Published in final edited form as:

Psychoneuroendocrinology. 2009 September ; 34(8): 1198–1207. doi:10.1016/j.psyneuen.2009.03.007.

Elevated cortisol and learning and memory deficits in cocaine dependent individuals: Relationship to relapse outcomes

Helen C. Fox^{*}, Eric D. Jackson, and Rajita Sinha

Yale Stress Center, Department of Psychiatry, Yale University School of Medicine, 2 Church Street South, Suite 209, Room 209Q, New Haven, CT 06519, United States

Summary

Objective—Cocaine dependence is characterized by stress system dysregulation, including elevated cortisol activity, emotional negativity, and behavioral disinhibition. High levels of stress and glucocorticoids are also known to affect learning, memory and executive function. Therefore, we examined the relationships between chronic cocaine use, elevated distress and learning and memory dysfunction in abstinent cocaine dependent (CD) individuals, and whether these measures were associated with cocaine relapse outcomes.

Method—Stress was assessed in 36 inpatient treatment engaged CD individuals and 36 demographically matched healthy control (HC) participants using the Perceived Stress Scale (PSS) and repeated morning salivary cortisol levels over three consecutive days. The Rey Auditory Verbal Learning Test (RAVLT) was conducted to measure verbal learning, memory, and executive function. Prospective assessment of cocaine use outcomes during 90 days following discharge from inpatient treatment was also conducted.

Results—CD patients showed higher levels of distress compared to controls in PSS scores and cortisol levels. They also demonstrated a significantly reduced learning curve, and fewer correct responses and more errors on recognition. Elevated cortisol was significantly associated with worse RAVLT performance in CD patients. Poor memory scores, but not distress measures, were significantly associated with greater cocaine use after inpatient treatment.

Conclusions—These findings are the first to demonstrate that learning and memory deficits in CD individuals are associated with enhanced cortisol and with cocaine use outcomes after inpatient treatment. The findings are consistent with recent addiction models suggesting that chronic cocaine-related neuroadaptations affects learning and memory function, which in turn, influences drug use outcomes.

Keywords

Cocaine; Memory; Cortisol; Stress; Learning; Relapse

1. Introduction

Increased distress and elevated cortisol levels are associated with selective cognitive impairment in various clinical groups including aging populations, individuals with Alzheimer's disease and Cushing's syndrome (Lupien et al., 2005). Chronic cocaine dependence also represents an analogous distress state marked by Hypothalamus—Pituitary

^{*}Corresponding author. Tel.: +1 203 737 3436; fax: +1 203 737 1272. E-mail address: helen.fox@yale.edu (H.C. Fox).

Conflict of interest

The authors declare that they have no competing financial interests or conflict of interest relating to the data included in this manuscript.

—Adrenal (HPA) dys-regulation and enhanced sensitivity to negative emotion (Sinha et al., 2003; Fox et al., 2008a,b). Persistent memory deficits have been associated with chronic cocaine abuse (Beatty et al., 1995; Bolla et al., 1999), although there is some ambiguity regarding the specificity of impairment. Furthermore, while preclinical models of addiction have shown that stress and corticosterone-related mechanisms contribute both to learning deficits (Lemaire et al., 2000; Ehninger and Kempermann, 2006) and drug-seeking (Goeders, 2002 for review) in rats, this has not been fully assessed in cocaine dependent (CD) individuals.

In the first aim, we hypothesized that the subjective and biological distress state as well as learning and memory function will be altered in treatment engaged inpatient CD individuals compared to demographically matched healthy controls. Our prior research has shown increased basal and response levels of cortisol, anxiety and emotional negativity in CD patients reflecting an enhanced stress state during early abstinence (Sinha et al., 2003; Fox et al., 2008a,b). Human studies have also documented difficulties in executive control, attentional tasks of cognitive flexibility, motor skills and verbal learning and memory in CD individuals (Beatty et al., 1995; O'Malley et al., 1992; Toomey et al., 2003), although findings have not always shown consistency. In the current study, learning and memory was assessed using the Rey Auditory Verbal Learning Task (RAVLT; Rey, 1998) which comprises a repetitive learning paradigm across multiple trials measuring immediate and delayed recall as well as recognition. It also assesses executive functions, recruited to inhibit incorrect responses following interference and has shown sensitivity to cognitive deficits associated with prolonged corticosteroid elevations in patients receiving chronic corticosteroid therapy for either asthma or rheumatic diseases (Brown et al., 2004).

In the second aim, we hypothesized that stress will be associated with learning and memory function in the CD and the HC participants. A wide range of experimental and clinical paradigms have shown stress to impact multiple memory systems in a highly selective manner. Recent findings show that declarative memory deficits relating to valence and working memory impairments are observed following exposure to stress in healthy volunteers (Luethi et al., 2008; Smeets et al., 2006). In addition, meta-analyses studies in PTSD populations have shown consistent verbal memory deficits relating to encoding strategies in both the RAVLT and the California Verbal Learning Test (CVLT) (Johnsen and Asbjørnsen, 2008, 2009). As cocaine dependence is a chronic stress state characterized by sensitized HPA-axis function (Sinha et al., 2006; Fox et al., 2008b), high levels of cortisol may represent one of the mechanisms underlying learning and memory impairment in these individuals.

High levels of cortisol are associated with a decrease in hippocampal neurogenesis in rats (Yamaguchi et al., 2005) as well as increases in hippocampal atrophy, neurotoxicity to the prefrontal cortex and memory deficits in human aging populations (Wolkowitz et al., 2007; Lupien et al., 1998). High levels of cortisol are also known to have detrimental effects on glutamate-related long-term potentiation (LTP) involved in learning and memory formation (Kerr et al., 1991; Lowy et al., 1995). Similarly, prolonged glucocorticoid therapy, often used clinically as an anti-inflammatory (Lim and Conn, 2001) is associated with deficits in declarative memory (Brunner et al., 2005; Wolkowitz et al., 1997) and decreased cognitive function has been observed in healthy adults following exogenous cortisol administration (De Quervain et al., 2000). Prolonged hippocampal disinhibition and cognitive decline have also been observed in aging and depressed human populations, often characterized by high cortisol levels (Lupien et al., 1998; Porter and Landfield, 1998; Brunner et al., 2005). While no previous study has examined stress and cortisol effects on learning and memory function in CD individuals, chronic cocaine-related alterations in frontolimbic-striatal brain regions are well documented in both animal and human research (Porrino et al., 2007; Goeders and Guerin, 2008; Kalivas and O'Brien, 2008). These include changes to catecholamine, corticotropin-releasing factor (CRF) and glutamatergic pathways known to modulate cognitive, emotional

and neuroendocrine function as well as cocaine self-administration (Goeders and Guerin, 2008; Kalivas and O'Brien, 2008).

Recent models have characterized addiction as a disruption of neural systems and synaptic plasticity involved in reward, motivation, and learning and memory acquisition required to record details of experiences. These include alterations to cortisol, dopamine and glutamate systems in the prefrontal cortex and mid-brain structures (Kalivas and O'Brien, 2008; Hyman, 2005) as well as reductions in hippocampal sub-granular neuronal proliferations (Kitabatake et al., 2007). Moreover, such disruption in learning and memory processes may significantly influence the maintenance of drug abuse and the high rates of relapse associated with addictive disorders (Hyman and Malenka, 2001). Consistent with these models, both stress-related HPA-axis responses and cognitive impairment have been found to represent risk markers for relapse vulnerability in cocaine dependence (Sinha et al., 2006; Aharonovich et al., 2003, 2006). Thus, in the third aim, we prospectively examined the relationship between stress during abstinence, learning and memory function and cocaine use outcomes following inpatient treatment.

2. Method

2.1. Participants

Thirty-six treatment-seeking CD individuals (18 M/18 F) were matched on age, gender, and race to 36 HC participants (16 M/20 F). All participants were recruited via advertisements placed either on-line or in local newspapers. The Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders IV (SCID IV; First et al., 1995) and urine toxicology screens were used to verify current cocaine dependence in the CD patients and absence of substance-related disorders in the HC group. CD participants were excluded if they met current or lifetime dependence criteria for any other illicit drug. However, patients with concurrent alcohol and nicotine use disorders were not excluded, due to high rates of alcohol and nicotine abuse comorbidity with cocaine dependence (Brookoff et al., 1996). Participants using any medication and those with current medical problems were also ineligible. After complete description of the study to participants, written informed consent was obtained and the study was approved by the Human Investigation Committee of the Yale University School of Medicine.

2.2. Inpatient procedures

CD participants were admitted to the Clinical Neuroscience Research Unit (CNRU) for 3–4 weeks of inpatient treatment (including individual and group therapy) and study participation. The CNRU is a locked treatment research facility with no access to alcohol or drugs and limited access to visitors. Drug testing was conducted regularly to ensure abstinence. All assessments were administered to CD participants following 2 weeks of inpatient treatment to account for the potential influence of acute withdrawal symptomatology on dependent measures. HC participants were tested during a 4 day/3 night stay at the Hospital Research Unit of the Yale Center for Clinical Investigation (HRU-YCCI), thus providing a similar controlled environment to the CD participants. All participants completed assessments to obtain socio-demographic history, DSM-IV psychiatric diagnoses (First et al., 1995), and estimated IQ using the Shipley Institute of Living Scale (Shipley, 1940).

2.3. Dependent measures

2.3.1. Salivary cortisol—Six saliva samples were collected using Salivette tubes on 3 consecutive mornings (two per morning between 8:45 AM and 9:00 AM prior to breakfast) to obtain an average measure of morning cortisol. Saliva swabs were collected in plastic tubes, placed directly on ice and stored at -20°C . Samples were assayed following standard radioimmunoassay kits with no modifications (Coat-A-Count Cortisol Kit, Diagnostic

Products Corporation, Los Angeles, CA) at the YCCI Core Laboratories. Intra-assay coefficients of variation ranged from 3.0% to 5.1%.

2.3.2. Perceived Stress Scale—PSS (Cohen et al., 1983)—PSS is a highly reliable and widely used self-report questionnaire that examines the extent to which general situations in the past week are appraised as stressful. It comprises 14-items, including statements such as: *“In the last week, how often have you been upset because of something that happened unexpectedly?”*, or *“In the last week, how often have you dealt successfully with irritating life hassles?”* with scores for each item response ranging from 0 (never) to 4 (very often), then summed. Positive items are reverse coded.

2.3.3. Rey Auditory Verbal Learning Test—RAVLT (Rey et al., 1998; see Fig. 1)—The RAVLT involved the repeated administration of one word list (List A) across 5 learning trials (Trials 1–5). Free recall immediately followed each presentation. After the last learning trial a second “interference” list (List B) was presented prior to the free recall of List B. Immediately following recall of List B, participants were again required to recall List A, without additional presentation (Trial 6). After a 45 min delay, during which all participants were administered a routine questionnaire, they were again asked to recall List A without presentation (Trial 7). All responses were recorded onto a tape for subsequent scoring. No time limit was applied to the recall trials and participants were prompted to recall all of the words (in any order) on each occasion, regardless of whether they had recalled them on previous trials. Both stimulus word lists (A and B) were presented to the participants on tape, at a rate of one word per second. Following the delayed recall trial, a recognition word list was presented comprising 45 words, 15 of which were target words from List A, and 15 that were from List B, and 15 that were either phonologically or semantically similar to the words in List A. Participants were instructed to check the 15 words presented in List A.

RAVLT scoring: A recall score for each trial (T1–T7) was obtained by calculating the total number of words correctly recalled. Confabulation errors (CE) for each trial were calculated by tallying the number of incorrectly recalled words that were unrelated to words in the stimulus list. Association errors (AE) for each trial were calculated by tallying the number of incorrectly recalled words that were either semantically or phonetically linked to words in the stimulus list. Repetitions on each trial were calculated by tallying the number of times any word was repeated. The total number of intrusion errors (List A to B and List B to A errors) was also calculated.

The recognition score was obtained by calculating the total number of words correctly recognized (i.e., hits). The number and type of false alarm errors were also recorded. These included words that were either phonologically similar to the target words (phonological errors), semantically similar to the target words (semantic errors), words that had appeared in List B (intrusion errors) and the total number of errors (total errors).

Learning summary scores were also calculated. Total Learning (TL) was calculated by summing the number of correct words recalled across the 5 learning trials. Learning Rate (LR) was calculated by subtracting Trial 1 recall from Trial 5 recall. Proactive Interference (PI) was calculated by subtracting Trial 1 recall from Interference list recall. Forgetting was assessed with 2 Long-Term Retention (LTR) scores. LTR-1 was calculated by subtracting Trial 5 recall from Trial 7 (delayed) recall, whereas LTR-2 was calculated by subtracting Trial 6 recall from Trial 7 (delayed) recall.

2.4. Cocaine use following inpatient treatment

All CD patients participated in a face-to-face follow-up interview at 90 days, where they provided urine and breath alcohol samples and a detailed daily assessment of cocaine use using the Time-line follow-back method on the Substance Use Calendar (SUC). This is a well established and reliable instrument for assessing self-reported alcohol and drug use outcome measures in treatment studies (Scheurich et al., 2005). The SUC was administered to CD participants while on the inpatient unit to assess baseline levels of cocaine use during the 90 days prior to treatment as well as at the 90-day follow-up interview. As in our previous studies (Sinha et al., 2006; Paliwal et al., 2008), the urine and the SUC data were matched for corroboration, and number of days of use (*frequency*) and average amount of cocaine used per occasion (*quantity*) in the 90 days follow-up period was calculated as measures of cocaine use outcomes.

2.5. Statistical analyses

The groups were compared on demographics and substance use measures using either *t* test or chi-square and measures on which groups differed were included as covariates in all analyses. Group differences in stress measures and RAVLT scores were assessed using analyses of variance and covariance (ANOVA/ANCOVA). Linear mixed effects (LME) models were performed on the repeated recall and error scores (Trials 1–7). Fixed effects factors included, Trials (7 within-subject levels) and Group (CD or HC). Analysis of recall errors included an additional within-subject factor, Error Type (association or confabulation). Significant effects were further explored using Bonferroni-corrected pair wise comparisons. Partial Pearson correlation coefficients were used to evaluate the relationship between RAVLT scores, morning salivary cortisol and PSS scores. Finally, stepwise multiple regression analyses were used to assess if there was any significant relationship between stress measures, RAVLT scores and cocaine use outcomes.

3. Results

3.1. Sample characteristics (see Table 1)

Significant effects and trends were tested between memory scores and relapse outcome and the following demographic factors in order to determine covariates: gender, age, race, smoking status, lifetime criteria for anxiety disorders, lifetime criteria for mood disorders (including depression), employment and marital status, years of education and Shipley estimated IQ. If any of these measures were associated with either memory scores or relapse outcome they were included as covariates in examining the association between stress, memory and relapse. Demographic measures of gender, age, race, lifetime criteria for mood disorders (including depression), employment and marital status were not associated with either learning or cocaine relapse outcomes.

Smoking status ($r = -0.47, p < 0.001$) and IQ ($r = 0.66, p < 0.001$) were both significantly correlated with memory and therefore used as covariates in all models. Although years of education was also associated with memory, IQ only was used as a covariate as it was more strongly associated with memory scores. Both factors were not included as covariates together as they were highly correlated with each other ($r = 0.60, p < 0.001$). Lifetime criteria for anxiety disorders were also used as a covariate due to significant variation between groups (see Table 1).

The CD group had significantly lower IQ, more nicotine smokers, and more individuals meeting lifetime criteria for anxiety disorder than the HCs. They were also more likely to be unemployed. Forty-seven percent of the CD sample also met criteria for alcohol dependence

and secondary analyses were conducted to examine whether the subgroup of CD patients with alcohol dependence and those without were different in the dependent measures.

3.2. Group differences in stress measures

CD patients reported greater perceived stress [without covariates: $F(1, 67) = 39.49, p < 0.001$; with covariates: $F(1, 64) = 6.19, p = 0.02$] and demonstrated higher levels of morning salivary cortisol [without covariates: $F(1, 70) = 8.99, p = 0.004$; with covariates: $F(1, 67) = 4.39, p = 0.04$] than the HC group. No differences between CD patients with and without alcohol dependence was observed.

3.3. Group differences in RAVLT learning and memory

3.3.1. List A recall—A main effect of Trial [$F(6, 172.5) = 37.4, p < 0.001$] indicated that scores in both groups incrementally improved following each presentation of List A and then declined after the interference and delay. Overall, the CD group recalled significantly fewer words from List A across all trials (Trials 1–7) than the HC group [main effect of Group without covariates: $F(1, 71.1) = 43.64, p < 0.001$; with covariates: $F(1, 67.4) = 6.01, p = 0.02$]. A significant interaction between Group and Trials [without covariates: $F(6, 229.7) = 3.72, p = 0.001$; with covariates: $F(6, 230.9) = 3.74, p = 0.001$] indicated that on all recall trials except for Trial 1 the CD group recalled significantly fewer words than the HC group (Fig. 2a). Analyses of Total Learning (TL) and Learning Rate (LR) summary scores confirmed this general pattern of results. Main effects of Group indicated that worse TL in the CD group [without covariates: $F(1, 70) = 41.2, p < 0.001$; with covariates: $F(1, 67) = 5.13, p = 0.03$] was the result of decreased LR across learning trials [without covariates: $F(1, 70) = 7.28, p = 0.01$; with covariates: $F(1, 67) = 5.13, p = 0.03$]. No significant group differences were observed in retention summary scores.

3.3.2. List A errors—The relative learning deficit in the CD group was accompanied by significantly more commission errors, as indicated by a significant main effect of Group [without covariates: $F(1, 72.1) = 21.5, p < 0.001$; with covariates: $F(1, 67.7) = 8.50, p = 0.01$] and interaction between Group and Trials [without covariates: $F(6, 629.0) = 2.32, p = 0.03$; with covariates: $F(6, 628.8) = 2.32, p = 0.03$]. Similarly, group differences in errors generally increased across trials (Fig. 2b). Although association errors were more common than confabulation errors overall [$F(1, 186.2) = 25.25, p < 0.001$], the interaction between Error Type and Group did not reach statistical significance [$F(1, 186.2) = 2.95, p = 0.09$]. On average, the CD group incorrectly recalled nearly two more words than the HC group (2.20 ± 0.59 vs. 0.31 ± 0.11).

The CD group also made more repetition errors than the HC group, but only on select trials [Group $\times$ Trial interaction without covariates: $F(6, 238.7) = 3.42, p = 0.003$; with covariates: $F(6, 237.9) = 3.41, p = 0.003$]. Pair wise comparisons showed that group differences reached statistically significant levels on Trial 5 [$F(1, 147.8) = 10.0, p = 0.002$] and Trial 7 [$F(1, 148.0) = 7.46, p = 0.01$], and reached trend levels on Trial 1 [$F(1, 148.8) = 3.68, p = 0.06$] and Trial 6 [$F(1, 146.9) = 3.43, p = 0.07$].

3.3.3. Interference trial (List B)—The CD group recalled significantly fewer words from the Interference trial than the HC group [main effect of Group without covariates: $F(1, 70) = 38.26, p < 0.001$; with covariates: $F(1, 67) = 10.82, p = 0.002$]. Analysis of the Proactive Interference (PI) summary score also detected a main effect of group [without covariates: $F(1, 70) = 3.55, p = 0.06$; with covariates: $F(1, 67) = 6.46, p = 0.01$]. Together, these results indicate that on the Interference Trial, supra-span immediate memory, which did not differ between groups on Trial 1, was detrimentally influenced by the other 4 learning trials in the

CD group but not the HC group. Analysis of Interference Trial errors detected no significant group differences.

3.3.4. Recognition—A main effect of Group was detected for recognition hits [without covariates: $F(1, 67) = 28.70, p < 0.001$; with covariates: $F(1, 64) = 7.37, p = 0.01$]. On average, the CD group recognized approximately two fewer words than the HC group (11.8 ± 0.42 vs. 14.2 ± 0.17). This relative deficit in recognition memory was accompanied by more semantic errors [1.25 ± 0.22 vs. 0.36 ± 0.08 ; without covariates: $F(1, 66) = 15.69, p < 0.001$; with covariates: $F(1, 63) = 5.76, p = 0.02$]. Group differences in phonological and interference errors did not reach statistical significance.

In all of the learning and memory analyses listed above, the CD group with alcohol dependence was not found to be different from the CD alone group.

3.4. Relationship between stress levels and learning and memory scores

Higher perceived stress in all participants was associated with worse memory during the learning Trials 1–5 ($r = -0.28, p = 0.02$), but not when analyzed separately in either group. However, higher salivary cortisol levels in the CD group were associated with worse Total Learning during Trials 1–5 (without covariates: $r = -0.35, p = 0.04$; with covariates: $r = -0.45, p = 0.01$; Fig. 3a). In the control group, the opposite pattern was found, indicating higher cortisol was associated with better Total Learning (without covariates: $r = 0.44, p = 0.01$; with covariates: $r = 0.44, p = 0.01$; Fig. 3b).

3.5. Relationship between stress, learning and memory and cocaine use measures

The number of days of cocaine use 90 days prior to treatment was associated with worse recall on memory Trial 6 (without covariates: $r = -0.32, p = 0.05$; with covariates: $r = -0.41, p = 0.02$) and Trial 7 (without covariates: $r = -0.35, p = 0.04$; with covariates: $r = -0.40, p = 0.03$) and the total amount of cocaine used was associated with worse retention (LTR-1 without covariates: $r = -0.38, p = 0.03$; LTR-1 with covariates: $r = -0.39, p = 0.03$; LTR-2 without covariates: $r = -0.38, p = 0.03$; LTR-2 with covariates: $r = -0.38, p = 0.03$). Prior cocaine use was not associated with cortisol or PSS scores.

Stepwise multiple regression was used to assess whether basal cortisol, perceived stress, and total learning were significantly associated with cocaine use outcomes after controlling for baseline cocaine use. Findings indicated that only Total Learning remained significant, even after covariates were included in the model. Worse Total Learning (TL) scores were predictive of poor cocaine use outcomes accounting for 29% and 12% of the variance in amount and frequency of cocaine used over the 90-day follow-up period (amount of cocaine used: $\beta = -0.49, R^2 = .29, F = 7.39, p = 0.002$; number of days cocaine used: $\beta = -0.34, R^2 = .12, F = 4.10, p = 0.05$) Fig. 3c and d.

4. Discussion

Current results indicate that abstinent, treatment engaged CD patients demonstrate increased levels of subjective stress, higher morning cortisol levels and selective learning-related deficits compared with healthy controls. Learning-related deficits included poor immediate and delayed verbal recall and recognition as well as selective working memory decrements. Moreover, in CD patients only, enhanced levels of basal cortisol were significantly associated with worse immediate recall during the learning trials. Poor verbal learning was subsequently associated with more extensive cocaine use following discharge from inpatient treatment. These results remained significant even after controlling for group differences in estimated IQ, smoking status and presence of lifetime anxiety disorder diagnoses. Therefore, the enhanced

distress state in CD patients (Sinha et al., 2003; Fox et al., 2008a,b) may contribute to selective memory and learning deficits, which in turn, may be associated with greater cocaine use outcomes after discharge from inpatient treatment.

In this study, high cortisol in the CD patients and increased perceived stress in all participants was associated with worse learning. This supports the “glucocorticoid-cascade” hypothesis, which proposes that exposure to increasing levels of glucocorticoids can mediate degeneration of the hippocampus in humans culminating in declarative memory dysfunction and hippocampal disinhibition (Sapolsky et al., 1986; Het et al., 2005). This is also supported by animal models which have shown that hippocampal-related cognitive and learning paradigms such as water maze and place recognition task (Madsen et al., 2003) regulate adult hippocampal neurogenesis (Kitabatake et al., 2007; Hairston et al., 2005). Notably, stress (Ehninger and Kempermann, 2006), elevated levels of corticosterone (Cameron and Gould, 1994; Wong and Herbert, 2004) and cocaine administration (Noonan et al., 2008; Yamaguchi et al., 2005) have all been shown to induce decreases in hippocampal cell proliferation and cell survival in rats, resulting in deleterious effects on learning (Lemaire et al., 2000).

In the current study, however, while higher levels of cortisol were associated with poorer verbal recall in the CD patients, increased basal cortisol in the HCs was associated with *improved* recall. Although appearing paradoxical at first, the data are consistent with the theory that circulating levels of cortisol affects memory following the inverted-U shaped function, where moderate increases in cortisol levels enhance hippocampal-based cognitive processes, while large increases are detrimental (De Kloet et al., 1999). Experimentally, this has been demonstrated by showing that the deleterious effects of hydrocortisone are observed in the morning when cortisol levels are at their peak, but not in the evening during the cortisol trough (Fehm-Wolfsdorf et al., 1993). In terms of current data, significantly increased cortisol levels within CD patients suggests a sensitized HPA system (Sinha et al., 2006; Fox et al., 2008b) with detrimental effects on memory and learning. Conversely, lower cortisol levels in controls suggest a normal HPA system wherein increases are associated with enhanced cognitive function. Future research is, however, warranted in order to fully assess the diurnal patterns of cortisol across a significant time period within these populations.

Although a comprehensive neuropsychological profile of cocaine abstinence is difficult without corresponding imaging data, current findings are suggestive of selective fronto-hippocampal dysregulation associated with cocaine dependence. Reduced declarative memory and recognition ability demonstrated by the CD patients are typically associated with damage to the hippocampal regions and may reflect temporal medial lobe dysfunction (Wixted and Squire, 2004). CD patients also demonstrated significantly poorer recall on the interference trial indicating that the presentation of previous trials detrimentally effected supra-span; not originally impaired on Trial 1. Moreover, a higher number of recall errors and recognition false alarms have consistently implicated the frontal cortex and medial temporal lobe memory areas (Schacter and Slotnick, 2004).

Notably, these brain regions are also associated with motivational dysfunction implicated in stress-related drug-seeking behavior. For example, compared with controls, CD individuals demonstrate less functional activity in frontal, hippocampal and para-hippocampal regions during stress-induced craving (Sinha et al., 2005). These data support current findings that fronto-hippocampal memory circuits may be compromised during distress states, and subsequently increase risk of relapse. This is highlighted by the fact that reduced verbal learning ability on immediate recall trials during early abstinence was predictive of greater cocaine use following discharge from treatment. More importantly, relapse severity was associated with learning deficits only and *not* morning cortisol levels, emphasizing the potentially unique effects of learning and memory dysfunction on cocaine use outcomes.

The ability to learn new skills are required in pursuing a drug-free lifestyle and coping with high-risk situations represent the cornerstone of several empirically validated treatments for CD individuals, such as Cognitive-Behavioral Therapy (CBT) (Aharonovich et al., 2006; Carroll et al., 2005). Recent studies are already indicating that mild cognitive impairments in cocaine abusers detrimentally affect retention and abstinence in outpatient CBT programs (Aharonovich et al., 2003, 2006). Furthermore, glutamatergic agents such as Modafinil, which have been shown to prolong cocaine abstinence (Dackis et al., 2005), also have beneficial effects on both executive control and episodic memory in patients with Major Depression (DeBattista et al., 2004) and ADHD (Turner et al., 2004). Together with the current findings, one implication of this research is that improvement in learning and memory function in cocaine dependence could serve as an added marker of drug efficacy in future treatment development research. Similarly, in addition to pharmacological intervention therapy, potential improvements in mnemonic function and learning could also serve as easily quantifiable markers of treatment efficacy for other clinical therapies ranging from psychotherapy to neuro-biofeedback.

In relation to study limitations, while findings support important associations between stress, learning and subsequent cocaine use outcomes, memory scores accounted for only 12% and 29% of the variance in cocaine use outcomes. This may reflect the fact that the association between recall score, morning cortisol and risk of cocaine use may be markedly increased under more emotionally charged, stressful situations. For example, several cortisol treatment studies have shown that the negative effects of glucocorticoids on memory retrieval are exacerbated with emotionally arousing stimuli (Wolf, 2008). Systematically increasing stress and cognitive demand when using tests such as the RAVLT may therefore allow for a more thorough assessment of retrieval abilities in challenged states. This may also highlight one of the reasons for not observing a direct association between cocaine use, basal cortisol levels and relapse factors in the current study. It maybe that the actual perturbations in cortisol levels either following acute stress (Sinha et al., 2006) or across time (Contoreggi et al., 2003; Buydens-Branchey et al., 2002) reflect more robust indicators of relapse vulnerability and cognitive impairment. It is also important to note that while the RAVLT represents a multi-factorial test assessing encoding, short and long-term memory, recognition and interference, neurocognitive assessment using a wider battery of tests is warranted in order to fully determine the nature of impairment specificity in CD populations. In addition, future research using larger subject samples and structured equation modeling analyses may illustrate more comprehensively the relationships between chronic cocaine use, stress, cognition and relapse.

Nonetheless, the present study is the first to report that a state of high distress may contribute to poor verbal learning and memory function in CD individuals, which in turn, is a significant factor affecting cocaine use outcomes and maintenance of dependence. Notably, compromised cognitive ability associated with heightened distress states in CD individuals may also promote habitual drug-seeking and could serve as a marker for treatment efficacy in the development of new treatments to combat cocaine dependence.

Acknowledgments

Role of funding source

Funding for this study was provided for by the National Institutes of Health and its Office of Research on Women's Health (ORWH), Bethesda, MD, USA. These funding bodies had no further role in study design; in the collection, analysis or interpretation of data; in the writing of the report or the decision to submit the paper for publication.

This study was supported in part by grants R01-AA13892 (Sinha), P50-DA16556 (Sinha), K02-DA17232 (Sinha) and NIH/NCRR/CTSA Program Grant #1 UL1 RR024139 from the National Institutes of Health and its Office of Research on Women's Health (ORWH), Bethesda, MD, USA. We also wish to thank the staff at the Clinical Neuroscience

Research Unit and the Hospital Research Unit of the Yale Center for Clinical Investigation at Yale University School of Medicine for their assistance in completing this study.

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Note. A: target (A List) words; B: B List words; S: words semantically similar to target words; P: words phonemically similar to target words.

* List A and B words presented at 1 second intervals

Figure 1.

Schematic diagram of RAVLT task including trials and items.

Figure 2.

(a) Group differences in the number of words recalled on each RAVLT List A trial between healthy control and cocaine dependent participants. (b) Group differences in the number of errors made on each RAVLT List A trial between healthy control and cocaine dependent participants.

Figure 3.

(a–d) Graphs showing the associations between verbal learning (Trials 1–5), salivary cortisol and cocaine use outcomes.

Table 1

Group demographics and drug use.

	Cocaine (CD) <i>n</i> = 36	Healthy (HC) <i>n</i> = 36	<i>p</i>
Age	37.0 ± 0.97	33.7 ± 1.7	ns
Gender (% male)	18 (50)	16 (44.4)	ns
Race (% Caucasian)	14 (38.9)	21 (58.3)	ns
Tobacco smoking (% smokers)	31 (86.1)	6 (16.7)	<0.001
Estimated IQ (Shipley Institute of Living Scale)	104.0 ± 1.88	116.56 ± 1.06	<0.001
Years of education	11.9 ± 0.28	14.8 ± 0.33	<0.001
Unemployed (%)	61.1	19.4	0.001
Lifetime anxiety disorder diagnosis (%)	17 (47.2)	3 (8.3)	<0.001
Lifetime mood disorder diagnosis (%)	6 (16.7)	2 (5.6)	ns
Lifetime alcohol dependence diagnosis (%)	17 (47.2)	—	
Perceived Stress Scale—total score	27.8 ± 1.2	17.4 ± 1.1	<0.001
Basal salivary cortisol—μg/dl	0.23 ± 0.01	0.18 ± 0.01	<0.01
Cocaine use 3 months prior to treatment			
Number of days used	45.8 ± 4.2	—	
Total amount used—grams	78.7 ± 21.6	—	
Number of years used	9.1 ± 1.0	—	
Cocaine use at 90-day follow-up			
Relapse rate (%)	29 (80.6)	—	
Number of days used	16.9 ± 3.4	—	
Total amount used—grams	12.7 ± 2.7	—	