be influenced by polydrug use and therefore may not be completely attributable to MDMA.

In studies of long-term cognitive effects, abstinent ecstasy users have most consistently displayed verbal memory impairments, measured by a variety of tests.[7–11] Examinations of spatial memory have yielded less consistent results.[3,8,10,12,13] There are also conflicting reports of memory function in longitudinal studies of memory performance.[14,15] Zakzanis and Young[14] found a decline in the memory ability of MDMA users after a year of continued use when compared with an initial baseline measure. In contrast, Gouzoulis-Mayfrank et al[15] later showed that continued use of ecstasy over an 18-month period did not result in progressive deterioration of memory, but also showed that abstinence over this period did not improve memory function. Long-term cognitive effects in humans may also include deficits on tasks which assess executive function.[7–9,12,16–18] However, these findings are not consistent across studies, and the period of minimum abstinence within each study differs, ranging from 3 to 14 days. Aside from the working memory studies described above,[4,6] other aspects of executive function have not been examined early after use. Furthermore, research has shown that abstinent, modest ecstasy users with minimal exposure to other drugs displayed no significant differences when compared with nonusers on multiple measures of cognitive performance.[19]

Many studies have examined long-lasting physiologic effects of MDMA, often focusing on serotonergic functioning. However, there is limited information on the transient effects of MDMA on physiologic functioning in humans. The use of ecstasy is associated with "midweek lows" regarding mood, proposed to be caused by the serotonin depletion associated with taking ecstasy several days earlier.[4,5,13] Imaging evidence of this serotonergic decrease in humans has been presented,[20–24] with greater susceptibility shown in female users,[21,24] but confounding variables exist, most notably polydrug use.[25] The persistence of this depletion was recently examined in humans using positron emission tomography and the findings suggest that serotonin transporter availability and duration of abstention from MDMA is positively correlated, indicating that recovery of serotonergic function may be possible with abstinence.[21] Research examining other aspects of physiologic functioning have reported that frontal lobe metabolites are decreased in ecstasy users, most notably *N*-Acetylaspartate, which reflects a nonspecific neuronal loss or dysfunction of neurons in this region.[26,27]

Studies examining the transient physiologic effects of MDMA in animal models are more abundant. In rats, desensitization of the α_2-adrenoreceptors occurs for up to 18 hours after repeated treatments of MDMA; returning to baseline measures 8 days afterward, possibly due to increased extracellular noradrenaline after acute MDMA administration.[28] Other alterations to the adrenergic system include decreased firing rates in the noradrenergic neurons in the locus coeruleus (LC) of rats after acute MDMA administration.[29] The LC is thought to be a mediator of the shifting of behavioral strategies; an aspect of cognition often attributed to the frontal lobe.[30] Observed serotonergic changes include biphasic serotonergic loss, beginning with a sharp decline of serotonin 3 to 6 hours postdrug administration followed by prolific recovery 6 to 24 hours postdrug administration then a gradual decline again 1 to 7 days postdrug administration.[31] Animal data suggests that this second phase of serotonergic decrease is due to the decline of tryptophan hydroxylase (TPH) which begins within 15 minutes of administration[32] and can last up to 2 weeks.[33] Animal studies have also linked serotonergic function and the hippocampus and memory.[34–36]

Furthermore, parkinsonian signs in ecstasy users have been reported in individual case studies,[37–39] and now retracted research findings once implicated MDMA as a possible cause of long-term dopaminergic damage.[40,41] Little quantifiable evidence has been presented for groups of ecstasy users in light of the case studies. This lack of evidence is reflected in Colado et al[42] where it is asserted that the human data is insufficient to suggest dopaminergic damage, and that previously reported damage is more likely the result of methamphetamine use, as seen in animal research.[43] Therefore, our study wished to separately address this question by introducing quantifiable clinical measures of parkinsonian signs. Our examination includes eye blink rate, as it has been noted that low eye blink rate is an early symptom of Parkinson disease (PD),[44–47] and a standardized test used for diagnosing PD as well as assessing for bradyphrenia on the neuropsychologic tests.

Farré et al[48] has demonstrated that, in humans, most subjective and peripheral physiologic changes due to acute MDMA administration begin to diminish 1 to 2 hours postdrug administration, with no significant effects observed after 8 hours. Therefore, we wished to examine whether there are transient effects of ecstasy that differ from the already reported long-term effects of ecstasy, which become evident in the immediate hours after physiologic or subjective effects of the drug have ceased. Our pilot study will attempt to address the transient effects of recent ecstasy consumption using a neuropsychologic evaluation with particular attention to executive function. In light of previous research described above, on the basis of the results of this study, follow-up studies can examine how such impairments might evolve over time after use, which has not been examined in this manner. Our hypothesis is that we would see impairments on tasks which assess frontal lobe function due to observed transient effects on adrenergic functioning seen in animals, deficits on most aspects of a verbal memory task, particularly immediate recall, and little to no evidence of parkinsonian signs for ecstasy users early postuse when compared with drug naive participants.

MATERIAL AND METHODS

Twenty-six total subjects (13 ecstasy users, 13 control subjects) were recruited through fliers posted on Ohio State University's campus and through social

websites that are frequented by ecstasy users. Nonusers were recruited concurrently through identical means. The 13 ecstasy subjects had used the drug 10 to 15 hours before testing assessed by self-report, whereas the 13 control subjects were drug naive for ecstasy. These groups were matched on multiple demographics (Table 1) from a self report questionnaire given when the subjects came in for testing, attempting to better control extraneous variables that might affect performance on tasks. To control for the lack of sleep seen in ecstasy users, testing for control subjects was performed early in the morning after nights in which participants planned to stay up late. There were no refusals to participate upon requesting the early morning arrival of control participants and no subjects were excluded for matching purposes. The questionnaire also assessed whether the subject had taken any other drugs, including alcohol, the night before testing. None of the participants in either group had any self-reported history of medical, psychiatric, or neurologic diseases, or any known history of learning disabilities and none were taking medication for treatment of those conditions. Formal toxicology and psychiatric screening were not performed in this pilot study. Performance tests were given by multiple members of the research team, including a PhD psychologist (A.H.) and research assistants (R.M.S., M.T., H.L.C.) who were instructed in administration of these tests. The standardized test for rating parkinsonian signs was administered by a board-certified neurologist (D.Q.B.). This study was done in accordance with the Institutional Review Board of The Ohio State University.

Performance Tasks

Premorbid IQ

The National Adult Reading Test (NART)[49] was used for subject matching purposes. This task has been demonstrated to be a reliable measure of premorbid IQ.[50]

TABLE 1. Demographics and Comparisons: Mean (St Dev)

	Controls	Ecstasy Users	*F* (1,24)	*P*
n	13	13	—	—
Age (mo)	242.5 (15.1)	257.1 (24.7)	3.33	0.080
Age range (mo)	221-275	230-305	—	—
Men/women	9/4	9/4	—	—
Education (y)	13.9 (1.0)	13.8 (1.3)	0.00	1.000
IQ (assessed by NART)	108.6 (5.2)	110.5 (4.7)	1.06	0.314
Sleep night before (h)	3.9 (1.1)	3.5 (1.6)	0.71	0.407
Drugs used night before				
Alcohol (no. users)	3	5	—	—
No. drinks	2.0 (4.3)	2.31 (4.4)	0.032	0.859
Marijuana (no. users)	—	6	—	—
Prescription pain medication (no. users)	—	4	—	—
Cocaine (no. users)	—	3	—	—
Ecstasy usage			Range	
Duration of use (mo)	—	30.9 (20.5)	1-60	—
Lifetime dose (pills)	—	42.8 (57.8)	1-200	—
Uses in last 6 mo	—	3.3 (2.6)	1-9	—
Last used (h)	—	11.3 (3.3)	10-15	—
Amount last used (pills)	—	1.3 (0.5)	1-2	—

Executive Function

To examine executive function, the Wisconsin Card Sorting Task (WCST)[51,52] required subjects to sort stimuli cards possessing unique attributes in relation to keycards with distinct attributes, and maintain or shift those sorting strategies depending on feedback from the examiner. Variables that were measured for analysis included total trials to complete the tasks, total errors, perseverative responses and errors, nonperseverative responses and errors, and the learning-to-learn score.

To assess spatial problem solving, subjects were also given the Raven's Standard Progressive Matrices (SPM) sets C, D, and E[53] which required participants to complete diagrammatic puzzles using specific implicit rules by choosing the correct matching pattern from provided options.[54] The number of correct responses was recorded for analysis.

To examine flexibility of access to the semantic network in problem solving, the Anagram Task[55] was also performed. This task required subjects to unscramble sets of 5 and 7 letters to make a word. Once the subjects had either written the correct response or their time limit of 120 seconds had expired, the time was recorded (120 s was recorded if no response was given) and they were immediately moved to the next set of letters. Correct responses and total time were recorded for analysis. As with previous research, the natural log of the recorded time for each anagram, summed, was also included.[55]

To test attention and response inhibition, subjects were given the color-word portion of the Stroop test.[56] Subjects were tested on a single card that required them to name the color of the ink the word is printed in and to disregard the verbal content of the word, as they conflicted. Total errors and total time to complete the task were measured for analysis.

To examine verbal fluency, also referable to frontal lobe function, the Controlled Oral Word Association (COWA) task[57] was performed. In this task the letters F, A, and S were used and subjects were instructed to produce as many words as possible beginning with the target letter within 1 minute for each letter. Once subjects were finished with 1 letter, they were prompted with the next letter. Total words produced and for the overall task were recorded for analysis.

Memory

Verbal memory was assessed using the standard version of the California Verbal Learning Test—Second Edition (CVLT-II).[58] Participants' ability to remember a list of target words and retain the target words in the presence of retroactive interference and temporal delays was measured to assess different aspects of memory. The measures recorded for analysis included the number of correct responses on short and long-delay free recall, short and long-delay cued recall, long-delay recognition, and long-delay forced-choice recognition. Other variables

recorded for analysis included the number of intrusions, characterized by the errant recall of words due to retroactive interference, and the number of repetitions of target words.

Spatial memory was assessed by the Rey-Osterrieth Complex Figure Test (CFT) Form A.[59,60] Subjects were first asked to copy the complex figure, then they were assessed on their ability to recall the figure from memory after a 30 minute delay. Variables included scores on a 36 point scale,[61] which assesses the participants' ability to copy the complex figure, and total time to complete the task.

Extrapyramidal Function

To determine the clinical relevance of any potential dopaminergic impairments after recent use, subjects were assessed with the motor portion (Part III) of the Unified Parkinson Disease Rating Scale (UPDRS).[62] This test consists of measurements of motor function that are commonly impaired in patients with PD, including tremors and rigidity as well as decreased speech volume and facial expression, and postural abnormalities.

As a second measure of possible parkinsonian signs, eye-blink rates were measured by the experimenter. Subjects were asked to "look at a cross" that was placed 2.5 ft from the subject for a total of 3 minutes and eye blinks were counted over this time span. Subjects were told that facial movements were being recorded by the experimenter. The cross was 9.5×9.5 cm, derived from Deuschl and Goddemeier.[47]

As an additional index of parkinsonian signs, comparisons were also made for all timed cognitive tasks described above to determine whether bradyphrenia is present in ecstasy users.

A 1-way analysis of variance (ANOVA) was conducted between the ecstasy group and the control group to compare performance on the neuropsychologic tests. For significant results, an analysis of covariance (ANCOVA) was conducted covarying for the age difference observed between our 2 groups. Sleep, recent alcohol use, and marijuana use were also included, as performance on cognitive tasks are known to be affected by these variables.[63–66] Marijuana use was included as a binomial covariate, determined by whether marijuana was reported as used the night before testing. All model assumptions for this analysis were satisfied. Pearson's correlation coefficient was used to determine whether total lifetime ecstasy dosage related to task performance.

RESULTS

Demographics

No significant group differences were observed for education level, premorbid IQ, or sleep as shown in Table 1, and a trend toward an age difference was found [242.5 ± 15.1 and 257.1 ± 24.7 mo ($P = 0.080$) for control and ecstasy users, respectively]. Other drug consumption the night before testing, including alcohol, is also displayed in Table 1.

Performance on Tasks

The results of our findings are summarized in Table 2.

Executive Function

On executive function tasks, ecstasy users performed significantly worse on multiple measures of the WCST, as determined by our initial ANOVA, including the amount and percentage of nonperseverative errors made and their learning-to-learn score, whereas total trials and total errors each approached significance as trends. After our ANCOVA, total trials and total errors did reach significance, whereas the learning-to-learn measure no longer reached significance. On the SPM task, ecstasy users performed significantly worse on the most difficult sets of the task. In a combined analysis of sets D and E, ecstasy users' total scores were significantly lower than those of control subjects (both groups scored near ceiling on set C). This finding was unaffected by our ANCOVA. This demonstrates that multiple measures of executive function were impaired in the recent ecstasy use subjects; however, our examination of anagram performance and word fluency revealed no significant group difference. A trend was actually detected, in the initial ANOVA, toward ecstasy users making fewer errors on the Stroop task for attention and response inhibition; however, this finding did not remain a trend after covarying for the aforementioned variables.

Memory

Upon examining memory we did find impairments on one measure of the CVLT-II, with ecstasy users performing worse on the short-delay free recall portion of the test. This finding was not affected by our ANCOVA. However, there was no significant difference between groups in any other aspect of the CVLT-II or in spatial memory.

Extrapyramidal Function

In our examination of extrapyramidal function, no significant differences were found between groups for eye blink rate or for any measure included in the UPDRS. The only points scored on the UPDRS in either group resulted from individual variability in the presence of postural tremors. There was also no suggestion of bradyphrenia, as no significant differences existed for any of the timed cognitive tasks described above.

Correlation of lifetime ecstasy doses used with task performance using Pearson's correlation coefficient revealed no significant results.

DISCUSSION

Our hypothesis of frontal lobe effects early after ecstasy use was, in part, supported by our findings. We did see impairments in some tests of executive function, although the tasks affected in our findings are not completely attributable to the frontal lobe, but to more global dysfunction.[67] However, contrary to our expectations, we found only minimal memory impairments. We

TABLE 2. Task Data: Mean (St Dev) and ANCOVA for Age, Sleep, and Acute Alcohol And Marijuana Use for Significant Results

Test	Control	Ecstasy Users	*F* (1,24)	*P*	ANCOVA *P*
Frontal lobe function					
Wisconsin Card Sorting Task (WCST)					
Total trials	79.2 (9.1)	86.9 (11.2)	3.71	0.066	0.042
Total errors	12.2 (5.7)	16.3 (6.2)	3.14	0.089	0.023
Perseverative responses	10.9 (5.6)	10.8 (2.2)	0.002	0.964	—
Perseverative errors	7.9 (4.4)	7.8 (2.0)	0.01	0.910	—
Nonperseverative errors	4.1 (3.0)	8.5 (5.3)	7.06	0.014	0.001
Learning-to-learn score	0.09 (1.4)	− 1.50 (1.7)	6.45	0.018	0.571
Raven's Standard Progressive Matrices (SPM)					
Total correct (C + D + E)	28.3 (2.8)	26.4 (3.5)	2.33	0.140	—
Total correct (D + E)	18.2 (1.8)	16.2 (2.4)	5.75	0.025	0.045
Anagrams					
Total correct	15.8 (2.7)	16.3 (3.1)	0.22	0.641	—
Total time	622.7 (318.5)	566.0 (378.8)	0.17	0.683	—
Σ [LN (anagram trial times)]	50.8 (9.8)	47.0 (13.9)	0.64	0.433	—
Controlled Oral Word Association (COWA)					
Total words generated	36.0 (8.8)	42.2 (9.8)	2.91	0.101	—
Stroop*					
Errors	0.45 (0.52)	0.18 (0.40)	3.33	0.080	0.169
Time (s)	21.8 (3.9)	23.2 (4.7)	0.69	0.416	—
Memory					
California Verbal Learning Test (CVLT-II)					
Total trial 1 correct	6.5 (1.9)	6.5 (1.5)	0.01	0.909	—
Total trial 1 to 5 correct	52.8 (7.2)	50.1 (10.4)	0.59	0.449	—
Total list B correct	6.9 (2.0)	6.2 (1.5)	1.21	0.283	—
Total list B plus trial 1 correct	13.4 (3.3)	12.7 (2.8)	0.33	0.572	—
Short-delay free recall correct	11.8 (1.7)	9.9 (1.6)	8.48	0.008	0.009
Short-delay cued recall correct	12.9 (2.0)	12.2 (1.2)	1.43	0.244	—
Long-delay free recall correct	12.1 (2.3)	11.6 (1.9)	0.31	0.581	—
Long-delay cued recall correct	13.2 (1.9)	12.2 (1.4)	1.96	0.175	—
Total intrusions	1.8 (1.9)	3.3 (3.9)	1.63	0.214	—
Total repetitions	3.3 (3.4)	4.9 (4.0)	1.24	0.277	—
Long-delay recognition hits	16.2 (3.3)	15.2 (1.2)	0.91	0.350	—
Long-delay false positives	1.3 (2.7)	0.7 (0.9)	0.61	0.444	—
Rey-Osterrieth Complex Figure Test (CFT)					
Copy (total score)	34.5 (1.6)	34.7 (1.4)	0.16	0.693	—
30-min delay (total score)	22.8 (3.7)	21.8 (5.1)	0.33	0.569	—
Parkinsonian assessments†					
Unified Parkinson's Disease Rating Scale (UPDRS)					
Total motor score	0.1 (0.3)	0.5 (0.9)	1.53	0.230	—
Postural tremors	0.1 (0.3)	0.5 (0.9)	1.53	0.230	—
Eye blink rate					
Blinks/min	17.9 (15.1)	13.2 (8.5)	0.88	0.359	—

*For each group n = 12; *F* (1.22).
†For control n = 10, ecstasy n = 13; *F* (1.21).

also found no evidence of parkinsonian signs for our battery of tests.

Of the previous studies examining transient effects of MDMA, only 2 of them explored executive function, both using working memory tasks.[4,6] Only one of those studies, the study by Curran and Travill,[4] showed an overall group effect between ecstasy users and nonusers over repeated testing sessions, but a significant impairment on the working memory task was only seen the day after use. In our study, recent ecstasy users exhibited deficits on multiple measures of executive function. Our findings revealed impairments related to learning in the WCST and the SPM. However, impairments in the measures of executive function most associated with frontal lobe function, perseverative errors on the WCST, were not found in our examination. The nonperseverative errors found in our study are not specific to frontal lobe function.[67] The ecstasy group's lack of impairment on the Stroop task may suggest that the executive function impairments are not secondary to attentional dysfunction, because attention can be a performance-limiting factor on measures related to executive function. The trend toward fewer errors we observed for the ecstasy group on the Stroop raises the possibility that the results might have been impacted by matching issues between groups, but this difference in the Stroop was not significant after ANCOVA.

Transient executive function impairments could be attributed to a number of interacting factors. Our findings on the WCST showed that ecstasy users had significantly more nonperseverative and total errors, while taking

more trials to complete the task. We speculate that these results might be explained by findings related to the noradrenergic system. High tonic adrenergic levels in the LC may be induced by a combination of the direct effect of MDMA,[68] serotonergic influence,[69] and α_2-adrenoreceptor desensitization.[28] This high tonic level, paired with typical phasic responses observed in reaction to novel stimuli, presumably the case with set-shifting on the WCST, may produce a low signal-to-noise ratio, which is expected to reduce attentional selectivity to allow greater behavioral responsiveness.[30] We speculate that this ratio led to the high level of nonperseverative errors, while sparing perseverative errors. The high tonic level would facilitate the subjects in responding to the novel stimuli, by changing their answer (ie, not perseverate), but would consequently hinder their ability to discriminate appropriately to find the correct answer by reducing the impact of phasic responses. This would contrast to low tonic adrenergic levels, which would reduce responsiveness to the novel stimuli, resulting in perseverative errors on the WCST. Although speculative, we believe that this is an area worthy of future investigation. Other possible contributors include changes in serotonergic functioning, most notably decreased TPH activity[32] superimposed on the decreased frontal metabolite ratios described above in ecstasy users.[26,27]

An impairment on the CVLT-II was expected, as 2 of the previous studies examining transient cognitive effects showed deficits on measures of verbal memory, particularly immediate recall.[4,5] However, most of the measures in our study did not reveal a difference. Serotonin has been related to the hippocampus and memory function in animal studies.[34–36] As mood and serotonergic loss may also be related,[5,9,11] the psychologic changes, such as depression, that peak around 2 days postuse[4,5] could imply that memory impairments become more evident later after use as well, coinciding with transient serotonergic loss presumably caused by TPH inhibition.[32] The study examining transient cognitive effects that did not find verbal memory to be significantly impaired examined memory function 25.5 to 26 hours post-MDMA administration.[6] As they discussed, the time window in which they conducted their cognitive tests may account for their lack of findings, considering animal models show prolific recovery of 5-HT within the first 24 hours postdrug administration. Our ecstasy group also characterizes usage in the low-to-moderate range, supporting longitudinal evidence that moderate users of ecstasy may not show the serotonergic loss[15] and subsequent memory impairments[14,15] associated with heavier use.

Our examination of extrapyramidal function found no significant impairment. This is in agreement with animal data that shows that the concentration of dopamine-related metabolites returns to baseline levels a few hours after administration of MDMA, with the most prolonged effects being seen in the uptake of dopamine in the synaptosomes returning to baseline 24 hours later.[70] This also supports the assertion by Colado et al[42] that damage to dopaminergic neurons due to ecstasy in the human brain is not compelling.

There are some major limitations to the current study. Owing to the nature of street-type ecstasy, one cannot be sure of the quality or quantity of the MDMA consumed when consumption is measured by self-report. It has also been shown that many pills are adulterated[71–74]; therefore, the effects shown in ecstasy users cannot be completely attributed to MDMA. Because of this, our study explicitly uses the term ecstasy when referring to our findings. Also, polydrug use is common among ecstasy users, significantly compromising ability to find matched controls. This is a potentially significant confound to our current pilot study given that nearly half of our ecstasy users had used marijuana the night before and studies have shown that concurrent marijuana use may contribute to some of the deficits seen in the ecstasy literature.[64,66] We did try to match the 2 groups, however, for alcohol use, and sleep as these may affect our results.[63,65] Also, as the ecstasy users examined in this study have, on average, less exposure to ecstasy than what is typically found in the literature, this could explain why performance on these tasks were not correlated with lifetime exposure. We also cannot rule out the possibility that the deficits found existed before exposure to ecstasy. Furthermore, given the nature of this small study, it is possible that other cognitive performance effects may not have been detected.

The findings of our neuropsychologic assessment of ecstasy users the morning after use suggest that further study on the impact of ecstasy at different time periods after use is warranted. We were able to only detect isolated short-delay free recall memory impairments but also found multiple executive function deficits early in the "hangover" period suggesting that transient cognitive performance deficits may exist. Additional research needs to follow-up these pilot findings with repeated testing, using tests with versions that can be given during multiple sessions over time, within subject, beginning with the acute phase and extending out through more chronic abstinence to obtain a more complete picture of the transient cognitive effects this drug has on humans. Furthermore, such follow-up studies should attend to variables such as acute polydrug use and lifetime drug history and the quantity of actual MDMA used. Recent findings highlighting physiologic sex differences[21] suggest another important area of future consideration in follow-up studies on this topic. Later studies will need to address these differences with sample sizes that will produce adequate power for such additional comparisons. On the basis of our findings, in the context of other related research, we propose that testing moderate ecstasy users in such a manner will reveal greater transient deficits in executive function measures early (0 to 24 h) in abstinence, whereas transient memory deficits will become more salient later in abstinence (48 to 96 h) with most functions returning toward baseline levels 1 to 2 weeks after last use. Differentiating transient effects of ecstasy from long-lasting impairments is an important distinction when attempting to determine the ramifications of using MDMA.

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