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Non-Dependent Stimulant Users of Cocaine and Prescription Amphetamines Show Verbal Learning and Memory Deficits

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Abstract

Background—Stimulants are used increasingly to enhance social (cocaine) or cognitive performance (stimulants normally prescribed, *prescription stimulants*, e.g. methylphenidate, amphetamines). Chronic use, on the other hand, has been associated with significant verbal memory and learning deficits. This study sought to determine whether subtle learning and memory problems characterize individuals who exhibit occasional but not chronic use of stimulants.

Methods—154 young (age 18–25) occasional, non-dependent stimulant users and 48 stimulant naïve comparison subjects performed the California Verbal Learning test (CVLT-II). Lifetime uses of stimulants and co-use of marijuana were considered in correlation and median split analyses.

Results—Compared to stimulant naïve subjects, occasional stimulant users showed significant performance deficits, most pronounced in the verbal recall and recognition domains. Lifetime uses of stimulants and marijuana did not affect CVLT-II performance. The type of stimulant used, however, was of major relevance: users of cocaine only were less impaired, while cumulative use of prescription stimulants was associated with impaired verbal learning and memory capacities.

Conclusions—These results support the hypothesis of subtle and possibly pre-existing neurocognitive deficiencies in occasional users of stimulants, which may be related to the motivation of using these drugs. More importantly, despite beneficial short-term effects, cumulative use, particularly of prescription amphetamines and methylphenidate, intensifies these deficits.

Keywords

Stimulant; cocaine; amphetamine; executive function; verbal learning; verbal memory

Introduction

Psychostimulants such as methylphenidate and amphetamine (*prescription stimulants*) have become drugs of choice for the treatment of attention deficit hyperactivity disorder (ADHD) (1). Given the increasing availability of recreational stimulants like powder cocaine,

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prescription medications and illegal drugs together contribute to the increasing rates of stimulants being abused, particularly by young adults. An estimated half-million Americans consume cocaine weekly and approximately 98,000 adolescents would meet criteria for stimulant abuse or dependence (2). The incentives for stimulant abuse are multifactorial; one of the frequently reported motivations is to improve “performance”, i.e. to do better on tests (prescription stimulants) or to feel more comfortable in social situations (cocaine). In line with those self-reports, 7–8% of college students reported to have used prescription stimulants in the past year (3;4) and about 17% of male and 11% of female undergraduates reported lifetime use of prescription stimulants (5). It is unclear, though, whether non-dependent users of such drugs show neurocognitive deficits and in particular whether deficits precede the use of stimulants.

In comparison, the chronic use of psychostimulants has been associated with neurocognitive deficits, such as verbal learning and memory deficits in cocaine users (6–12), which are not explained by insufficient attentional and working memory capacities (7;10). On verbal learning and memory tests like the California Verbal Learning Test (CVLT-II, (13)), cocaine dependent subjects showed impaired word recall, learning and recognition performance (7;10), and increased intrusion and repetition error rates (7). These deficits are also measurable during abstinence and withdrawal (11;12;14;15) and cumulative cocaine use was shown to negatively impact learning and memory performance (8;16). Visuospatial learning and recall performance on the other hand was increased in cocaine users (6;15), supporting the view of a specific *verbal* learning and memory impairment. Others, however, have not been able to replicate verbal memory and learning weaknesses in cocaine users (17;18), a fact that may be related to small effect sizes and sample sizes drawn on as meta analyses and effect size analyses (19) on cocaine use reveal that higher effect sizes were achieved for tests on attentional capacities. Moreover, differential working memory capacities in users and comparison subjects, which were shown to be of above median effect size (19), may account for some of the discrepancies. The effect of prescription stimulants on learning and memory has mainly been investigated in administration studies in stimulant naïve subjects, where a positive effect of amphetamine on novel word learning (20;21) and on the retention of verbal material has been described (22–24).

The identification of neurocognitive deficits in very early stages of stimulant use, thus in users who have used these drugs only rarely, could provide evidence that these deficiencies preceded the use of such drugs. Moreover, such deficits may act as an incentive to initiate use and thus serve as a vulnerability marker for stimulant use and dependence. Nevertheless, such studies are rare. Here, we assessed verbal learning and memory in *occasional* young (age 18–25) users of cocaine and/or prescription stimulants (amphetamine, methylphenidate) – users who only recently started using psychostimulants and who have not developed problems with stimulant use – to identify potential learning and memory deficits. The off-prescription use of normally prescribed stimulants is associated with lower grade point averages (4) and longitudinal analyses of children at high risk of substance use report that deficits in ‘neurobehavioral inhibition’ at age 16 predicted substance use disorders at age 19 with a 85% accuracy (25); (26) and thus point towards a pre-existing neuropsychological deficiency. Additionally, higher rates of cocaine use were negatively associated with verbal memory (10) and learning (12), suggesting progressive deficits with use. Taken together, the scarce literature suggests that some deficiencies may precede stimulant initiation and that verbal memory and learning is differentially affected by cumulative use of prescription stimulants and cocaine. We hypothesized occasional users of cocaine and prescription stimulants would show weaknesses of recall, learning and recognition capacities and increased error rates (6;7;10;15). Acknowledging the cumulative effect of cocaine, we hypothesized deficits to be subtle compared to chronic users. Lastly, differential effects of cocaine and prescription stimulants were anticipated, with cumulative use of cocaine being

associated with increased deficits. Based on prior studies with prescription stimulants, we hypothesized two complementary scenarios: (1) if verbal capacities of users had been comparable to comparison subjects prior to use initiation, users of prescription stimulants would show improved verbal skills compared to stimulant naïve subjects; (2) if there were initial deficiencies in verbal capacities prior to stimulant use, we hypothesized that stimulant use may attenuate these deficiencies.

The use of cannabinoids (Δ^9 tetrahydrocannabinol, THC) is a major confound when examining neurocognitive functioning in stimulant users as almost all individuals who report use of stimulants also admit to use THC. An estimated 76% of America's 14.8 million drug users used marijuana either alone (59%) or in conjunction with other drugs (17%), and college students reporting the abuse of prescription stimulants were ten times as likely to report marijuana use than students not using stimulants (4). Cannabis abusers have shown impaired performance on a variety of cognitive tasks (27) with deficits being attributed to duration and frequency of use and performance deteriorating with increasing years of heavy frequent use (28). To address a potential influence of marijuana on stimulant users' verbal performance, we classified stimulant users into low and high marijuana users (see data analysis for details).

Methods and Materials

Sample Description

The study protocol was approved by the local Human Subjects Review Board and was carried out in accordance with the Declaration of Helsinki. Stimulant users were recruited via flyers mailed to >7000 students at local universities, internet ads, and using local university newspapers. 1025 stimulant users underwent intensive phone screens. 154 non-dependent users of cocaine, prescription amphetamines and/or methylphenidate and 48 comparison subjects were included into the study. Participants were informed that this study was aimed to examine behavior and brain functioning of people who use stimulants occasionally and all subjects gave written informed consent. Subjects were between the ages 18 and 25. Inclusion criteria for comparison subjects were (1) no lifetime use of stimulants and (2) no lifetime history of substance or alcohol related problems. Stimulant users were defined as (1) at least three off-prescription uses of cocaine and/or prescription stimulants (amphetamines/methylphenidate) over the past six months; (2) no evidence for lifetime stimulant dependence and (3) never sought treatment of drug related problems. Subjects were assessed by experienced interviewers using the SSAGA (Semi Structured Assessment for the Genetics of Alcoholism (29)) and diagnoses were based on consensus meetings with a board-certified psychiatrist (MPP) and trained study personnel. 5 subjects met abuse criteria when participating in the study. The following were exclusion criteria for both groups (1) evidence for ADHD; (2) use of stimulants for medical reasons; (3) lifetime use of ecstasy >20; (4) evidence for current (and past 6 months) of the following diagnoses: Panic Disorder, Social Phobia, Post-traumatic stress disorder, Major Depressive Disorder; (5) evidence for lifetime Bipolar Disorder, Schizophrenia or other cognitive disorders, OCD; (6) evidence for Antisocial Personality Disorder; (7) positive urine toxicology test (exception: marijuana) and (8) head injuries or loss of consciousness >5 minutes. 21 stimulant users reported previous use of methamphetamine; 15 of these had taken methamphetamine less than 10 times. For use of nicotine and alcohol, please refer to Supplement 1.

Task Description

Verbal learning and memory capacities were tested using the CVLT-II (13) where subjects were required to learn a list of 16 words (List A) over repeated immediate-recall trials before a distracting list (List B) is given. Short and long-delayed recall tasks are administered in

free and cued conditions and yes/no recognition testing further allows for an assessment of components of verbal memory. Unbeknown to the subjects, both wordlists are composed of four words of four semantic categories. The distracting second list contains two of the four semantic categories as the first while the other categories are semantically unrelated. On all trials, responses are recorded verbatim and no feedback is provided on the subject's performance.

At the onset of CVLT-II testing, List A is presented orally for immediate recall. The wordlist is read aloud at a pace slightly longer than one second per word and the subject is prompted to recall all of the words in any order (*Immediate Free Recall*). Responses, including intrusions and repetitions, are recorded until the subject cannot remember more or has listed twenty words. List A is presented and recalled five times before List B is presented for one immediate recall trial. In the following trial, subjects recall List A without hearing it again (*Short-Delay Free Recall*). For the subsequent *Short-Delay Cued Recall*, the four categories of List A are provided and the subject recalls corresponding words. A 20-minute delay is required before long-delay testing continues (unknown to the subject). After the delay, the subject is instructed to recall List A (*Long-Delay Free Recall*). A yes/no recognition task follows directly afterward as 48 words (6 target words from List A, 16 distractor words from List B, and 16 phonologically or semantically related to List A) are read one at a time and the subject states if a presented word was part of List A (*Long-Delay Cued Recall*). Following another 10-minute delay, 32 words are presented in pairs and the subject identifies words belonging to List A (*Long-Delay Forced-Choice Recognition*). Each pair contains a target word from List A with a new distractor word.

Data Analysis

Performance data was entered into the program for the analysis of CVLT-II data, also scoring the data. To investigate whether stimulant users and comparison subjects differed on verbal recall capacities, scores on immediate recall measures (correct responses for *List A Trial 1*, *Trial 5*, *Trials 1–5*, and *List B*) and delayed recall measures (correct responses for *Short-Delay Free Recall*, *Short-Delay Cued Recall*, *Long-Delay Free Recall*, and *Long-Delay Cued Recall*) for List A were analyzed. Performance on immediate recall measures relies heavily on auditory attention span while short and long-delay recall measures assess the subject's ability to retrieve information from short term memory storage following a time delay and exposure to an interference list. Regarding recognition capacities, *False Positives* and *Total Recognition Discriminability Index* deriving from the yes/no recognition task were calculated with *Total Recognition Discriminability Index* representing the ability to correctly identify all 16 target words while rejecting the 32 distractors, providing a score for correct responses relative to false positives. To assess effective encoding and retrieving of the wordlists, the following scores were obtained: *Semantic Clustering*, the process by which subjects actively reorganize the words into their respective categorical groups, *Serial Clustering Bidirectional*, a “stimulus-bound”, less effective strategy of recalling target words in the same sequential forward or backward direction that they were presented, *Learning Slope Trials 1–5*, which determines the degree to which subjects learned more words in each successive immediate-recall trial of List A and *Recall Discriminability*, which assesses the ability to cite target words relative to the number of intrusion errors. To reveal problems in learning and memory, recall error measures including the sum of repetition errors (words repeated during the same trial) across all recall trials (*Total Repetitions*) and intrusion errors (non-target words) reported during immediate recall of List A Trials 1–5 (*Immediate Intrusions*), short and long-delay recall trials (*Delayed Recall Intrusions*) and short and long-delay cued recall trials (*Cued Recall Intrusions*) were analyzed.

Performance data were analyzed using SPSS. Kolmogorov-Smirnov tests were carried out to test whether CVLT-II performance data in stimulant users and comparison subjects followed

a normal distribution. Only three of the eighteen variables were normally distributed and variances between groups were inhomogeneous for five variables as tested with Levene's tests. Hence, assumptions for parametric analyses were not fulfilled and we performed non-parametric Kruskal-Wallis tests to compare performance between stimulant users and comparison subjects. Mann-Whitney tests were applied for subsequent pair wise comparisons.

The underlying idea of our analysis approach was, first, to identify differences in CVLT-II performance between stimulant users and comparison subjects, acknowledging one of the most striking potentially conflicting factors: marijuana use. The number of lifetime THC uses, as assessed with the SSAGA and Timeline Follow-Back methods, differed between stimulant users and comparison subjects ($p < 0.001$, Tab. 1). In stimulant users, THC use preceded stimulant use by 2.61 ± 2.01 years and lifetime stimulant use was correlated with lifetime marijuana co-use ($r = 0.281$, $p < 0.001$). To account for a potential effect of lifetime THC use on verbal memory performance, we divided stimulant users into below and above median THC users based on their lifetime marijuana use ($\ln_{(1+\text{lifetime marijuana uses})}$, $\ln\text{THC}$). 77 stimulant users (*Below Median THC Stimulant Users*) reported a lifetime marijuana use below the stimulant users' median of 5.897 ($\ln\text{THC}$) and were compared to 77 stimulant users classified as *Above Median THC Stimulant Users* and 48 comparison subjects (see Tab. 1).

Second, we examined the effect of cumulative *stimulant* use on verbal learning and memory performance by directly comparing stimulant users with low and high lifetime stimulant use. According to their declared lifetime use of stimulants, users were divided into *Below* ($n=77$) and *Above Median* ($n=77$) *Stimulant Users* ($\ln_{(1+\text{lifetime stimulant uses})}$, $\ln\text{STIM}$, median 3.239). Correlation analyses were performed between $\ln\text{STIM}$ and those verbal learning and memory measures differing between stimulant users and comparison subjects.

Third, the effect of stimulant type of choice on CVLT-II performance was examined. 111 stimulant users had consumed any type of prescription stimulant (methylphenidate and/or prescription amphetamines) at least once. 4 subjects had used methylphenidate only and 67 had used prescription amphetamines only. Stimulant users were split into pure prescription stimulant users ($n=35$), pure cocaine users ($n=13$), and users with no preference for a stimulant type ($n=56$). Due to the limited number of subjects describing the use of cocaine only, we also grouped stimulant users into users with a dominant use of prescription stimulants ($\geq 80\%$ of total stimulant use of prescription amphetamines and/or methylphenidate, $n=55$) or cocaine ($\geq 80\%$ cocaine, $n=43$). Subgroups were compared to comparison subjects and correlation analyses with lifetime stimulant use and CVLT-II performance were run for subgroups.

Results

154 Stimulant users (93 males) and 48 healthy comparison subjects (22 males) did not differ on age (Tab. 1, $t_{200} = 1.172$, $p = 0.246$), education ($t_{198} = 1.013$, $p = 0.312$), or gender distribution ($\chi^2 = 3.162$, $p = 0.095$). Groups did not differ on estimated verbal IQ ($t_{192} = 0.901$, $p = 0.369$) as assessed using the Wechsler Test for Adult Reading (WTAR).

Comparison of Stimulant Users and Comparison Subjects

For the majority of recall, learning and recognition measures, we observed medium effect sizes (partial η^2 squared, η^2 , see Tab 2 and 3). Among stimulant users, the frequency of marijuana use did not affect CVLT-II performance as indicated by the fact that below and above median marijuana users did not differ on any of the verbal learning and memory measures (p 's > 0.32). Both, stimulant users with below and those with above median

marijuana use performed significantly worse than comparison subjects on the CVLT-II as measured by most of the immediate and all delayed recall variables (Tab. 2). Both subgroups of stimulant users produced more intrusion errors than comparison subjects; analyses which reached statistical significance for delayed and cued recall intrusions (Fig. 1, Tab. 3). Stimulant users also showed deficits on recall and recognition discriminability measures relative to stimulant naïve comparison subjects (Tab. 3).

Effect of Lifetime Stimulant Use

To evaluate whether cumulative use affects performance in early stages of stimulant use, we first examined if those CVLT-II measures identified in the above analyses as differing between users and comparison subjects showed a significant correlation with lifetime stimulant use (correlations with lnSTIM in stimulant users). None of these correlations were significant (p 's > 0.146), i.e. cumulative stimulant use was not associated with CVLT-II performance of the combined group of users of cocaine and prescription stimulants.

As an alternative categorical approach, stimulant users were subdivided according to their cumulative lifetime *stimulant* use into users with below and above median stimulant uses. Performance of these subgroups and comparison subjects was compared using t-tests as assumptions for parametric analyses were fulfilled. Stimulant users with low and high lifetime uses did not differ on any of these CVLT-II measures (p 's > 0.35), further underlining that cumulative use of stimulants was not related to verbal learning and memory performance in early stages of stimulant use. Correlations of verbal measures and lifetime stimulant use in both subgroups separately were not significant. Thus, individuals with relatively greater lifetime exposure to stimulants did not show worse performance on measures of learning and memory.

Effect of Preferred Stimulant Type

Unlike other stimulant users, individuals who reported exclusive use of cocaine did not differ from comparison subjects for all but one measure (Cued Recall Intrusions, $p = 0.049$, Tab. 4). However, given the relatively smaller sample ($n = 13$ for pure cocaine users vs. $n = 48$ for comparison subjects), caution is needed when interpreting these results. Respective effect sizes (Cohen's d) were medium to high (Tab. 4) supporting the relevance of our findings. The other subgroups (pure prescription users, dominant prescription users, dominant cocaine users, user with no preference for either stimulant type) in most parts showed the deficits compared to stimulant naïve subjects which were revealed for the entire group of stimulant users (Tab. 4; see also Supplement 1).

To examine the relationship between the number of lifetime uses of different types of stimulants, we performed correlation analyses with CVLT-II performance in subgroups of stimulant users preferring cocaine or prescription stimulants or stating no preference for either stimulant type. There were no significant correlations between the amount of specific type of stimulants consumed and CVLT-II performance in pure or dominant cocaine stimulant users, dominant prescription stimulant users and users with no preference.

However, for the subgroup of users consuming prescription amphetamines and/or methylphenidate only, correlation analyses revealed that greater lifetime exposure to prescription stimulants was associated with poorer verbal recall performance (Trial 5: $r = -0.458$, $p = 0.006$; Total Trial 1–5: $r = -0.357$, $p = 0.036$; Short-Delay Free Recall: $r = -0.382$, $p = 0.024$; Short-Delay Cued Recall: $r = -0.404$, $p = 0.016$; Long-Delay Cued Recall: $r = -0.405$, $p = 0.016$; Fig. 2). Thus, despite the self-reported incentive to use prescription stimulants to improve cognitive performance, greater lifetime exposure to amphetamine type stimulants was associated with relatively more impairment in verbal recall performance. Estimations of

verbal IQ, which is known to remain relatively unaffected by brain changes, verified comparable verbal capacities in these users of prescription stimulants and comparison subjects ($p=0.92$). Moreover, in users of prescription stimulants, verbal IQ was not correlated with lifetime uses ($p=0.284$) further opposing the notion that greater pre-use deficiencies could have served as the incentive to use (more) prescription stimulants.

Discussion

This study aimed to determine whether subtle learning and memory problems characterize individuals who exhibit occasional but not chronic use of stimulants. Our study yielded two main results. First, stimulant users showed significantly worse performance on a task requiring the recall of verbal material. Recall capacities were impaired on immediate and delayed trials and even when cues were provided. Second, we identified characteristic patterns of learning and memory performance in users preferring a certain type of psychostimulant. Specifically, increasing use of prescription stimulants but not cocaine was associated with stronger recall deficits. Thus, these results indicate that even individuals who have used stimulants minimally nevertheless showed learning and memory problems, which consistent with the idea that these problems preceded the initiation of drugs use. On the other hand, continued use of these drugs in general, and of prescription type stimulants in particular, contribute to further exaggeration of learning and memory problems.

Besides significant verbal recall deficits, stimulant users generated more intrusion errors than comparison subjects. Along with an increased rate of *False Positives*, which has recently been described in chronic cocaine users (7), these findings reflect a tendency in occasional users to confabulate. We also found that occasional users, similar to cocaine dependent subjects (7;10), exhibited a diminished ability to distinguish target words from distractors during recognition testing. This recognition deficit was accompanied by a deficiency in rejecting semantically related distractors. Interestingly, a similar pattern of learning and memory deficiencies has previously been described in chronic cocaine users (6;7;10;15) while little had been known about the neurocognitive profile of individuals who misuse prescription stimulants infrequently. The fact that learning and memory weaknesses were identified in individuals with very limited exposure to stimulants suggests that these deficits preceded stimulant use. Moreover, the experience of these problems in academic environments, which demand a high level of cognitive performance, may have contributed to the incentive to use drugs that are perceived to enhance performance. Alternatively, recall and memory deficits could have been a consequence of stimulant use. However, this possibility would be more plausible if there was a dose-relationship to the observed dysfunctions, i.e. if individuals with greater numbers of stimulant use would exhibit stronger problems. In contrast, in the combined group of occasional cocaine and prescription stimulant users, cumulative stimulant use was not associated with performance and deficiencies were found to be on similar levels in high and low amount users. The fact that no effect of age or the amount of lifetime use on CVLT-II performance could be detected in this sample homogeneous in age further supports the notion of a pre-existing neurocognitive profile. Taken together, these results are consistent with the view of a pre-morbid, pre-existing neuropsychological trait characteristic (26;30;32;33) that may have led to stimulant initiation and clearly invite the hypothesis that deficits in learning and memory are a trait characteristic that precedes stimulant use. Though unlikely given the above, we cannot entirely rule out that the limited variability in age and amount or duration of use may have covered dose-performance relationships.

In contrast to our results of the combined group of users of cocaine and prescription stimulants, those users with a lifetime use of cocaine only did not differ from comparison subjects. While these results have to be replicated as they rely on a small subsample, we

found clear evidence for an association of impaired recall capacities with cumulative use in users consuming prescription stimulants only. It is important to point out that, despite the self-reported use of prescription stimulant to improve performance on tests and exams, we observed a negative impact of cumulative use of these medications on verbal recall performance. Given the cross-sectional study design, we cannot rule out the possibility that originally more severely impaired subjects consumed more prescription stimulants to boost deficient performance. In pure prescription stimulant users, reading skills, which have been found to remain relatively unaffected by brain changes, did not differ from comparison subjects and were not associated with cumulative use. It thus seems unlikely that initially more severely impaired subjects consumed more prescription stimulants, but rather that prescription stimulants increasingly impair verbal recall skills.

It is important to point out that verbal learning and memory deficits were not due to the frequent co-use of marijuana, which is common in this population. Moreover, CVLT-II inherent measures (Trials 1 and B) point at comparable attention or working memory capacities in users and comparison subjects, a hypothesis which would need to be supported by specific assessments. One limiting factor of our study is that the design was not completely prospective. Our cross-sectional data cannot directly account for pre-existing neurocognitive characteristics. We addressed this methodological challenge by investigating stimulant users with only minimal use and comparing users with relatively low and high lifetime uses, and, lastly, by correlation analyses with cumulative stimulant use.

Summary

Individuals who have used prescription stimulants and cocaine rarely show significant deficits in verbal recall, learning and memory. These deficits resemble those of chronic users and are most pronounced in recall domains. There is some evidence for differential effects of cocaine and prescription stimulants. Surprisingly, cumulative use of prescription stimulants rather than cocaine was associated with stronger verbal recall deficits. Taken together, our results support the idea that pre-existing verbal learning and memory deficiencies may lead individuals to seek means to attenuate these deficits by using stimulants. Although short-term effects of stimulants may be beneficial, cumulative use, particularly of prescription amphetamines and methylphenidate, may ultimately intensify learning and memory problems.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Intrusion Errors

Compared to stimulant naïve comparison subjects, occasional users of cocaine or prescription stimulants (amphetamine, methylphenidate) generate significantly more delayed and cued recall intrusions.

Figure 2. Recall Deficits in Users of Prescription Stimulants

Users of prescription stimulants (amphetamine, methylphenidate) show increasing verbal recall deficits with cumulative exposure to stimulants. These deficits are present at shorter and longer delays between encoding and recall and also when recalling cues are provided.

Sociodemographics and drug use measures in 154 non-dependent stimulant users and 48 comparison subjects and in subgroups of stimulant users with below and above median marijuana (THC) use.

Table 1

	Stimulant Users, n=154		Below Median THC Stimulant Users, n=77		Above Median THC Stimulant Users, n=77		Comparison Subjects, n=48	
	m	sd	m	sd	m	sd	m	sd
Sociodemographics								
Age	20.79	1.517	20.62	1.539	20.95	1.486	21.19	2.218
Education	14.44	1.247	14.34	1.273	14.53	1.22	14.65	1.370
Females	40%		46%		34%		54%	
Race/Ethnicity								
Caucasian (n)	128		62		66		34	
Afro-American (n)	2		1		1		0	
Asian (n)	14		10		4		12	
Other/Mixed (n)	10		4		6		2	
Verbal IQ (WTAR)	108.38	7.235	107.49	7.677	109.32	6.716	109.50	6.890
Drug Use (# life time)								
Prescription Stimulants	31.12	74.399	20.56	38.365	41.69	97.187	N/A	
Recreational Stimulants	24.92	46.027	13.06	21.333	36.77	59.373	N/A	
THC	864.86	1358.404	123.47	113.548	1606.25	1608.766	29.69	101.260

Table 2

Immediate and delayed verbal recall performance in stimulant users with below (n=77) and above (n=77) median marijuana (THC) use and 48 comparison subjects (non-parametric Kruskal-Wallis tests). Post hoc Mann-Whitney tests revealed that stimulant users with relatively lower and higher marijuana co-use do not differ in performance. Instead, significant group differences are due to stimulant users performing worse than comparison subjects. Effect sizes were calculated applying partial eta squared (η^2).

	Below Median THC Stimulant Users, n=77		Above Median THC Stimulant Users, n=78		Comparison Subjects, n=48		Kruskal- Wallis	Effect Size
	m	sd	m	sd	m	sd	p	η^2
Immediate Recall								
<i>Trial 1</i>	6.62	1.850	6.83	1.650	7.38	1.942	0.191	0.026
<i>Trial 5</i>	12.58	2.692	12.92	1.652	13.81	1.593	0.009	0.049
<i>Total Trials 1–5</i>	52.48	9.624	52.70	7.293	57.29	7.255	0.005	0.056
<i>Trial B</i>	6.39	2.059	6.32	1.743	6.90	2.253	0.411	0.013
Delayed Recall								
<i>Short-Delay Free Recall</i>	11.18	2.963	11.49	2.303	12.48	2.895	0.012	0.034
<i>Short-Delay Cued Recall</i>	12.10	2.703	11.90	2.485	12.88	3.064	0.017	0.020
<i>Long-Delay Free Recall</i>	11.45	3.319	11.26	3.369	12.67	3.360	0.014	0.028
<i>Long-Delay Cued Recall</i>	12.12	3.244	11.96	2.760	13.04	2.805	0.038	0.021

CVLT-II error, learning and recognition measures

Table 3

Stimulant users produce significantly more Delay Recall and Cued Recall Intrusions than comparison subjects. Compared to stimulant naïve comparison subjects, stimulant users were impaired on Recall Discriminability, Recognition Discriminability Index Total, Semantic Recognition Discriminability and Delay Recognition False Positives. Effect sizes were calculated applying partial eta squared (η^2).

	Below Median THC Stimulant Users, n=77		Above Median THC Stimulant Users, n=77		Comparison Subjects, n=48		Kruskal- Wallis	Effect Size
	m	sd	m	sd	η^2	sd	p	η^2
Repetitions								
<i>Total Repetitions</i>	7.09	5.446	8.94	7.083	6.58	6.181	0.095	0.025
Intrusions								
<i>Immediate Intrusions</i>	1.73	2.088	1.51	2.125	0.92	0.919	0.431	0.027
<i>Delayed Recall Intrusions</i>	2.65	3.463	2.29	3.039	1.35	2.088	0.045	0.027
<i>Cued Recall Intrusions</i>	1.68	2.425	1.53	2.257	0.81	1.347	0.039	0.025
Learning Measures								
<i>Semantic Clustering</i>	0.597	1.339	0.555	1.203	1.079	1.761	0.349	0.023
<i>Recall Discriminability</i>	2.200	0.461	2.219	0.334	2.450	0.346	0.001	0.066
<i>Serial Clustering Bidirectional</i>	1.089	0.986	1.197	0.916	1.204	1.664	0.252	0.002
<i>Learning Slope 1–5</i>	1.483	0.627	1.460	0.425	1.531	0.506	0.585	0.003
Recognition Measures								
<i>Recognition Discriminability Index Total</i>	2.19	0.534	2.19	0.370	2.45	0.437	0.002	0.058
<i>Delay Recognition False Positives</i>	1.30	2.027	1.29	2.006	0.58	0.919	0.043	0.027

Table 4

Comparison of verbal learning and memory performance of comparison subjects and subgroups of stimulant users with preferences for prescription stimulants (amphetamines/methylphenidate) or cocaine. Cocaine only users are less impaired; however, despite medium to high effect sizes, results need to be replicated due to the presently small sample size.

	Pure Prescription Users (n=35) vs. Comparison Subjects	Prescription Users (n=55) vs. Comparison Subjects	Pure Cocaine Users (n=13) vs. Comparison Subjects [Cohen's d]	Cocaine Users (n=43) vs. Comparison Subjects	No Preference (n=56) vs. Comparison Subjects
Recall Measures					
<i>Trial 5</i>	0.022	0.002	0.371 [0.37]	0.015	0.047
<i>Total 1–5</i>	0.048	0.008	0.156 [0.49]	0.003	0.016
<i>Short-Delay Free Recall</i>	0.050	0.009	0.129 [0.38]	0.013	0.026
<i>Short-Delay Cued Recall</i>	0.073	0.066	0.392 [0.22]	0.023	0.008
<i>Long-Delay Free Recall</i>	0.050	0.028	0.200 [0.35]	0.020	0.008
<i>Long-Delay Cued Recall</i>	0.110	0.064	0.292 [0.29]	0.082	0.017
Learning Measures					
<i>Recall Discriminability</i>	0.020	0.001	0.196 [0.47]	0.001	0.013
Error Measures					
<i>Delayed Recall Intrusions</i>	0.047	0.036	0.055 [0.42]	0.017	0.076
<i>Cued Recall Intrusions</i>	0.042	0.042	0.049 [0.60]	0.014	0.046
Recognition Measures					
<i>Recognition Discriminability Index Total</i>	0.016	0.006	0.159 [0.48]	0.002	0.003
<i>Delay Recognition False Positives</i>	0.109	0.061	0.408 [0.36]	0.038	0.021