Original Paper

Cognitive function in aging cocaine smokers

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Abstract

Background: Little is known about the functional status of older drug users, who may pose challenges to public health systems in coming years. Here, we assessed cognitive function in aging cocaine smokers compared to demographically matched controls.

Methods: A total of 22 non-treatment-seeking aging (50–60 years old) cocaine smokers (⩾twice/week; ⩾15 years of weekly use) and 19 controls completed a comprehensive cognitive battery. Controls with cannabis, tobacco, and alcohol use were included to better match the cocaine users. All cocaine users, and current cannabis- or alcohol-using controls, completed testing after 4 drug-free inpatient days to better control for acute and residual drug effects.

Results: Cocaine users (52.9 ± 2.5 years old, four female; cocaine use 3.9 ± 1.4 days/week) and controls (52.7 ± 2.6 years old, four female) were well matched demographically, but cocaine users reported a more extensive substance use profile. Cocaine users showed marginally worse verbal learning than controls, recalling on average one word fewer across immediate and delayed word recall trials. Their performance was intact relative to controls across all other measures of cognitive function. Bayesian analysis indicated the absence of group differences was not due to power limitations.

Conclusion: These data suggest that aging, long-term cocaine users have similar cognitive functioning to appropriately matched controls when tested under drug-free conditions, with only marginal decreases in verbal learning. Findings, although reassuring with regard to broad cognitive capacities in aging cocaine smokers, suggest that future investigations of cognitive function in aging drug users are warranted.

Keywords
Cocaine, aging, cognitive function, neuropsychological function

Introduction

Medical advances have resulted in the growth of average life expectancies in the United States and other developed countries, with corresponding increases in national average ages. By 2030, one-fifth of the United States population will be 65 years or older (Mather et al., 2015). Coinciding with the aging population is an increase in the number of older people using drugs of abuse (Chhatre et al., 2017; Duncan et al., 2010; Han et al., 2009; White et al., 2011). The increase of older drug users appears primarily attributable to aging of the "baby boomers", who represent some 21% of past-month drug users (SAMSHA, 2016). Given that high levels of drug use in older adults compared to previous generations (Wu and Blazer, 2011) will likely pose major challenges to public health systems in coming years (Rosen et al., 2013; Rowe, 2008), determining the functional status of these groups is imperative. In particular, establishing whether aging substance abusers have cognitive difficulties over and above those that accompany normal aging (Blow, 1999; Searby et al., 2015) is an important first step. To date, few studies have investigated cognitive function in aging illicit drug users (Bell et al., 2016; Dowling et al., 2008; Iudicello et al., 2014), despite the established relevance of cognitive problems to both aging and drug use (Salthouse et al., 2003; Spronk et al., 2013; Stockel et al., 2017). Cognitive difficulties predict poor outcomes in psychotherapy for substance use disorders (Aharonovich et al., 2003; Aharonovich et al., 2006; Aharonovich et al., 2008), further emphasizing the need to investigate this question in relation to aging drug users.

The above issues are particularly relevant to cocaine use. From 2000 to 2012, the number of cocaine users aged 55 or older presenting for drug treatment in the US increased by 63% (Chhatre et al., 2017). Cocaine is one of the most commonly used drugs in 50 to 59-year-old people in treatment for substance use disorders (Wu and Blazer, 2011), and older cocaine users are more likely than their younger counterparts to smoke cocaine

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(Martin et al., 2014; Whitehead et al., 2014). Indeed, past-year cocaine smoking in people aged 50 years or older has almost tripled since 2011 (John and Wu, 2017). Cocaine smoking among aging users is concerning because smoked cocaine is associated with poorer physical health and treatment outcomes, longer use, and greater severity of dependence compared to intranasal use (Chen and Anthony, 2004), likely due to the more rapid onset of effects achieved via this route (Cone, 1995).

Despite the potential susceptibility of aging cocaine smokers to poor outcomes, little is known about their function. In terms of cognition, normal aging is associated with the decline of a broad range of cognitive functions (Salthouse et al., 2003), including motor dexterity, processing speed, cognitive flexibility (Stockel et al., 2017), attention (Jennings et al., 2007), working memory (Kirova et al., 2015; Verhaeghen and Cerella, 2002), task-switching, and planning (Salthouse et al., 2003). There appear to be some similarities in brain structure and neurocognitive function in cocaine-dependent younger adults and older healthy individuals, prompting speculation that cocaine use may be associated with "fast-tracked" aging (Ersche et al., 2013; Sanvicente-Vieira et al., 2016). It is unknown whether long-term cocaine use confers a risk of additional cognitive decline over and above decrements observed in normal aging.

To our knowledge, the only study to have addressed this question was a pilot conducted in our laboratory (Kalapatapu et al., 2011) that compared basic neuropsychological function in older (51–70) cocaine users and healthy controls (CTRLs) and younger (21–39) cocaine users and healthy CTRLs (i.e. four groups of 20). Older cocaine users performed more poorly on a verbal attention and immediate memory test relative to both younger cocaine users and older CTRLs. They also had poorer visual processing and psychomotor speed than younger cocaine users. Although these findings provide initial evidence of cognitive issues in aging cocaine users, there were several limitations, including a limited neuropsychological battery, group differences on important clinical and demographic characteristics and, due to outpatient testing, limited control for drug effects and potentially confounding lifestyle factors (e.g. poor sleep and nutrition). Thus, more controlled research examining this question is warranted.

Here, we conducted a comprehensive assessment of cognitive functioning in non-treatment-seeking aging cocaine smokers relative to demographically matched CTRLs, employing an inpatient protocol for participants with current drug use. We examined verbal learning and memory, attention network efficiency, motor response inhibition, processing speed, mental flexibility, visual working memory, and verbal attention, working memory and fluency. We hypothesized that aging cocaine users would have poorer cognitive performance relative to demographically matched CTRLs.

Methods

Participants

Participants were 50- to 60-year-old male and non-pregnant female cocaine smokers and CTRLs who were fluent in English. They were excluded for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association, 1994) past-year mood, anxiety or eating disorder, lifetime mania or psychosis, neurologic or autism spectrum disorder, and medical conditions likely to interfere with participation.

Cocaine smokers. Cocaine smokers (COC) were non-treatment-seekers reporting (1) smoking cocaine ⩾2x/week for the past 6 months (current use verified by urine tests); (2) initiating cocaine use ⩾20 years prior; and (3) ⩾weekly cocaine use for ⩾15 years. COC were excluded if they met DSM-IV criteria for current substance dependence except cocaine or nicotine, current abuse except cocaine, alcohol, cannabis or nicotine, and past dependence except cocaine, cannabis, alcohol, or nicotine.

CTRLs. CTRLs were excluded for current dependence except nicotine, current abuse except cannabis, alcohol or nicotine, and past dependence except cannabis, alcohol or nicotine. Cannabis, alcohol and nicotine use was permissible for CTRLs, to better match the cocaine users (Vadhan et al., 2014). Additionally, we accepted those reporting ⩽10 occasions of lifetime cocaine use without use in the past year, because occasional cocaine use has been reported among people in the demographic group of interest (Cornish and O'Brien, 1996).

Participants provided informed consent in accordance with procedures approved by the New York State Psychiatric Institute (NYSPI) Institutional Review Board.

Experimental protocol

Candidates did three to five screens, comprising physical exam, psychiatric assessment (Structured Clinical Examination for DSM-IV Diagnoses; First et al., 2002), electrocardiogram, and blood/urine analyses. A doctoral-level interviewer assessed drug use via structured interview. At each screen, urine toxicology (five-panel, All Test North America, Gilbert, AZ), breath alcohol (Select S80, BACTrack, San Francisco, CA), and urine pregnancy tests (females; Alere hCG Dipstick, Alere, Orlando, FL) were conducted.

All COCs and CTRLs with current regular alcohol or cannabis use, completed as inpatients to control for recent drug use and sleep and food intake. They were admitted to the NYSPI Clinical Research Unit for 5 days and tested on the fifth day. On the morning of testing, participants were provided breakfast and screened for alcohol and other drug use, and pregnancy (females). They completed a magnetic resonance (MR) scan assessing different hypotheses; data are reported separately (Bedi and Redman, 2008). Following lunch, they completed a self-report mood state measure and the cognitive battery. Inpatients were discharged on the morning following the assessment day.

A total of 13 CTRLs reporting no current drug or regular alcohol use (biochemically verified as negative urine drug and breath alcohol tests in each of two to five screening sessions) completed the testing as outpatients, and six CTRLS were admitted as inpatients. Those in the outpatient protocol were asked to ensure no alcohol consumption for at least 4 days, no caffeine and medications for 24 hours, and no cigarettes for 12 hours before the session. They were tested for recent alcohol, drug, and cigarette use at the beginning of the outpatient day using breathalyzer, breath carbon monoxide, and urine drug tests. The same procedures were followed as for the inpatient testing day. Outpatients were compensated, debriefed, and discharged after the cognitive battery. To reduce effects of nicotine withdrawal, all participants who smoked cigarettes were allowed to smoke after lunch, before cognitive testing.

Measures (in order of administration)

Positive and Negative Affect Schedule. Before testing, participants completed the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988), comprising Negative and Positive Affect scores (range 10–50).

Word Reading Test. The Word Reading Test (WRT) is a subtest of the Wide Range Achievement Test – 3rd Edition (Wilkinson, 1994). Participants read 42 English words with irregular pronunciations aloud without pause, hesitation, or phonemic decoding. WRT assesses crystalized verbal intelligence, which has limited vulnerability to brain injury and, as such, is used to estimate premorbid intellectual capacity (Spreen and Strauss, 1998). The WRT outcome is total accuracy.

Rey Auditory Verbal Learning Test. The Rey Auditory Verbal Learning Test (RAVLT) measures immediate and delayed verbal memory encoding, recall, and recognition (Schmidt, 1996). Participants are read a list of 15 words five times, with each presentation of the list followed by free recall (the learning phase). An interference list of 15 new nouns is then presented and tested. Participants then freely recall as many words as possible from the initial list (immediate recall). After 30 minutes, they again recall as many words as possible from the first list (delayed recall). Participants then complete a recognition task, identifying words from the first list from a list comprising target words, distractors (from the second list), and new words. Dependent variables comprise the number of correct words during free recall and recognition phases, as well as total false-positive recognition errors.

Attention Network Task – Revised. The Attention Network Task – Revised (ANT-R) tests the efficiency of three visual attention networks: alerting, orienting, and executive control (Fan et al., 2009). On each trial, a valid, invalid or neutral cue, or no cue signal the position of impending target arrows. Participants react to the direction of a target arrow flanked by (congruent, incongruent, neutral) distractor arrows. Outcome measures are differences in reaction time (RT) and accuracy between the three conditions (congruent, incongruent, neutral) with the four specific types of cues (valid, invalid, neutral, or no cue). *Alerting* network efficiency is reflected in RT changes in response to a cue (no cue minus neutral cue). The *Orienting* network is measured as the RT time for voluntary relocation of attention in response to a spatial cue (neutral cue minus valid cue). The executive control network underlies more complex mental operations in resolving attentional conflict (incongruent minus congruent conditions).

Stop Signal Task. The Stop Signal Task (SST) assays motor impulsivity (Reynolds et al., 2006) or motor response inhibition, specifically the ability to prevent prepotent responses (Logan, 1994). Participants respond as quickly as possible to a series of X's and O's onscreen by pressing computer keys corresponding to each letter. On stop trials, an auditory tone signals to participants to inhibit their response. Delay between the letter presentation and the auditory stop-signal is adjusted online to converge on the stop-signal reaction time (SSRT; Band et al., 2003). We used the quantile method to estimate SSRT, the average time required to successfully inhibit 50% responses on stop trials, because this method is robust to violations of assumptions (Band et al., 2003). SSRT and mean RT on correct Go trials are the outcome variables.

Trail Making Test A and B. Trail Making Test A and B (TMT) measures visual attention, psychomotor function, mental flexibility, and processing speed (Lezak, 1995; Reitan and Wolfson, 1985; Spreen and Strauss, 1998). TMT is comprised of two sections. In Part A, participants draw a line connecting numbers on a page sequentially from 1 to 25. Part B includes both numbers (1 to 13) and letters (A to L), where participants connect these in ascending order, alternating between numbers and letters (i.e. 1-A-2-B-3-C). Participants complete the task as quickly as possible. The main outcome measurements are total errors and time to completion for each section.

Berg Card Sorting Test. The Berg Card Sorting Test (BCST) is a computerized measure of cognitive set-shifting (Mueller and Piper, 2014). Participants are required to match a series of cards presented sequentially to one of four stimulus cards displayed at the top of the screen, on the basis of one of three criteria: the color of the objects on the card, the shape of the objects, or the number of objects. To do this, they must use trial and error to learn the matching rule (i.e. based on color, shape, or number). After 10 correct sorts, the rule changes, requiring mental flexibility, a component of executive function (Spreen and Strauss, 1998). Indices for mental flexibility are: total categories (or rules) completed, perseverative errors (using the same incorrect rule to continue sorting new cards), non-perseverative errors, and failure to maintain set (failing a sort after at least five previous cards have been sorted correctly in a row; Nyhus and Barcelo, 2009).

Self-Ordering Working Memory Task. Self-Ordering Working Memory Task (SOWMT) is a test of visual executive working memory yielding a measure of working memory capacity (Van Snellenberg et al., 2014). Participants are presented with eight simple line drawings depicting three-dimensional objects onscreen. They are instructed to select each object only once in any order. Between selections, objects are pseudo-randomly rearranged, preventing the use of spatial location to aid recall. If an object is chosen twice, or the participant does not make a selection within the 7-second response time, the computer selects an object and the participant is instructed to recall that as if they had selected it themselves. A trial is completed once all objects are selected. Working memory performance (capacity) and an attention parameter are computed as outcome variables (see Van Snellenberg et al., 2014). The SOWMT is sensitive to working memory changes associated with normal aging (Chaytor and Schmitter-Edgecombe, 2004).

Digit Span. Digit Span (DST) is a subtest of the Wechsler Adult Intelligence Scale – Third Edition (Wechsler, 1997). Participants are read strings of digits from two to nine digits long and asked to repeat them in the same order (forward) or in reverse (backward). DST outcome variables are total digit strings correctly reproduced. Forward DST measures attention and short-term memory span and backwards trials assess auditory working memory (Lezak et al., 2004).

Controlled Oral Word Association Test. The Controlled Oral Word Association Test (COWAT), a measure of verbal association fluency and executive function (Spreen and Strauss, 1998), requires participants to spontaneously generate as many words as possible based on phonetic (starting with F, A, and S) and semantic (animal names) criteria. Per category, 1 minute is allowed. The dependent variables are total words and errors in each category.

Statistical analyses

Data from two participants were excluded from analyses: one male CTRL who disclosed extensive past cocaine and heroin use during debriefing and one male COC who had congenital brain abnormality indicated by neuroradiologist review of his structural MR imaging scan (this participant was referred to clinical follow up). Demographic and drug-use data were compared between groups using Chi-square tests of independence and independent samples *t*-test. Mixed analysis of variance (ANOVA) was conducted on the RAVLT recall scores, with trials (learning trials one to five, interference trial, immediate recall, and delayed recall) as the within-subject factor and group (COC, CTRL) as the between-subject factor. If a significant interaction effect was observed, we planned to conduct simple main effects analysis. We used independent sample *t*-tests to compare RAVLT recognition scores. ANT RT and accuracy were analyzed separately using ANOVAs, with attention network (alerting, orienting, executive control) as the within-subject factor and group as the between-subject factor. ANT data from two COC and three CTRL were excluded from analyses due to poor performance (<50% accuracy on incongruent trials). For ANT RT analyses, trials with incorrect/missing responses and RTs <200ms or >1500ms (<2.5% of all correct responses) were removed (Gu et al., 2008). Because ANT median RT was 24ms fewer than mean RT with an average SD of 194.79, we used median RT to compute ANT outcome given positive skew in the data. Differences between groups on all remaining cognitive tests were examined using independent sample *t*-tests. We excluded SST data from one COC and four CTRLs due to poor performance (<25% correct inhibition on stop trials). We also computed separate SST results with four additional COCs and three CTRLS removed based on more stringent performance criteria: (1) 25–75% inhibition on Stop trials, (2) >60% Go response, (3) <10% Go error, and (4) negative or <50ms SSRT (see Congdon et al., 2012). SST results from both criteria were reported. The less stringent data approach was used to retain greater power in the analysis. Lastly, we compared performance on standardized neuropsychological measures (WRT, RAVLT, TMT, DST, COWAT) to those of published norms to assess the clinical relevance of our findings.

Isolated univariate outliers with *z*-scores > 3.29 were truncated to one increment higher or lower than the closest non-outlier value within that group (Tabachnick and Fidell, 2013). Because outlier truncation did not alter results, we report results using original data. Because ANOVAs and *t*-tests are relatively robust to violations of normality when not due to outliers, non-normal data were retained (Gravetter and Wallnau, 2004). Alpha was set at 0.05 for omnibus analyses with Bonferroni-corrected post-hoc tests. We interpreted Levene's adjusted degrees of freedom where equal variance could not be assumed and Greenhouse Geiser corrected degrees of freedom where Mauchly's test indicated violation of sphericity. Effect sizes are presented as Cohen's *d* and partial η^2 for any statistically significant effects. We computed Bayes factor (BF_{01}), representing likelihood estimates of the null over the alternative hypothesis (COC; Rouder et al., 2009). Analyses were conducted using IBM SPSS statistics 24 (IBM, Armonk, NY) and JASP (Version 0.9, Amsterdam, Netherlands).

Table 1. Demographic characteristics.

	Cocaine users	Controls
N	22 (4 female)	19 (4 female)
Race (Black/mixed)	22/0	18/1
Ethnicity (Hispanic/ non-Hispanic)	22/0	19/0
Age	52.9 ± 2.5	52.7 ± 2.6
Education (years)	13.3 ± 1.7	14.1 ± 2.0
Mood and trauma		
Depression: BDI	4.5 ± 5.5	3.0 ± 4.1
Anxiety: STICSA	24.5 ± 4.1	23.4 ± 2.9
Trauma Exposure: TAA	1.2 ± 1.3#	2.4 ± 2.1
Cocaine		
Past month use days/week	3.9 ± 1.4	-
Past month money spent	$258.64 ± $225.66	-
Heaviest use days/week	5.9 ± 1.6	-
Heaviest weekly cocaine cost	$695.45 ± $624.32	-
Years regular use (⩾weekly)	21.7 ± 4.4	-
Cannabis		
Lifetime weekly users (*n*)	16*	6
Past month weekly users (*n*)	3	0
Past month use days/week[a]	3.5 ± 3.1	N/A
Heaviest days/week[a]	6.4 ± 1.5#	3.8 ± 2.5
Cigarettes		
Past month daily smokers (*n*)	15*	5
Past month daily smokers cigarettes/day[b]	7.8 ± 5.5	7.2 ± 3.0
Alcohol		
Lifetime weekly drinkers (n)	17	10
Past month weekly drinkers (n)	17*	4
Past month use days/week[a]	2.8 ± 1.4	2.6 ± 0.9
Heaviest days/week[a]	4.8 ± 2.4	4.2 ± 2.3

Data presented as means ± SD, except where otherwise specified.
BDI: Beck Depression Inventory; N/A: not applicable; STICSA: State Trait Inventory of Cognitive and Somatic Anxiety; TAA: Trauma Assessment for Adults.
#$p = .05$, cocaine users significantly different from control.
*$p < .05$, cocaine users significantly different from control.
[a]Data from those who reported regular (⩾weekly) alcohol or cannabis use.
[b]Data from those who reported daily cigarette smoking.

Results

Participants

Table 1 shows demographic data on the 22 (four females) COC participants and 19 (four females) CTRLs included. Participants were well matched on demographics.

Table 1 also presents drug use data. In addition to the drug use listed, two CTRL participants tried cocaine once and one reported using cocaine 3–4 times in their lifetime, but none had used the drug in the past year (and none tested positive for drugs during screening). Five COC participants had tried opioids, one had used ecstasy, one reported amphetamine use, four had used hallucinogens, and five phencyclidine. None reported past-month use of drugs except cocaine, cannabis, nicotine, or alcohol. COCs and CTRLs differed in current regular alcohol and cigarette use, and lifetime cannabis use, with COC users showing a trend (p = .05) for more frequent cannabis use during their heaviest use period (Table 1). Groups were similar in number of current regular (⩾weekly) cannabis smokers and lifetime regular alcohol drinkers, alcohol consumption reported by current regular drinkers, and cigarettes smoked in daily cigarette smokers.

Affective state

COC users reported more negative affect before cognitive testing than did CTRLs (t(25.4) = 2.1, p = .04, d = .65). On average, COC had one-point higher scores on PANAS negative affect than CTRLs (range 10–50). There were no differences in positive affect (p = .21; see Table 2).

Premorbid intellectual capacity

There were no differences in WRT word reading, suggesting that premorbid intellectual capacities were similar between COC users and CTRLs (Table 2).

Verbal learning and memory

There was no interaction between trial and group on RAVLT words recalled across the eight recall trials (five learning trials, interference, immediate recall and delayed recall; F(4.0, 154.3) = 0.9, p = .47). There was a marginal main effect of group (F(1,39) = 4.0, p = .054, partial η^2 = .09), such that COCs recalled on average one word fewer per trial than did COCs (see Figure 1). There were no differences in RAVLT recognition scores or false-positive recognition errors (Table 2).

Attention network efficiency

There were no group differences in attention network RT or accuracy for alerting, orienting, or executive control on the ANT (Tables 2 and 3).

Motor inhibition

There were no group differences in SSRT or SST RT on Go trials (Tables 2 and 4).

Processing speed and mental flexibility

There were no differences in TMT completion time or total errors, in either trial A or B, and no group differences in mental flexibility across BCST indices (Table 2).

Visual working memory

There were no group differences in the SOWMT working memory capacity or attention parameters (Table 2).

Verbal attention, working memory, and fluency

There were no group differences in DST forwards or backwards and no differences between groups on COWAT word count or errors (Table 2).

Discussion

This study compared aging cocaine users and matched healthy CTRLs on a broad range of cognitive functions. Cocaine users exhibited similar performance to CTRLs on all cognitive measures employed, except verbal memory, where they showed an average one-word decrement relative to CTRLs across recall trials. This finding, however, was only marginally significant (p = .054). Thus, with the exception of verbal memory, groups had similar cognitive function, despite cocaine users endorsing more polydrug use and greater negative affect before testing than did CTRLs. Importantly, Bayesian analysis (see Table 2) indicated that the null results were not due to power limitations.

The marginal finding of lowered verbal learning in aging cocaine users has a precedent in the literature on cocaine use more broadly. One prior study compared younger cocaine-dependent adults in inpatient treatment to matched healthy CTRLs on RAVLT performance, finding that cocaine users underperformed non-users by around two words per trial. Verbal learning predicted relapse to cocaine use after treatment discharge (Fox et al., 2009). A two-word verbal learning decrement has also been reported in younger non-treatment-seeking adult cocaine smokers (Vadhan et al., 2014). Other evidence suggests a relationship between the extent of cocaine use and worse RAVLT performance following a short period of abstinence (Bolla et al., 2000). Verbal learning has also been documented to be lower in cocaine users relative to CTRLs in meta-analyses (Jovanovski et al., 2005; Potvin et al., 2014). Thus, regular cocaine use does appear to be associated with reduced verbal learning capacity in general, and potentially in older adulthood. Of note, the current findings suggest a smaller cocaine-related decrement in aging cocaine users than those reported previously (e.g. Fox et al., 2009). These findings therefore do not suggest interactive or synergistic effects of aging and cocaine use on verbal learning capacity.

Meta-analyses have indicated reduced functioning in cocaine users compared to CTRLs across several other cognitive domains, with the largest differences in attention, processing speed, visual memory, and working memory (in addition to verbal memory; Jovanovski et al., 2005; Potvin et al., 2014). By contrast, our study found aging cocaine users to show equivalent neurocognitive performance across a range of functions (with the exception of verbal learning), when compared to well-matched CTRLs. There are several possible explanations for this discrepancy. Past study samples have predominantly comprised younger adults who use cocaine (i.e. with ages from approximately 25 to 45). It is possible that cocaine-associated cognitive decrements are more pronounced among younger adults. For

Table 2. Cognitive test results.

	Cocaine users $N = 22$	Controls $N = 19$	p	BF_{01}
Affective state				
Positive affect: PANAS	34.4 ± 10.0	37.9 ± 7.8	.21	-
Negative affect: PANAS	11.0 ± 1.6	10.2 ± 0.5	.04	-
Premorbid IQ				
WRT – Total	27.9 ± 3.9	29.8 ± 5.7	.24	1.8
Verbal learning and memory				
RAVLT – recognition	11.0 ± 2.1	11.8 ± 2.3	.25	1.9
RAVLT – false-positive errors	3.3 ± 2.9	3.1 ± 2.6	.84	3.2
Attention network efficiency				
ANT RT – alerting[a]	0.4 ± 56.7	23.9 ± 71.6	.29	1.9
ANT RT – orienting[a]	42.7 ± 48.9	25.1 ± 42.5	.27	1.9
ANT RT - executive control[a]	179.9 ± 74.1	178.4 ± 58.7	.95	3.1
ANT accuracy – alerting[a]	–0.1 ± 3.0	-0.7 ± 2.6	.53	2.6
ANT accuracy – orienting[a]	–1.0 ± 2.2	-0.3 ± 1.4	.30	2.0
ANT accuracy – executive control[a]	–1.1 ± 1.8	-2.2 ± 2.4	.14	1.3
Motor inhibition				
SST – SSRT[b] (milliseconds)	246.6 ± 146.8	243.7 ± 98.2	.95	3.1
SST – Go RT[b] (milliseconds)	690.4 ± 139.3	773.0 ± 187.1	.16	1.3
SST – SSRT[c] (milliseconds)	237.7 ± 110.0	256.8 ± 105.5	.64	2.6
SST – Go RT[c] (milliseconds)	663.8 ± 127.9	717.6 ± 163.0	.35	2.0
Processing speed and flexibility				
TMT A – time (seconds)	40.0 ± 20.5	38.4 ± 18.3	.80	3.2
TMT B – time (seconds)	107.7 ± 37.2	97.1 ± 35.5	.36	2.3
TMT A – error	0.5 ± 0.8	0.2 ± 0.5	.11	1.2
TMT B – error	2.2 ± 2.5	1.8 ± 2.9	.64	3.0
BCST – categories complete	4.0 ± 2.9	5.1 ± 2.9	.27	2.0
BCST – perseverative errors	50.6 ± 10.7	50.2 ± 16.5[d]	.92	3.2
BCST – non-perseverative errors	20.4 ± 13.9	13.4 ± 7.2[d]	.06	0.8
BCST – failure to maintain set	1.5 ± 1.5	1.1 ± 1.4	.34	2.2
Visual WM				
SOWMT – capacity	2.8 ± 1.1	3.1 ± 1.7	.60	3.2
SOWMT – attention	0.9 ± 0.1	0.9 ± 0.1	.80	2.9
Verbal attention, WM, and fluency				
DST – forward	9.4 ± 2.1	10.1 ± 2.3	.32	2.2
DST – backward	5.2 ± 2.2	5.8 ± 2.6	.46	2.6
COWAT – FAS words	37.4 ± 9.9	37.7 ± 14.3[d]	.94	3.2
COWAT – animal words	18.7 ± 4.4	19.6 ± 6.0	.59	2.9
COWAT – FAS errors	2.7 ± 2.3	1.8 ± 2.7	.26	1.9
COWAT – animal errors	1.2 ± 1.1	0.7 ± 0.8	.11	1.2

Data presented as means (± SD).
ANT: Attention Network Task; BCST: Berg Card Sorting Task; COWAT: Controlled Oral Word Association Test; DST: Digit Span; FAS: words beginning with F, A, and S; Go RT: mean reaction time on correct Go trials; PANAS: Positive and Negative Affect Schedule; RAVLT: Rey Auditory Verbal Learning Task; SOWMT: Self-Ordering Working Memory task; SSRT: Stop Signal Reaction Time; SST: Stop Signal Task; TMT: Trail Making Test; WM: working memory; WRT: Word Reading Test.
[a]Cocaine: $n = 19$, controls: $n = 16$, due to excessive errors.
[b]Cocaine: $n = 21$, controls: $n = 15$, due to excessive errors.
[c]Cocaine: $n = 17$, controls: $n = 12$, after removal of outliers based on "lenient outlier criteria" (see Congdon et al., 2012).
[d]$n = 18$, due to missing data.

instance, neurocognitive declines associated with normal aging in CTRLs (Ersche et al., 2013; Sanvicente-Vieira et al., 2016) could render differences between cocaine users and CTRLs no longer detectable in older adults. This possibility is not, however, supported by our previous pilot study, which found older cocaine users to have poorer attention and memory span compared to age-matched CTRLs (Kalapatapu et al., 2011), a finding that we did not replicate here.

Another possibility relates to our stringent control in this study for potential confounds, which have been addressed to widely varying degrees in previous research. We excluded for psychiatric disorders, known to alter cognitive function, and

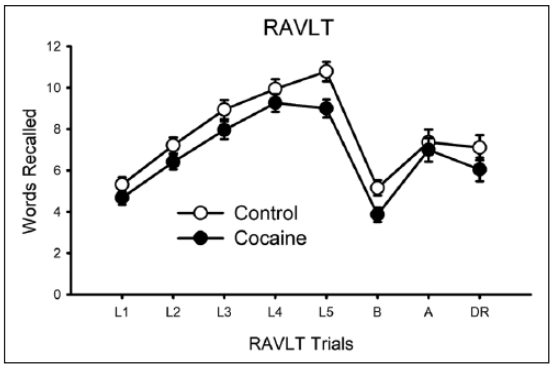

Figure 1. Mean words recalled correctly on the Rey Auditory Verbal Learning Task across recall trials (excludes recognition trial): L1-5: List A learning trials; B: List B interference; A: List A immediate recall; DR: List A 20 minute delayed recall. Error bars represent standard error. There was a trend for the main effect of group ($p = .054$).

groups were well matched on current symptom measures of depression and anxiety. In some previous studies (including our own), cocaine-using groups endorsed more primary psychopathology than did CTRLs (e.g. Kalapatapu et al., 2011), which could have impacted cognitive function. We included control participants with cannabis, alcohol, and cigarette use, to better match the cocaine-using group. CTRLs were also well matched to cocaine users for sex, race, and education, all of which are associated with cognitive outcomes. Finally, cocaine users were tested after several inpatient days; this enabled control of acute and residual drug effects, which can affect cognitive function (Potvin et al., 2014), as well drug-related lifestyle factors such as poor nutrition and sleep deprivation (Bedi and Redman, 2008).

To assess the clinical relevance of the findings, we compared performances on the standardized neuropsychological tasks (WRT, RAVLT, TMT, DST, COWAT) to published norms. After converting individual raw-scores to the demographically adjusted *T*-scores that best-matched participants in terms of age, education, and race (Heaton et al., 2004; Strauss et al., 2006; Wechsler, 1997), the resulting means were within 1 standard deviation of normative means (see Table 5), except for the initial RAVLT learning trials in COCs. Thus, participants overall appear to have performed within the normative range based on their demographic features, supporting the interpretation that cocaine users' function may have been bolstered by control for transient confounds such as recent drug use and sleep deprivation. Future research empirically assessing this possibility would aid interpretation of the overall body of research showing lowered cognition in cocaine users (Jovanovski et al., 2005; Potvin et al., 2014).

Table 3. Attention network task performance.

	Cue condition			Flanker condition	
	No cue	Double	Valid	Congruent	Incongruent
Cocaine users, RT	853.2 ± 137.9	852.8 ± 148.7	810.1 ± 134.4	744.9 ± 124.1	924.8 ± 151.3
(% accuracy)	*(97.4 ± 5.9)*	*(97.5 ± 4.2)*	*(98.5 ± 3.0)*	*(98.6 ± 4.0)*	*(97.5 ± 3.8)*
Controls, RT	872.9 ± 164.1	839.1 ± 167.5	823.8 ± 146.8	760.3 ± 153.2	938.7 ±155.8
(% accuracy)	*(97.7 ± 3.7)*	*(98.5 ± 2.1)*	*(98.8 ± 1.2)*	*(99.5 ± 0.7)*	*(97.3 ± 2.8)*

Data presented as means (±SD), in milliseconds and percentages. RTs are average median reaction times and accuracy. Accuracy scores are percentage of correct responses in each cue and flanker condition.
RT: reaction time.

Table 4. Stop signal task performance.

	Cocaine users[a]	Controls[a]	Cocaine users[b]	Controls[b]
Go trials				
% correct Go	94.5 ± 5.6	93.6 ± 8.2	96.9 ± 2.0	97.2 ± 2.7
% errors	1.0 ± 1.2	0.3 ± 0.6	1.0 ± 1.3	0.3 ± 0.6
% missing	4.5 ± 5.7	6.1 ± 8.2	2.0 ± 2.0	2.4 ± 2.8
RT errors	644.1 ± 232.4[c]	435.3 ± 15.2[d]	613.9 ± 235.9[e]	433.1 ± 16.6[f]
STOP Trials				
% fail stop	47.6 ± 9.0	45.3 ± 8.2	46.8 ± 8.2	46.4 ± 8.6
RT fail stop	620.6 ± 132.7	717.9 ± 174.4	587.1 ± 115.3	665.2 ± 145.6
Stop signal delay	402.4 ± 177.7	512.3 ± 228.7	380.5 ± 137.2	443.3 ± 193.5

Data presented as means (±SD), in milliseconds and percentages.
RT: reaction time.
[a]Cocaine: $n = 21$, controls: $n = 15$, due to excessive errors.
[b]Cocaine: $n = 17$, controls: $n = 12$, after removal of outliers based on "lenient outlier criteria" (see Congdon et al., 2012).
[c]$n = 12$, data from those who made errors on Go trials.
[d]$n = 5$, data from those who made errors on Go trials.
[e]$n = 10$, data from those who made errors on Go trials.
[f]$n = 4$, data from those who made errors on Go trials.

Table 5. Neuropsychological normative comparisons.

	Cocaine users	Controls	Source of normative data
	T-score	*T*-score	
WRT	42.9 ± 5.9	46.6 ± 8.9	Wilkinson, 1994[a]
RAVLT			Strauss et al., 2006[a]
Trial 1	39.2 ± 8.9	43.4 ± 11.2	
Trial 2	38.9 ± 7.2	43.4 ± 10.6	
Trial 3	39.2 ± 8.9	44.7 ± 13.1	
Trial 4	42.9 ± 9.6	46.2 ± 10.2	
Trial 5	40.5 ± 9.1	48.6 ± 9.2	
Total 1-5	38.1 ± 8.5	44.5 ± 10.5	
List B	41.5 ± 7.7	48.7 ± 9.8	
Trial 6	42.9 ± 7.6	44.2 ± 10.9	
Delay recall	41.2 ± 7.8	44.7 ± 9.5	
Recognition	46.8 ± 11.2	51.6 ± 8.2	
TMT A	48.2 ± 9.8	49.7 ± 12.0	Heaton et al., 2004[b]
TMT B	49.3 ± 8.4	51.5 ± 8.7	Heaton et al., 2004[b]
DST	44.5 ± 8.5	48.0 ± 8.6	Weschler, 1997[a]
COWAT – FAS	50.7 ± 8.7	50.2 ± 12.1	Heaton et al., 2004[b]
COWAT – Animals	51.0 ± 8.5	52.0 ± 10.6	Heaton et al., 2004[b]

Data presented as mean *T*-scores (± SD) for cognitive performance, relative to demographically-adjusted normative samples. *T*-scores have a mean of 50 and a standard deviation of 10.
COWAT: Controlled Oral Word Association Test; DST: Digit Span; FAS: words beginning with F, A, and S; RAVLT: Rey Auditory Verbal Learning Task; TMT: Trail Making Test; WRT: Word Reading Test.
[a]Normative data based on age only.
[b]Normative data based on age, race, and education.

As one of the first studies in this population, this study has some limitations. First, given the cross-sectional, non-experimental design and group differences in use of drugs other than cocaine, the specific etiology of marginal group differences in verbal memory cannot be established. However, given potential clinical implications (Aharonovich et al., 2003; Aharonovich et al., 2006; Aharonovich et al., 2008; Fox et al., 2009), characterizing function in this domain is important regardless of causality. Second, cocaine users self-rated higher negative affect before testing than did CTRLs. We did not control for negative affect in analyses, because the difference was small in absolute terms and negative affect was not correlated with any of the verbal learning outcomes ($p > .05$), suggesting it did not influence results. Third, the methods we used to verify compliance with drug abstinence for the outpatient participants did not cover the full length of the abstinence period we asked participants to sustain. For instance, participants were asked to refrain from alcohol use for at least 4 days prior to testing. The breathalyzer is only capable of detecting alcohol exposure within several hours following alcohol consumption. Full compliance with abstinence thus cannot be confirmed. Moreover, CTRLs who completed the study as outpatients did not experience the same controlled environment of a locked psychiatric unit as inpatients or receive a similar level of monitoring days prior to testing, which may have potentially contributed to our results. However, all CTRL participants were required to test negative for alcohol and drug use repeatedly across separate screening days, supporting our conclusion that these CTRLs were not current drug or heavy alcohol users. Fourth, the length of the testing session may have produced fatigue-related performance decrements on tests administered later in the day (e.g. SOWMT). However, group similarities, and the normal clinical range of performance on most tasks indicate at least no preferential effects of fatigue. Fifth, the exclusion of cocaine users with other comorbidities potentially limits the generalizability of our results, given that many cocaine users have other psychiatric or physical conditions. Psychiatric comorbidities were excluded because they have been previously shown to independently affect cognitive performance; a similar approach has been employed in many other studies of cognitive function in cocaine users (Bolla et al., 2000; Di Sclafani et al., 2002; Pace-Schott et al., 2008; Potvin et al., 2014; Woicik et al., 2009). Whereas the focus of the initial study in aging cocaine users was on isolating neurocognitive correlates of cocaine use specifically, an important direction for future research will be to examine cognitive function in relation to cocaine use in the context of psychiatric and physical comorbidities. Finally, we chose to focus resources on recruiting well-matched CTRLs and optimizing the circumstances of testing rather than maximizing the sample size, which likely reduced power to detect small effects. However, Bayesian analysis suggested the absence of group differences was not driven by power limitations – as shown in Table 2, in 28 of the 29 non-significant results the Bayes factor was >1, indicating the null was more likely than the alternative hypothesis given the data (see Table 2).

Study limitations notwithstanding, these data indicate that when tested under controlled conditions, aging cocaine users perform similarly to well-matched CTRLs on most aspects of cognitive function, with marginally lower verbal learning. These results underline the importance of careful matching of comparison samples, and use of inpatient procedures to control for recent drug use and other factors, in studies of this type. Although somewhat reassuring with regard to broader cognitive capacities in aging cocaine smokers, these findings also support further investigation of cognitive function in this and other aging drug using populations.

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