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Residual Neurocognitive Features of Long-Term Ecstasy Users With Minimal Exposure to Other Drugs

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Abstract

Aims—In field studies assessing cognitive function in illicit ecstasy users, there are several frequent confounding factors that might plausibly bias the findings toward an overestimate of ecstasy-induced neurocognitive toxicity. We designed an investigation seeking to minimize these possible sources of bias.

Design—We compared illicit ecstasy users and non-users while 1) excluding individuals with significant lifetime exposure to other illicit drugs or alcohol; 2) requiring that all participants be members of the "rave" subculture; and 3) testing all participants with breath, urine, and hair samples at the time of evaluation to exclude possible surreptitious substance use. We compared groups with adjustment for age, gender, race/ethnicity, family-of-origin variables, and childhood history of conduct disorder and attention deficit hyperactivity disorder. We provide significance levels without correction for multiple comparisons.

Setting—Field study.

Participants—Fifty-two illicit ecstasy users and 59 non-users, age 18-45.

Measurements—Battery of 15 neuropsychological tests tapping a range of cognitive functions.

Findings—We found little evidence of decreased cognitive performance in ecstasy users, save for poorer strategic-self-regulation, possibly reflecting increased impulsivity. However this finding might have reflected a premorbid attribute of ecstasy users, rather than a residual neurotoxic effect of the drug.

Conclusions—In a study designed to minimize limitations found in many prior investigations, we failed to demonstrate marked residual cognitive effects in ecstasy users. This finding contrasts with many previous findings—including our own—and emphasizes the need for continued caution in interpreting field studies of cognitive function in illicit ecstasy users.

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Keywords

ecstasy; MDMA; substance abuse; cognitive function; neurotoxicity

INTRODUCTION

"Ecstasy," as used below, refers to illicit ±3,4-methylenedioxymethamphetamine (MDMA), with the recognition that actual "street" preparations may be adulterated or even contain no MDMA at all (1). Ecstasy has been used by some 12 million individuals in the United States alone and millions more worldwide (2-5). An extensive animal literature suggests that ecstasy can be neurotoxic, especially to the 5-HT system, with consequent possible effects on cognitive performance (6-9)—, but it is unclear whether these findings can be fully extrapolated to humans (10). To address this question, numerous naturalistic studies have assessed cognitive function in illicit ecstasy users. These studies, reviewed in several recent papers , generally suggest that illicit ecstasy users display negative residual effects on various cognitive measures, with the most consistent and robust finding being lowered verbal memory (3,11-13). Such findings are of concern not only with regard to illicit ecstasy use, but for recent studies proposing therapeutic applications for MDMA, such as in treatment of posttraumatic stress disorder (14).

However, as we (15) and others (3,10,16,17) have discussed, such naturalistic studies are vulnerable to methodological limitations, many of which might plausibly bias findings towards an overestimate of differences between ecstasy users and non-users. First, comparison non-users in many studies were not *members of the "rave" subculture.* Thus, unlike ecstasy users, they lacked repeated exposure to sleep and fluid deprivation from all-night dancing—factors that themselves can produce long-lasting cognitive effects (18). Second, few studies screened participants for MDMA, other illicit drugs, and alcohol on the day of testing—leaving open the possibility of surreptitious recent drug use. Third, ecstasy users in virtually all studies reported extensive lifetime use of *other drugs*, including cannabis, amphetamine, other hallucinogens, and cocaine—which might themselves contribute neurotoxicity. Studies have typically addressed this issue by statistically adjusting for other drug use or by matching groups for non-ecstasy drug use—but such methods are likely imperfect.

Fourth, cognitive difficulties in ecstasy users might be attributable to *premorbid attributes* rather than ecstasy exposure. For example, users might be less intelligent or more impulsive than non-users even before using ecstasy—possibilities that can be explored, but never eliminated, in cross-sectional studies.

To address these problems, we performed a 2004 pilot study (15) assessing cognitive function in 23 ecstasy users and 16 non-users, all reporting minimal exposure to other illicit drugs or alcohol and all reporting a history of all-night dancing. We tested all participants for alcohol and illicit drugs, including MDMA, at the time of testing, and excluded positive cases. We then compared cognitive test results in non-users vs. "moderate" users (reporting 22-50 lifetime episodes of use) vs. "heavy" users (60-450 episodes) while adjusting for numerous potentially confounding attributes, including age; gender; family-of-origin attributes; estimated verbal IQ; and Beck Depression Inventory (BDI) scores. Moderate users exhibited virtually no significant differences vs. non-users, but heavy users differed significantly from non-users on several measures, involving mental processing speed, strategic self-regulation, and executive functioning. These findings seemed unlikely to represent an artifact of the methodological limitations enumerated above, since each had

been addressed in the study design. We than sought to replicate the findings in a similar larger investigation, reported here.

MATERIALS AND METHODS

Participants

Case finders in Salt Lake City, Utah advertised for study participants at raves and other sites frequented by the local all-night dance subculture. Potential participants were screened by telephone for lifetime use of ecstasy and other drugs, together with the other inclusion and exclusion criteria described below. The telephone-screening instrument intentionally included irrelevant questions (e.g., questions about tobacco and caffeine consumption) to reduce the chances that individuals might guess the study criteria and then misrepresent their histories simply to gain entrance into the study.

We recruited participants aged 18-45 years who reported 1) at least 17 lifetime episodes of ecstasy use or 2) no lifetime ecstasy use. These participants represented a fresh sample, not including any participants from the prior pilot study (15). Participants in both groups were required to be native speakers of English and to report experience in the rave culture, as demonstrated by having attended at least 10 all-night dance parties, defined as staying awake until at least 4:30 AM. We excluded participants reporting: 1) more than 100 lifetime episodes of using cannabis, or more than 10 episodes of using any other class of illicit drugs other than ecstasy (cocaine, stimulants, opioids, hallucinogens, sedative-hypnotics, gamma hydroxybutyrate, phencyclidine, ketamine, or hydrocarbon inhalants); 2) more than 50 lifetime episodes of alcohol intoxication, defined as consuming, at least 4 drinks (defined as 12 ounces of beer, 4 ounces of wine, or 1.5 ounces of distilled spirits) within a 4-hour period; 3) history of head injury with loss of consciousness judged clinically significant, or history of other medical illnesses that might affect cognitive function; or 4) current use of psychoactive medications, such as antidepressants or benzodiazepines. Our criteria for maximum lifetime episodes of alcohol and illicit drug use were chosen, based on practical experience from our pilot study (15), to exclude non-ecstasy drug use as much as possible without being so strict that we would excessivelyreduce the participant pool. Note that participants reporting psychiatric disorders were not excluded, since some psychiatric syndromes might plausibly be caused by ecstasy use, and exclusion of such cases might bias the sample of ecstasy users. Individuals rejected on telephone screen were not told the reasons for rejection, to minimize the possibility that others might deduce the study criteria and then misrepresent their histories to gain entry to the study.

Baseline Evaluation

Individuals qualifying on telephone screen were scheduled for an in-person baseline evaluation in Salt Lake City by a study psychiatrist. Upon arriving for this evaluation, participants were first requested to sign informed consent for the study, which was approved by the McLean Hospital Institutional Review Board. We then administered instruments similar to those used in our pilot study (15), including demographic questions; a semi-structured interview assessing lifetime episodes of use of alcohol and other drug use, plus a detailed history of episodes, doses, and settings of lifetime ecstasy use; lifetime history of psychiatric disorders as determined by the Structured Clinical Interview for DSM-IV (SCID) (19); the 21-item Hamilton Rating Scale for depression (20); the Hamilton Rating Scale for Anxiety (21); and the Symptom Checklist-90 (22). The baseline evaluation also covered other attributes potentially associated with premorbid cognitive function, including 1) history of childhood conduct disorder, assessed using questions covering the 15 DSM-IV criterion items for conduct disorder (23); 2) childhood attention deficit hyperactivity disorder (ADHD), assessed via the Wender Utah Rating Scale (24) and a modified ADHD

rating scale (25); and 3) family history of substance abuse or other psychiatric disorders, assessed as in our previous studies of cannabis users (26). These measures were not grounds for excluding participants, but were used as adjustment variables in the regression analyses (see below). The baseline evaluation also included a brief neurological examination to exclude marked neurological abnormalities.

Neuropsychological Testing Visit

Participants meeting all criteria at baseline were scheduled to return at a later date (usually within 4 weeks) for neuropsychological testing. All participants were required to abstain from ecstasy, other illicit drugs, or all-night parties for at least 10 days prior to testing. The 10-day minimum criterion was based on practical experience from our pilot study (15).

Upon arriving for testing, all participants were administered a breathalyzer test for alcohol (Alco-Sensor IV, Intoximeters, Inc., St. Louis, MO) and provided a urine sample for an immediate dipstick test for tetrahydrocannabinol, opioids, cocaine metabolites, barbiturates, amphetamines, benzodiazepines, and phencyclidine (Triage Drugs of Abuse Panel, Biosite, San Diego, CA). Participants failing these tests were excluded.

A second aliquot of urine was preserved to be sent to an outside laboratory (Quest Diagnostics, Teterboro, NJ) to test for MDMA. In addition, we obtained a hair sample from the participant's head (or lacking adequate head hair, from the axilla) to be analyzed by Psychemedics Corporation (Culver City, CA) for drug residues, including MDMA, from the past 90 days. For 10 mg of hair, the sensitivity thresholds were: cocaine, 5 ng; opiates, 2 ng; phencyclidine, 3 ng; amphetamines 5 ng; and marijuana, 0.01 ng. Specificity of hair analyses was very high, with false-positive readings expected in less than 0.1% of cases (Schaffer, M, personal communication, September, 2010). If a participant's urine returned positive for MDMA, or hair returned positive for any drug that the participant had denied, that participant's results were discarded from analysis.

We then administered a battery of 15 neuropsychological tests: the subtests of 1) Vocabulary, 2) Digit Span, 3) Digit Symbol, and 4) Block Design from the Wechsler Adult Intelligence Scale, Revised (WAIS-R) (27); 5) the Rey-Osterreith Complex Figure Test (28); 6) the Wisconsin Card Sorting Test (29); 7) Trail Making Tests A and B from the Reitan Battery (30); 8) Raven's Progressive Matrices (31); 9) the Benton Controlled Verbal Fluency Task (often called the "FAS" test) (32); 10) the Stroop Test (33); 11) the California Verbal Learning Test, Second Edition (34); 12) Logical Memory, Verbal Paired Associates, and Spatial Span from the Wechsler Memory Scale, Third Edition (35); 13) the Revised Strategy Applications Test (RSAT) (36); 14) a computerized version of the Iowa Gambling Task (37); and 15) the Grooved Pegboard (Purdue Pegboard) Test (38). Participants also completed the Beck Depression Inventory (BDI) (39) to assess current depressive symptoms.

Participants received $100 for completing the baseline evaluation, another $100 for completing the neuropsychological tests, and an additional $150 via mail upon confirmation of appropriate urinary MDMA and hair testing results.

Statistical Analyses

Using the same definitions as our pilot study (15), we divided the ecstasy users into "moderate" users reporting 17-50 lifetime episodes of using ecstasy and "heavy" users reporting more than 50 lifetime episodes. We then performed 2 analyses, the first comparing all ecstasy users with non-users, and the second comparing the subgroups of moderate users and heavy users with non-users. All comparisons used linear regression adjusting for age; gender; race/ethnicity; 4 family-of-origin variables (mother's plus father's level of

education, parents' income when the participant was growing up, family history of psychiatric disorder, and family history of substance use disorders, modeled as previously (15)); history of childhood conduct disorder (modeled as presence versus absence of the diagnosis by DSM-IV criteria); and childhood ADHD (modeled as a continuous variable representing the score on the modified ADHD rating scale, as in our previous studies (26)).We would note in passing that although we adjusted for this entire range of variables, not all differed significantly between groups (see Table 1 below).

Finally, in our comparisons of the heavy users versus non-users, we calculated the maximum effect sizes that we could exclude at the 0.05 level of significance, using a test for non-equivalence, based on the 90% confidence intervals of our measured effect sizes (40,41). This test generates a measure of effect size such that there is less than 5% probability that the true difference between groups exceeds this magnitude.

We fitted all models using Stata 9.2 software, with alpha set at 0.05, 2-tailed. Although our multiple comparisons increased the likelihood of type I errors, there was no good way to correct for this, since methods such as Bonferroni correction are too conservative and inflate type II error rates (42). Hence, following the advice of some prior authorities (43,44), we present results without correction, but caution readers to consider this issue when interpreting the findings.

RESULTS

Of about 1500 potential participants screened by telephone, only about 250 qualified for the baseline evaluation, of whom only 116 met all criteria and completed neuropsychological testing. Of these, 5 were rejected for drugs subsequently found in hair or urine analyses, leaving 111 evaluable participants, comprising 52 ecstasy users and 59 non-users. Given the difficulty in recruiting fully qualifying participants, we slightly relaxed our criteria for 6 individuals near the end of the project: 2 reported lifetime cocaine use 15 and 20 times, respectively; 3 reported use of other hallucinogens 11, 14, and 22 times; and one reported cannabis 250 times.

The 52 ecstasy users and 59 non-users appeared similar on many measures, but users were more frequently non-white, reported lower levels of parental education, and showed lower vocabulary scores (Table 1). Among ecstasy users, the shortest time from last ecstasy use to cognitive testing was 25 days, with only 3 (6%) participants below 40 days. The subgroups of 22 heavy and 30 moderate ecstasy users showed no significant differences ($p > 0.05$) on any variable in Table 1 save for lifetime episodes of ecstasy use (by definition), lifetime raves (median [interquartile range]: 150 [70, 238] versus 56 [35, 107]; P = 0.004), and Hamilton Depression Scale scores (6.5 [2.5, 10.25] versus 2 [0, 6]; P = 0.02). Comparing the overall group of users with non-users on the entire range of neuropsychological tests, we found few differences reaching statistical significance (Table 2). Comparing "moderate" and "heavy" user subgroups with non-users, we again failed to find significant differences on most outcome variables (Table 3). Performance on the Raven's Progressive Matrices, WAIS-R Digit-Symbol Subtest, and WCST total categories was significantly reduced only among moderate users, but not heavy users. Heavy users were significantly slower than non-users when using the non-dominant hand on the grooved pegboard, but we found no comparable differences with the dominant hand. Perhaps most notably, the proportion of "brief" items on the RSAT, which represents the primary outcome variable on this test (36), was strikingly and significantly lower in heavy users--and this difference remained virtually unchanged when we adjusted further for verbal IQ and current BDI scores. Also, within the overall group of ecstasy users, the proportion of brief items was significantly associated with lifetime episodes of use (coefficient [95% confidence interval]: −1.4 [−2.3, −0.4]; P = 0.004

using log-transformed values for lifetime ecstasy episodes, and with adjustment for age, gender, and race/ethnicity). Inspection of a scatter plot (Figure 1) indicated that this association was not driven by outliers. We also repeated all of the comparisons in Tables 2 and 3, first using a simplified model adjusting only for age, gender, and race/ethnicity; and second with exclusion of the 6 individuals who slightly exceeded our criteria for other drug use. Both exercises yielded differences and significance levels very similar to those of the primary analysis.

Finally, looking at cognitive tests where we failed to show significant differences between heavy users and non-users, we assessed the magnitude of the differences between these groups that we could *exclude* at the 0.05 level of probability, as explained above. We found that we could exclude even a medium effect (Cohen's $d \geq 0.5$) on many cognitive measures and could exclude a large effect (Cohen's $d \geq 0.8$) on all of the measures selected (Table 4).

DISCUSSION

We assessed neurocognitive performance in 52 ecstasy users and 59 closely matched non-users in a study designed to minimize potentially confounding variables. Specifically, we chose participants reporting minimal use of drugs other than ecstasy, and we excluded all participants showing undisclosed alcohol or drug use on breath, urine, and hair analyses. We also required that participants in both groups be members of the all-night-dancing subculture. Finally, we adjusted for numerous potentially confounding variables. Using this rigorous approach, we found few consistent differences between ecstasy users and non-users on wide-ranging measures of verbal and visuospatial memory, verbal fluency, attention, processing speed, manipulative dexterity, and executive cortical functions. Ecstasy users exhibited lower vocabulary scores than non-users, but this finding likely indicates differences in premorbid ability rather than neurotoxicity of ecstasy since vocabulary is generally preserved even after neurological insults (26,45,46). Indeed, assuming that these differences in premorbid verbal ability are valid, the absence of significant differences on most other tests, including tests of verbal memory, becomes even more striking. Although we found a few other significant differences between the overall groups of users and non-users, these differences proved to be concentrated primarily in moderate users, rather than heavy users—suggesting that they were unlikely due to neurotoxicity of ecstasy. More likely, such differences represent chance associations—a phenomenon to be fully expected, given that we performed multiple comparisons without formal statistical correction. Exploratory analyses suggest that even the more robust difference on the grooved pegboard with the non-dominant hand in heavy users (Table 3) was likely due to chance. Overall, differences between non-users and heavy users were sufficiently modest on most cognitive measures that we could exclude a large effect of ecstasy ($d \geq 0.8$) at the 0.05 level.

Our only consistently significant finding was that heavy users exhibited a lower proportion of "brief" items on the RSAT, suggesting poorer strategic self-regulation and hence perhaps greater reflection impulsivity (i.e., insufficient information-gathering before launching into the task). Notably, many prior studies have suggested associations between ecstasy use and increased impulsivity (13)—but it must be cautioned that these observed associations are complex and inconsistent (11,13,47,48), perhaps in part because impulsivity is multifactorial (49,50). Indeed, one recent study paradoxically found reflection impulsivity reduced in ecstasy users (51). Furthermore, neither our study nor other cross-sectional studies establishes that greater impulsivity is necessarily caused by ecstasy. Some prospective data suggest that impulsivity may be an effect, rather than a cause, of ecstasy use (52), whereas other studies (53,54) favor the hypothesis that, impulsivity is a risk factor for substance abuse (for review, see (50)).

Our largely negative findings appear inconsistent with many past studies as well as some more recent investigations (55-57) that report lowered cognitive functions in ecstasy users. Indeed, our findings are inconsistent with several findings in our own pilot study (15)—possibly because heavy users in the earlier study were tested after briefer median abstinence (59.5 vs. 121 days), possibly because of differences in unmeasured confounders, or possibly because of chance alone. Conversely, our present findings appear congruent with several other recent studies suggesting that cognitive effects of ecstasy use are modest (16,58) and perhaps mediated or confounded by trait impulsiveness (47), comorbid substance use (48), and sleep deprivation (48,59)—although this last possibility remains uncertain (60).

Recent longitudinal studies of ecstasy users have also produced somewhat inconsistent findings. For example one study analyzed 118 individuals, all ecstasy-naïve at baseline, of whom 58 subsequently used ecstasy and 60 remained ecstasy-naïve (61). The groups showed no differences on any cognitive measures at baseline, but at follow-up, ecstasy initiators displayed significantly lower scores than still-naïve individuals on verbal memory, though not other cognitive tests. However, ecstasy initiators had consumed a median of only 1.5 lifetime tablets at follow-up—raising possible doubt about the causal role of ecstasy. By contrast, another group (62) examined memory performance in 38 ecstasy users longitudinally over 18 months. Those who stopped ecstasy following baseline examination (n=17) did not improve, and those who continued ecstasy (n=21) did not deteriorate in performance—thus questioning a causal connection between cumulative ecstasy exposure and cognitive effects.

Recent reviews of cognitive performance in ecstasy users have acknowledged these inconsistencies. One meta-analysis of 26 studies found a substantial association between ecstasy use and lowered verbal memory but noted that the lifetime number of ecstasy tablets consumed did not predict memory performance (63). Another recent meta-analysis concluded that ecstasy was associated with lowered cognitive performance but found only small to medium effect sizes (12). Other recent reviews have concluded that ecstasy-associated cognitive effects are likely modest or subtle (11,13) and have noted that confounding effects of premorbid traits and other illict drug use cannot be excluded (11). Another recent review, enumerating many of the methodological concerns raised in our own discussion above, emphasizes the hazards of concluding that ecstasy plays a causal role in observed cognitive findings and speculates that the matter will likely remain controversial (3).

In short, our findings combine with many of the above reports to dictate continued caution in ascribing neuropsychological deficits to ecstasy exposure. On the one hand, it is possible that ecstasy indeed causes residual cognitive neurotoxicity, albeit perhaps only in individuals with high-level exposure (56), or with possible co-factors predisposing them to ecstasy-induced neurotoxicity (47). If so, we might have failed to detect a difference when a true difference exists, perhaps because we evaluated only 6 participants with very high ecstasy exposure (≥ 150 lifetime episodes) or perhaps because our population included few individuals with vulnerability-inducing co-factors.

On the other hand, our findings might not represent false-negative results, but might instead correctly reflect that illicit ecstasy use, by itself, does not generally produce lasting residual neurotoxicity. In support of this possibility, it should be noted that we took unusual care to minimize common methodological factors that might possibly bias results away from the null, as discussed above. Therefore it is plausible that the positive results in some prior studies were attributable to these confounding factors, and that our present negative results are valid and reflect lower levels of confounding. Whatever the case, our findings indicate that the neurotoxicity of human ecstasy use remains incompletely resolved.

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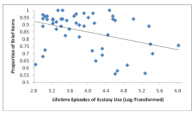

Figure 1.
Scatterplot showing the association of log-transformed lifetime episodes of ecstasy use with the proportion of Brief items chosen on the Revised Strategy Applications Test. Pearson's $r = -0.37$.

Table 1

Demographic Features of Non-Users vs. Users of Ecstasy

	Non-Users (N = 59)		Users (N = 52)		
Demographic Feature	**Number**	**%**	**Number**	**%**	**P Value** [a]
Sex, male	38	64.4	30	57.7	0.56
Ethnicity, white	54	91.5	40	76.9	0.04
Father's education, high school or less	16	27.1	28	53.9	0.006
Mother's education, high school or less	16	27.1	32	61.5	< 0.001
Parents' household income ≤ $30,000	16	27.1	16	30.8	0.68
Family history of subtance abuse[b]	22	37.9	26	50.0	0.25
Family history of psychiatric disorder[b]	18	31.0	20	38.5	0.43
Current major depressive disorder	4	6.8	3	5.8	1.0
Current anxiety disorder[c]	9	15.3	5	9.6	0.41
	Median	**Interquartile range**	**Median**	**Interquartile Range**	
Age	24	21, 27	22	19.3, 24.8	0.06
Lifetime episodes of ecstasy use	0	0	43.5	27, 87.3	<0.001
Days since last ecstasy use when tested	.	.	121	60, 209	.
Lifetime all-night "raves"	45	25, 90	98	45, 200	0.005
Lifetime alcohol intoxications	10	0, 24.3	10	2.3, 27.5	0.31
Lifetime marijuana intoxications	1	0, 6	10	4, 30	<0.001
Cigarattes smoked per day	0	0, 0	0	0, 0.3	0.04
Hamilton Depression Scale score[d]	2	0, 6	4	0.25, 8	0.15
Hamilton Anxiety Scale score[d]	2	0, 5	3	0, 6	0.24
Beck Depression Inventory score[d]	2.5	1, 7	1	0, 5	0.10
Wender Utah Rating Scale score	12	8, 24	13	5, 25	0.72
ADHD Rating Scale score (see text)	7	3, 13	9	2, 15	0.50

[a] Two-tailed significance of difference between groups by Fisher's exact test for proportions and the Wilcoxon rank sum test for continuous variables.

[b] At least one first-degree relative reported to display symptoms judged likely to meet DSM-IV criteria for a substance abuse disorder or another Axis I disorder, respectively; note that N = 58 for non-users because one non-user was raised in foster environment.

[c] Panic disorder, agoraphobia, social phobia, simple phobia, obsessive compulsive disorder, or posttraumatic stress disorder

[d] Note that the two Hamilton scales were administered at screen; the Beck Depression Inventory was administered at the time of neuropsychological testing.

Table 2

Representative Neuropsychological Test Scores in Non-users vs. Users of Ecstasy

Measure	Mean Scores (SD)		Comparison Between Groups		
	Non-Users (N=59)	Users (N = 52)	Estimated Mean Difference[a]	95% Confidence Interval	P Value[b]
Wechsler Memory Scale - III:					
Logical memory - immediate recall	49.2 (9.7)	46.6 (11.6)	0.7	−3.6, 5.0	0.75
Logical memory - delayed recall	31.1 (7.2)	29.4 (8.0)	0.7	−2.4, 3.8	0.65
Verbal paired associations- immediate	22.4 (7.8)	21.6 (8.7)	1.3	−2.0, 4.6	0.44
Verbal paired associations- delayed	6.8 (1.8)	6.8 (1.8)	0.1	−0.7, 0.8	0.90
Spatial span - forward	9.7 (1.8)	9.0 (1.9)	0.8	0.0, 1.6	0.04
Spatial span - backward	9.2 (1.6)	8.8 (1.7)	0.4	−0.3, 1.2	0.22
Spatial span - total	18.9 (2.9)	17.7 (3.2)	1.3	0.0, 2.6	0.06
Stroop test:					
Color reading time (sec)	57.1 (10.0)	56.3 (8.7)	−0.1	−4.2, 3.9	0.94
Color reading errors	0.9 (1.1)	1.0 (1.0)	−0.1	−0.5, 0.4	0.79
Word reading time (sec)	45.0 (7.4)	44.1 (7.2)	0.5	−2.6, 3.5	0.77
Word reading errors	0.9 (1.2)	0.6 (0.8)	0.2	−0.3, 0.6	0.43
Interference time (sec)	103.5 (18.8)	100.1 (16.5)	2.7	−4.9, 10.3	0.48
Interference time errors	2.3 (2.4)	3.4 (3.5)	−0.7	−1.9, 0.6	0.28
Ravens Progressive Matrices- Total Score	52.7 (5.0)	49.8 (5.9)	2.2	0.0, 4.3	0.05
Trails:					
Trails A time (sec)	26.0 (9.5)	24.0 (5.6)	2.3	−1.1, 5.7	0.18
Trails A errors	0.1 (0.3)	0.1 (0.3)	0.0	−0.1, 0.2	0.71
Trails B time (sec)	55.4 (15.5)	56.0 (15.5)	−1.2	−7.6, 5.1	0.70
Trails B errors	0.3 (0.6)	0.3 (0.6)	0.0	−0.3, 0.2	0.87
Rey-Osterreith Figure:					
Copy (number of elements)	32.9 (2.8)	33.2 (2.4)	−0.4	−1.5, 0.7	0.44
Immediate recall (number of elements)	21.8 (6.4)	21.3 (6.4)	0.6	−2.1, 3.3	0.66
Delayed recall (number of elements)	21.5 (6.0)	20.7 (6.4)	0.8	−1.8, 3.4	0.55
FAS Test:					

Measure	Mean Scores (SD)		Comparison Between Groups		
	Non-Users (N=59)	Users (N = 52)	Estimated Mean Difference[a]	95% Confidence Interval	P Value[b]
Total words	42.1 (12.0)	38.1 (9.4)	2.9	−1.5, 7.3	0.19
Total perseverations	0.6 (0.9)	0.4 (0.6)	0.2	−0.1, 0.5	0.28
Revised Strategy Applications Test:					
Proportion of Brief items in Total2 (%)	88.5 (8.8)	85.6 (12.9)	2.2	−2.3, 6.7	0.35
Number of Action Slips[c,d]	0.4 (0.6)	0.8 (1.1)	−0.1	−0.4, 0.3	0.62
California Verbal Learning Test:					
Level of recall - trial 1	8.1 (2.3)	8.2 (2.8)	−0.3	−1.3, 0.8	0.60
Level of recall - trial 5	14.4 (1.5)	14.1 (1.9)	0.0	−0.7, 0.6	0.91
Level of recall - trials 1-5 total	61.6 (8.3)	60.6 (10.3)	−0.5	−4.2, 3.2	0.79
Level of recall - trial B	8.1 (2.8)	7.9 (2.6)	0.2	−0.9, 1.2	0.78
Wechsler Adult Intelligence Scale-Revised:					
Vocabulary	52.9 (8.4)	45.8 (11.2)	4.7	1.1, 8.4	0.01
Block design	39.8 (8.8)	36.9 (7.9)	2.3	−1.3, 5.8	0.21
Digit-symbol	72.7 (14.6)	64.5 (13.6)	7.1	1.0, 13.2	0.02
Digits forwards	9.4 (2.1)	9.3 (2.6)	0.2	−0.9, 1.2	0.77
Digits backwards	8.0 (2.3)	7.2 (2.0)	0.9	0.0, 1.9	0.05
Verbal IQ	108.4 (16.5)	99.3 (13.3)	6.0	−0.2, 12.2	0.06
Grooved pegboard:					
Dominant hand (time in seconds)	63.9 (7.1)	65.2 (8.6)	−1.6	−4.8, 1.6	0.33
Non-dominant hand (seconds)	67.2 (7.6)	72.4 (12.4)	−5.0	−9.3, −0.7	0.02
Iowa Gambling Task[e]	28.4 (32.0)	19.5 (32.0)	8.1	−5.7, 22.0	0.25
Wisconsin Card Sorting Test:					
Total categories (decks 1 + 2)	8.9 (1.5)	8.4 (1.8)	0.5	−0.2, 1.2	0.16
Total perseverations (decks 1 + 2)[d]	2.8 (0.9)	3.0 (1.2)	−0.2	−0.6, 0.2	0.44

[a] Represents nonusers minus users.

[b] By linear regression with adjustment for age, gender, race/ethnicity, parents' level of education, parents' income, family history of substance abuse or psychiatric disorder, childhood attention deficit disorder, and childhood conduct disorder (see text).

[c] Number of proscribed items performed (large items or items on pages with faces)

[d] Square-root transformed values due to skewed distribution.

[e] Score represents the number of cards chosen from safe decks, minus the number from risky decks, in 100 successive cards.

Table 3

Representative Neuropsychological Test Scores in Non-users vs. Moderate Users vs. Heavy Users of Ecstasy

		Mean Scores (SD)		Non-users vs Moderate Users			Non-users vs Heavy Users		
	Non-Users (N=59)	Moderate Users (N = 30)	Heavy Users (N = 22)	Estimated Mean Difference[a]	95% Confidence Interval	P Value[b]	Estimated Mean Difference[a]	95% Confidence Interval	P Value[b]
Wechsler Memory Scale - III:									
Logical memory - immediate recall	49.2 (9.7)	45.9 (11.2)	47.6 (12.4)	2.1	−2.8, 7.1	0.39	1.6	−4.1, 7.2	0.58
Logical memory - delayed recall	31.1 (7.2)	29.4 (7.9)	29.8 (8.2)	1.3 −2.2,	4.8	0.46	−0.2	−4.3, 3.8	0.92
Verbal paired associations - immediate	22.4 (7.8)	22.2 (9.5)	20.7 (7.7)	1.0	−2.8, 4.8	0.60	1.8	−2.6, 6.1	0.43
Verbal paired associations - delayed	6.8 (1.8)	6.8 (2.2)	7.0 (1.3)	0.2	−0.6, 1.1	0.62	−0.2	−1.2, 0.8	0.67
Spatial span - forward	9.7 (1.8)	8.9 (2.2)	9.1 (1.6)	0.9	0.0, 1.8	0.04	0.7	−0.3, 1.7	0.18
Spatial span - backward	9.2 (1.6)	8.9 (1.2)	8.5 (2.2)	0.2	−0.6, 1.0	0.61	0.8	−0.1, 1.7	0.09
Spatial span - total	18.9 (2.9)	17.8 (3.0)	17.6 (3.5)	1.1	−0.4, 2.6	0.14	1.5	−0.2, 3.2	0.09
Stroop Test:									
Color reading time (sec)	57.1 (10.0)	55.8 (9.5)	57.0 (7.5)	0.4	−4.2, 5.0	0.87	−1.0	−6.2, 4.3	0.72
Color reading errors	0.9 (1.1)	0.9 (0.9)	1.2 (1.1)	0.0	−0.5, 0.5	1.0	−0.2	−0.7, 0.4	0.61
Word reading time (sec)	45.0 (7.4)	43.9 (7.5)	44.6 (6.8)	0.7	−2.9, 4.2	0.71	0.2	−3.9, 4.2	0.94
Word reading errors	0.9 (1.2)	0.5 (0.7)	0.9 (0.9)	0.3	−0.2, 0.8	0.18	−0.1	−0.6, 0.5	0.80
Interference time (sec)	103.5 (18.8)	97.2 (15.8)	104.1 (16.8)	5.6	−3.0, 14.2	0.20	−1.8	−11.6, 8.1	0.72
Interference reading errors	2.3 (2.4)	3.2 (3.4)	3.6 (3.7)	−0.5	−1.9, 1.0	0.51	−1.0	−2.7, 0.6	0.22
Ravens Progressive Matrices- Total Score	52.7 (5.0)	49.1 (5.5)	50.8 (6.5)	3.0	0.5, 5.4	0.02	1.0	−1.8, 3.8	0.47
Trails:									
Trails A time (sec)	26.0 (9.5)	23.4 (5.7)	24.5 (5.5)	2.8	−1.1, 6.7	0.16	1.5	−2.9, 6.0	0.50
Trails A errors	0.1 (0.3)	0.1 (0.3)	0.1 (0.4)	0.0	−0.1, 0.2	0.65	0.0	−0.2, 0.2	0.91
Trails B time (sec)	55.4 (15.5)	54.4 (15.8)	58.1 (15.3)	0.6	−6.7, 7.8	0.88	−4.0	−12.3, 4.3	0.34
Trails B errors	0.3 (0.6)	0.4 (0.7)	0.2 (0.4)	−0.1	−0.4, 0.2	0.53	0.1	−0.2, 0.4	0.59
Rey-Osterreith Figure:									
Copy (number of elements)	32.9 (2.8)	33.2 (2.4)	33.2 (2.4)	−0.5	−1.7, 0.8	0.46	−0.4	−1.7, 1.0	0.62
Immediate recall (number of elements)	21.8 (6.4)	21.0 (5.9)	21.7 (7.2)	0.9	−2.2, 4.0	0.46	0.2	−3.4, 3.7	0.93
Delayed recall (number of elements)	21.5 (6.0)	20.4 (6.3)	21.3 (6.7)	1.7	−1.9, 4.2	0.46	0.2	−3.2, 3.7	0.90
FAS Test:									

		Mean Scores (SD)		Non-users vs Moderate Users			Non-users vs Heavy Users		
	Non-Users (N=59)	Moderate Users (N = 30)	Heavy Users (N = 22)	Estimated Mean Difference[a]	95% Confidence Interval	P Value[b]	Estimated Mean Difference[a]	95% Confidence Interval	P Value[b]
Total words	42.1 (12.0)	37.2 (8.3)	39.4 (10.8)	3.3	−1.7, 8.4	0.19	2.2	−3.6, 8.0	0.45
Total perseverations	0.6 (0.9)	0.3 (0.5)	0.5 (0.6)	0.2	−0.2, 0.6	0.28	0.1	−0.3, 0.6	0.51
Revised Strategy Applications Test:									
Proportion of Brief items in Total2 (%)	88.5 (8.7)	90.0 (9.0)	79.5 (15.0)	−2.1	−7.0, 2.8	0.40	8.7	3.1, 14.4	0.003
Number of Action Slips[c,d]	0.4 (0.6)	0.8 (1.0)	0.8 (1.2)	−0.1	−0.5, 0.3	0.61	−0.1	−0.5, 0.4	0.79
California Verbal Learning Test:									
Level of recall - trial 1	8.1 (2.3)	8.0 (3.1)	8.3 (2.3)	0.1	−1.2, 1.1	0.93	−0.6	−2.0, 0.7	0.37
Level of recall - trial 5	14.4 (1.5)	14.2 (1.8)	14.0 (2.0)	0.0	−0.8, 0.8	0.98	−0.1	−1.0, 0.8	0.85
Level of recall - trials 1-5 total	61.6 (8.3)	60.6 (10.5)	60.5 (10.2)	0.0	−4.2, 4.2	0.99	−1.3	−6.1, 3.6	0.60
Level of recall - trial B	8.1 (2.8)	8.2 (2.8)	7.4 (2.3)	−0.1	−1.3, 1.2	0.89	0.5	−0.9, 2.0	0.47
Wechsler Adult Intelligence Scale-Revised:									
Vocabulary	52.9 (8.4)	45.9 (11.4)	45.5 (11.1)	4.6	0.4, 8.8	0.03	5.0	0.2, 9.8	0.04
Block design	39.8 (8.8)	37.1 (7.8)	36.6 (8.3)	1.9	−2.1, 6.0	0.34	2.8	−1.9, 7.4	0.24
Digit-symbol	72.7 (14.6)	63.3 (12.2)	66.2 (15.4)	8.4	1.4, 15.3	0.02	5.2	−2.8, 13.1	0.20
Digits forwards	9.4 (2.1)	9.5 (2.7)	9.0 (2.6)	0.0	−1.2, 1.2	0.99	0.4	−1.0, 1.7	0.58
Digits backwards	8.0 (2.3)	7.2 (2.2)	7.3 (1.8)	1.0	−0.1, 2.0	0.07	0.9	−0.3, 2.1	0.15
Grooved Pegboard:									
Dominant hand (time in seconds)	63.9 (7.1)	64.3 (7.9)	66.4 (9.5)	−0.8	−4.5, 2.9	0.66	−2.8	−7.0, 1.5	0.20
Non-dominant hand (seconds)	67.2 (7.6)	70.0 (12.1)	75.6 (12.4)	−2.8	−7.7, 2.0	0.25	−8.4	−13.9, −2.8	0.003
Iowa Gambling Task[e]	28.4 (32.0)	18.0 (31.1)	21.7 (31.8)	10.2	−5.9, 26.2	0.21	5.2	−12.9, 23.3	0.57
Wisconsin Card Sorting Test:									
Total categories (decks 1 + 2)	8.9 (1.5)	8.1 (2.0)	8.9 (1.3)	0.9	0.1, 1.7	0.03	0.0	−0.9, 0.8	0.95
Total perseverations (decks 1 + 2)[d]	2.8 (0.89)	3.2 (1.2)	2.8 (1.2)	−0.3	−0.9, 0.2	0.24	0.0	−0.6, 0.6	0.98

[a] Represents nonusers minus users.

[b] By linear regression with adjustment for age, gender, race/ethnicity, parents' level of education, parents' income, family history of substance abuse or psychiatric disorder, childhood attention deficit disorder, and childhood conduct disorder (see text).

[c] Number of proscribed items performed (large items or items on pages with faces)

[d] Square-root transformed values due to skewed distribution.

[e] Score represents the number of cards chosen from safe decks, minus the number from risky decks, in 100 successive cards.

Table 4

Maximum Effect Size of Ecstasy on Various Cognitive Measures in Heavy Users versus Non-users

Measure[a]	Maximum Effect Size[b]
Wechsler Memory Scale - III:	
Logical memory - immediate recall	0.49
Verbal paired associations- immediate recall	0.55
Spatial span - total	0.76
Stroop Test, interference time	0.48
Ravens Progressive Matrices- Total Score	0.53
Trails B time	0.58
Rey-Osterreith Test, delayed recall	0.40
Controlled Verbal Fluency Task, total words	0.54
California Verbal Learning Test, Trials 1-5 total	0.49
Wechsler Adult Intelligence Scale, Block Design Subtest	0.64
Wechsler Adult Intelligence Scale, Digit-Symbol Subtest	0.66
Wechsler Adult Intelligence Scale, Digits Backwards	0.69
Iowa Gambling Task	0.50
Wisconsin Card Sorting Test, total perseverations	0.37

[a] Chosen measures represented either the primary measure of a given test, or for tests involving multiple measures, the measures showing the largest effect sizes in the comparison of nonusers and heavy users (see Table 3).

[b] Magnitude of effect (Cohen's *d*) that can be rejected at the 0.05 level of significance.