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Severity of neuropsychological impairment in cocaine and alcohol addiction: association with metabolism in the prefrontal cortex

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Abstract

We used exploratory and confirmatory statistical approaches to study the severity of neuropsychological (NP) impairment in 42 crack/cocaine addicted subjects and in 112 comparison subjects (40 alcoholics and 72 controls). Twenty neuropsychological test indices most reliably defining predetermined cognitive domains were submitted to exploratory factor analysis. A four-dimensional model of neurocognitive function was derived: Verbal Knowledge, Visual Memory, Verbal Memory, and Attention/Executive functioning accounted for 63% of the variance. We then examined this model's association with resting glucose metabolism in the brain reward circuit measured with 2-deoxy-2[^{18}F]fluoro-D-glucose positron emission tomography. Results revealed that (1) cocaine addicted individuals had a generalized mild level of neurocognitive impairment (<1 S.D. below control mean); and (2) controlling for age and education, relative metabolism in the dorsolateral prefrontal cortex significantly predicted the Visual Memory and Verbal Memory factors and relative metabolism in the anterior cingulate gyrus significantly predicted the Attention/Executive factor. Nevertheless, it remains to be determined whether metabolic changes in these regions are associated with addiction. Our results also suggest that compared to cocaine, alcohol has a more detrimental effect on Attention/Executive functioning, as assessed with traditional NP measures. We conclude that relative to other psychopathological disorders (such as schizophrenia), the severity of neuropsychological impairment in cocaine addiction is modest, albeit not indicative of the absence of neurocognitive dysfunction. The impact of such small differences in performance on quality of life, and possibly on craving and relapse, may be substantial. Tasks that simulate real-life decision-making or that target specific putative cognitive-behavioral or motivational–emotional mechanisms might offer greater sensitivity in characterizing the changes that accompany addiction to drugs. Obtaining valid estimates of alcohol use in cocaine addicted subjects is essential in characterizing neurocognitive functioning in individuals addicted to drugs.
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1. Introduction

Despite the growth of the research on the cognitive deficits in cocaine abusers (reviewed in Rogers and Robbins, 2001), the nature of these deficits is uncertain and the study of their putative neuropathological mechanisms is still in its infancy. Variability in research findings comparing cocaine users to non-users contributes to the delay in establishing a consensus on the magnitude and pattern of the neuropsychological (NP) deficits in cocaine addic-

tion. Thus, although significant decrements are revealed in many of the NP studies (e.g., Beatty, Katzung, Moreland, & Nixon, 1995; Gillen et al., 1998; Rosselli & Ardila, 1996), lack of significant differences between cocaine users and non-users are common (e.g., Bolla, Rothman, & Rothman, 1999; Selby & Azrin, 1998) and counterintuitive results, where cocaine users outperform controls, are also frequently reported (e.g., Bolla et al., 1999; Gillen et al., 1998; Hoff et al., 1996; van Gorp et al., 1999).

Characterizing the underlying cognitive domains instead of analyzing multiple single test indices of cognitive functioning, might minimize some of this variability. Factor analytic techniques are ideal for reducing the redundant

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information contained within multiple single measures into a few separate dimensions. This is important because most tests in common clinical NP use place simultaneous demands on several cognitive functions. Analyzing this smaller set of variables would also increase sample-to-variable ratio, thereby reducing chance findings while preserving the measured content.

The analysis of cognitive domains in drug addiction has been previously undertaken in our laboratory (Hoff et al., 1996) and by others (e.g., Beatty et al., 1995; Di Sclafani, Tolou-Shams, Price, & Fein, 2002; Gillen et al., 1998; Robinson, Heaton, & O'Malley, 1999; Selby & Azrin, 1998). However, factor analytic techniques were not employed and no effort was made to empirically test the a priori assignment of test measures into the predetermined cognitive clusters.

Moreover, the relationship of these cognitive domains with brain function (e.g., Hoff et al., 1996; Holman et al., 1991; Mittenberg & Motta, 1993; Strickland et al., 1993) has not been determined. Associations between cerebral perfusion and neurocognitive performance in drug addicted individuals have been previously deducted from the co-occurrence of perfusion abnormalities and NP impairments in the same individuals (see for example Gottschalk, Beauvais, Hart, & Kosten, 2001; Holman et al., 1991; Strickland et al., 1993). When the analysis of correlations between functional measures of brain and behavior was conducted, sample sizes were limited (Wang et al., 1993), specific cognitive domains were not examined (Woods et al., 1991), or regional brain measures were not used (e.g., Di Sclafani et al., 1998).

In the present study, 20 NP test indices most reliably defining six predetermined cognitive domains in 42 crack/cocaine addicted subjects and 72 comparison subjects were submitted to exploratory factor analysis. A group of 40 alcoholics was additionally included for comparison and to increase statistical power. We then examined the association of the empirically (factor-analytically) derived four cognitive scales with measures of regional cerebral glucose metabolism obtained at resting baseline using positron emission tomography with 2-deoxy-2-[^{18}F]fluoro-D-glucose (PET ^{18}FDG). Six regions of interest (ROIs) were selected for these correlation analyses: the orbitofrontal gyrus, anterior cingulate gyrus, dorsolateral prefrontal cortex, hippocampus, thalamus, and basal ganglia. These regions comprise the brain reward circuit most frequently implicated in the neurobiology of drug addiction (see Goldstein & Volkow, 2002; Volkow & Fowler, 2000).

2. Methods

2.1. Subjects

A comprehensive battery of NP tests was administered to 42 cocaine addicted subjects, 40 alcoholics, and 72 comparison subjects who participated in PET studies at Brookhaven

National Laboratory between 1988 and 1996. The NP functioning of subgroups of the current study's population was previously described (e.g., Hoff et al., 1996; Wang et al., 1993). The NP battery was administered a mean of 60 days (range −13–1466 days; 90% of the subjects were tested within 6 months and 98% within 1 year of the PET study) before (seven subjects) or after the PET study (this information was not available for 15 controls, two cocaine, and five alcohol subjects). This interval (in days) between the PET and NP studies was larger within the non-using group than the cocaine or alcohol groups, which did not differ significantly (controls: $M = 21.9$, S.D. $= 212.1$, range −6–1466 days, three subjects were tested more than 1 year after the PET study; cocaine: $M = 8.4$, S.D. $= 25.2$, range −13–124 days, four subjects were tested more than 1 month from the PET study, two subjects within 2 months; alcohol: $M = 13.3$, S.D. $= 22.6$, range −9–99 days, eight subjects were tested more than 1 month from the PET study, seven subjects within 2 months). This interval between the NP and PET studies was incorporated in subsequent analyses as described below. All cocaine and alcohol subjects were abstinent for at least 2 weeks prior to the PET study. In addition, subjects underwent NP testing only if they had remained drug or alcohol free for the entire duration between the PET and NP studies.

The cocaine and alcohol subjects were mostly recruited from the detoxification unit of the Northport Veterans Affairs Hospital. All had a DSM-III-R (<1994) or DSM-IV (>1994) diagnosis of cocaine or alcohol dependence, respectively. The cocaine subjects had used cocaine (freebase or crack), at least 4 g a week, for at least the preceding 6 months (see Table 1 for drug use information). We excluded cocaine subjects with a current or past history of dependence on alcohol or if their use of alcohol led to regular (once a week) inebriation. However, we did not exclude cocaine subjects who used alcohol to come down from a cocaine binge (3–4 times a week). Twenty-three cocaine subjects reported current ($N = 18$) or past ($N = 5$) alcohol use (mean number of beer equivalent drinks[1] for this subgroup, $N = 22$, was 4.9 ± 5.3) while 15 cocaine subjects denied history of regular alcohol use. This data was missing for four cocaine subjects. In the alcohol group, 32 subjects denied regular cocaine use and eight alcohol subjects reported current ($N = 2$) or past ($N = 6$) cocaine use (mean grams per use for this subgroup, $N = 5$, was 0.5 ± 0.35).

Other exclusion criteria were current or past psychiatric (other than cocaine or alcohol dependence, respectively), neurological, cardiovascular, or endocrinological disease; history of hepatic encephalopathy or delirium tremens for the alcoholics; history of head trauma; current medical illness; and dependence on any substance other than cocaine/alcohol, nicotine, or caffeine. Controls were paid

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[1] Ounces of hard liquor or wine were converted to beer ounces (1 beer equivalent drink = 12 ounces of beer = 1.5 ounces of hard liquor = 5 ounces of wine).

Table 1
Demographic variables, drug use information[a], and PET ^{18}FDG[b] regional (absolute/relative) metabolism in reward ROIs for all study subjects, Brookhaven National Laboratory 1988–1996

	Comparison group ($N = 72$)	Cocaine group ($N = 42$)	Alcohol group ($N = 40$)
Sex (% male)	77.8	100[c]	75
Handedness (% right)	100	86[d]	80[e]
Age (years)	40.7 (14.5)	35.4 (6.7)[f]	41.5 (7.2)
Education (years)	14.8 (3.0)	12.8 (1.6)[g]	12.8 (1.6)[h]
Age at onset (years)	–	25.3 (9)	18.1 (6.5)
Duration of use (years)	–	10.5 (5.6)	23.8 (8.2)
Amount used (g/number of beer equivalent drinks)[i]	–	2.1 (1.9)	16.7 (10.2)
Length of abstinence (days)	–	22.9 (26.5)	16.9 (12.4)
Orbitofrontal cortex	50.5 (7.3)/1.4 (0.13)	49.1 (7.3)/1.4 (0.13)	47.1 (8.9)/1.40 (0.15)
Anterior cingulate	48.25 (7.7)/1.35 (0.11)	48.5 (5.9)/1.34 (0.07)	43.2 (9.1)[j]/1.28 (0.12)[k]
Dorsolateral prefrontal cortex	49.1 (7.4)/1.38 (0.09)	49.9 (6.4)/1.38 (0.07)	44.1 (8.1)[l]/1.30 (0.08)[m]
Hippocampus	46.9 (6.9)/1.32 (0.12)	47.3 (6.1)/1.31 (0.11)	44.5 (8.7)/1.32 (0.13)
Thalamus	49.9 (7.9)/1.40 (0.13)	49.8 (7)/1.37 (0.09)	47.5 (8)/1.41 (0.11)
Basal ganglia	47.2 (6.1)/1.32 (0.09)	47.7 (6)/1.32 (0.07)	44.6 (7.5)/1.33 (0.11)

[a] Drug use information is missing for one cocaine subject. Cocaine use history is presented for the cocaine group and alcohol use history is presented for the alcohol group. For use of other drugs by these groups (e.g., alcohol use by cocaine group) see text.

[b] PET ^{18}FDG data is missing for two comparison subjects and one cocaine subject (these subjects had PET and [^{11}C]raclopride).

[c] Cocaine group is different than controls: $\chi^2_{d.f.=1} = 10.9$, $P < 0.001$.

[d] Cocaine group is different than controls: $\chi^2_{d.f.=1(continuity\ corrected)} = 8.2$, $P < 0.01$.

[e] Alcohol group is different than controls: $\chi^2_{d.f.=1(continuity\ corrected)} = 12.6$, $P < 0.0001$.

[f] Cocaine group is different than controls: $t_{d.f.=107.7(corrected\ for\ heterogeneity\ of\ variance)} = 2.7$, $P < 0.01$.

[g] Cocaine group is different than controls: $t_{d.f.=111.7(corrected)} = 4.7$, $P < 0.0001$.

[h] Alcohol group is different than controls: $t_{d.f.=110(corrected)} = 4.6$, $P < 0.0001$.

[i] Amount used refers to the average daily grams of crack/cocaine in the cocaine group and number of beer equivalent drinks (see text) in the alcohol group.

[j] Alcohol group is different than controls: $t_{d.f.=108} = 3.1$, $P < 0.01$.

[k] Alcohol group is different than controls: $t_{d.f.=108} = 3.3$, $P < 0.001$.

[l] Alcohol group is different than controls: $t_{d.f.=108} = 3.4$, $P < 0.001$.

[m] Alcohol group is different than controls: $t_{d.f.=108} = 4.1$, $P < 0.0001$.

volunteers from the community, screened for a lack of history of substance dependence (excluding caffeine/nicotine). Exclusion criteria were otherwise as for the drug dependent subjects. No subject was taking medications at the time of the study, prescan urine tests were conducted to ensure absence of psychoactive drugs at time of study, and structural magnetic resonance imaging was performed to ensure lack of circumscribed brain damage or atrophy in most of the subjects. Inclusion/exclusion criteria were based on a psychiatric interview conducted by trained study personnel (participating physician). The validity of diagnosis was corroborated by concordance from two clinicians. Written informed consent was obtained for all subjects after procedures were fully explained.

2.2. Derivation of neuropsychological scales

The NP battery included 16 tests from which 27 variables were selected to characterize six NP domains represented by the following scales (contributing variables in parentheses): language (Controlled Oral Word Association Test number correct across three letters in 3 min, age corrected; Boston Naming Test number of correct responses; Wechsler Adult Intelligence Scale-Revised, WAIS-R, similarities subtest scaled score), immediate verbal memory (California Verbal Learning Test, CVLT, number correct on trials 1–5; Wechsler Memory Scale, WMS, logical memory immediate; WMS paired associates immediate), delayed verbal memory (WMS logical memory delayed; CVLT delayed free-recall; CVLT recognition hits), visual memory (WMS visual reproduction immediate; WMS visual reproduction delayed; Benton Visual Retention Test, BVRT, number of errors; BVRT number correct), attention (Symbol Digit Modalities Test written; Trail Making Test, part A seconds; WMS digit span subtest scaled score; Cancellation Test seconds), and executive functioning (Wisconsin Card Sort Test, WCST, number of categories; WCST preservative errors; Stroop Color-Word Interference Score age corrected; Trail Making Test, part B seconds; Booklet Categories Test number of errors). A scale for measuring premorbid intellectual ability (WAIS-R information scaled score; WAIS-R vocabulary scaled score; Wide Range Achievement Test-Revised reading scaled score; Raven's Progressive Matrices age corrected; and Woodcock–Johnson word attack subtest number of errors) was also constructed. Loading of these test variables on their respective scales was based on a priori decisions (see Bilder et al., 2000; Hoff et al., 1996).

Scores for each scale were computed by averaging Z scores on contributing variables. These Z scores were based on performance of the comparison group, which by definition had mean scale scores of zero and standard deviations set to one. All scales were computed so that higher values indicated better performance. At each stage of scale construction, contributing variables were restandardized before means were computed over all non-missing data. Additional scaling procedures were applied to improve psychometric properties. First, within each study group, each test variable was examined for extreme values, and in several instances these extreme scores were replaced by scores within the tails (which were under three standard deviations from the mean) of their underlying distributions (this procedure affected 13 variables and a total of 11 comparison, 9 cocaine and 4 alcohol subjects scores). Second, the distributions were examined both within and between groups, with special attention to problems involving heteroscedasticity, and variance-stabilizing algorithms were applied (this affected six variables) to optimize homogeneity of variance between groups for each variable (Levene's test was used as a criteria). Third, reliability analyses were conducted for each scale, using the initial a priori variable assignment, and any test variable that decreased the internal consistency of the composite (as assessed by Cronbach's coefficient alpha) was eliminated (seven tests were eliminated: Controlled Oral Word Association Test number correct; WMS logical memory delayed; WMS digit span; WCST number of categories; Stroop Color-Word Interference Score; Raven's Progressive Matrices; and Woodcock-Johnson word attack subtest number of errors). Fourth, the 20 remaining test variables were submitted to an Exploratory Factor Analysis, using all non-missing data across the three study groups. The principal-component method extracted components with eigenvalues >1, and these components (factors) were retained for varimax rotation. Only variables sharing at least 15% of the variance with the factor and only statistically significant loadings (>0.41) (Stevens, 1986) were used for the final stage of scale construction, where these test variables were averaged to create their respective scales across all non-missing data. Fifth, further tests on homogeneity of variance were conducted and transformations were applied where indicated for the scales, as was done for the individual test variables.

2.3. PET scans

PET scans were performed with the CTI 931 (15 slices, spatial resolution: $6\,mm \times 6\,mm \times 6.5\,mm$ full width at half maximum) scanner (Siemens, Knoxville, TN). Details on procedures for positioning, arterial and venous catheterization, quantification of radiotracer, and transmission and emission scans have been published (Wang et al., 1993). Briefly, one 20 min emission scan was taken 35 min after an intravenous injection of 4–6 mCi of ^{18}FDG. During the study, subjects were kept lying in the PET camera with their eyes open; the room was dimly lit and noise was kept to a minimum. A nurse remained with the subjects throughout the procedure to ensure that the subject did not fall asleep during the study.

Regions of interest were selected by using a previously published template that locates 115 nonoverlapping ROIs (Wang et al., 1993). In brief, we used small ROIs to minimize the contribution of partial volume effects on the metabolic values. The size and orientation of the ROIs were the same in all subjects. Placement of the regions was determined by reference to an atlas of axial tomographic anatomy (Matsui & Hirano, 1978) by an experienced investigator (G.J.W.). To minimize the variation effect of global metabolism on the absolute regional measure, we computed the ratio of the absolute regional to the metabolism in all available ROIs (gray matter only), thus obtaining relative (scaled) regional measures of metabolism. It has previously been shown that scaling the regional values to compensate for the effects of changes in whole brain metabolism provides a stable reflection of the metabolic characteristics of clinical as well as normal populations (Bartlett et al., 1991).

2.4. Statistical analysis

Each of the two drug abusing populations was compared to the controls on select demographic and metabolism variables. Group differences in continuous variables were examined using unpaired Student's t-tests (two-tailed). Levene's test for equality of variances was used and whenever significant, the corrected t-statistic and degrees of freedom were used. For dichotomous variables, chi-square tests with Fisher's exact statistic were used. Group differences on the NP scales were examined using univariate ANOVAs with post hoc tests (with Bonferroni correction). Deviations from flatness in the subject profiles were assessed by contrasting the mean for each individual scale with the mean of all other scales using paired t-tests. Within each group (the comparison group and both drug groups combined), Pearson product-moment correlation analyses were conducted between the four NP scales and the following 12 variables: (1) age and education; (2) relative metabolism in the six reward ROIs (orbitofrontal gyrus, anterior cingulate gyrus, dorsolateral prefrontal cortex, hippocampus, thalamus, and basal ganglia); and (3) age at onset of drug use, duration of use, amount of last daily use, and length of abstinence (this was done within each drug group separately). All variables that significantly correlated with the NP scales were then entered into four separate regression equations predicting the four NP scales across all subjects. These regression analyses were repeated including a test interval variable, i.e., the interval in days between the NP and PET studies over all non-missing values. A 0.01 level was set to protect against Type I error in all analyses.

3. Results

3.1. Demographics, drug use, and PET ^{18}FDG measures

Means and standard deviations for demographics, drug use variables, and measures of regional absolute and relative metabolism in the reward ROIs for the three study groups are presented in Table 1. There were significant differences between the cocaine addicted subjects and comparison subjects in distribution of sex and handedness, and in age and education. For the alcohol group, there were significant differences from the comparison subjects in distribution of handedness, in education, and in metabolism in the anterior cingulate gyrus and dorsolateral prefrontal cortex (absolute and relative). Effects of these demographic differences are examined in subsequent analyses, and their implications to findings are discussed at length below.

3.2. Derivation of neuropsychological model

Factor patterns after principal component method and orthogonal rotation of the correlation matrix, loadings, communalities (the proportion of variance of a particular item/variable that is shared with other items calculated as the squared multiple correlation of a variable with all other variables), and percents of variance are displayed in Table 2. Variables are ordered and grouped by size of loading to facilitate interpretation. Loadings under 0.41 were replaced by zeros. The four factors accounted for 63% of the total variance. All factors were internally consistent and defined by five variables with factor loadings greater than 0.48. Factor 1 (Visual Memory) was dominated by loadings of all tests measuring memory for visual designs and by the Booklet Categories test, which we have a priori assigned to an executive functioning factor. Factor 2 (Verbal Knowledge) was characterized by the clustering of all WAIS-R subtests, WRAT-R reading, and Boston Naming Test, representing a combination of the a priori language and premorbid functioning scales. Factor 3 (Verbal Memory) was characterized by the clustering of all CVLT measures and by the WMS immediate verbal memory scales, representing a combination of the a priori immediate and delayed verbal memory scales. Factor 4 (Attention/Executive functioning) was characterized by three attention and two executive functioning variables, representing a combination of the a priori respective scales. A similar factor solution emerged when analyzing data separately by group. For both drug groups (combined due to small N within each drug subgroup) the factor solution was identical. For the comparison group, the factor structure was more suggestive of a three-factor solution, characterized by a combined Visual Memory/Attention/Executive factor in addition to similar Verbal Knowledge and Verbal Memory factors. Table 3 presents the means and standard deviations of all tests and

Table 2
Factor loadings, communalities[a] (h^2), and percentages of variance for principal factor extraction with varimax rotation for all study subjects, Brookhaven National Laboratory 1988–1996

	Neuropsychological factors				
	F1	F2	F3	F4	h^2
BVRT number of errors	0.82				0.75
WMS, visual reproduction II	0.80				0.75
WMS, visual reproduction I	0.78				0.75
BVRT correct	0.78				0.73
Booklet Categories Test, number of errors	0.66				0.55
Boston Naming Test		0.80			0.67
WAIS-R, vocabulary		0.79			0.69
WRAT-R, reading		0.79			0.66
WAIS-R, information		0.71			0.58
WAIS-R, similarities		0.60			0.45
CVLT, total trials 1–5			0.83		0.77
CVLT, delay free recall			0.82		0.78
CVLT, recognition			0.68		0.53
WMS, verbal paired associates			0.53		0.45
WMS, logical memory I			0.48		0.46
Cancellation Test				0.83	0.69
Trail Making Test, part A				0.70	0.66
Trail Making Test, part B				0.68	0.64
Symbol Digit Modality Test				0.61	0.63
WCST, preservative errors				0.51	0.39
% of variance	19.3	16	15	12.6	

F1, Visual Memory; F2, Verbal Knowledge; F3, Verbal Memory; F4, Attention/Executive functioning. *Abbreviations*: BVRT is Benton Visual Retention Test; WMS is Wechsler Memory Scale; CVLT is California Verbal Learning Test; WAIS-R is Wechsler Adult Intelligence Scale-Revised; WRAT-R is Wide-Range Achievement Test-Revised; WCST is Wisconsin Card Sorting Test.

[a] Communality refers to the proportion of variance of a particular item/variable that is shared with other items, and is calculated as the squared multiple correlation of a variable with all other variables. The proportion of variance that is unique to each item is the respective item's total variance minus the communality.

NP scales for each of the study groups for descriptive purposes. Variables are organized by the exploratory factor analysis results.

3.3. Comparing the study groups on neuropsychological functioning

Fig. 1 shows the means on the four NP scales for the cocaine and alcohol groups relative to the comparison group. Both drug groups were more impaired than the comparison group on all four NP dimensions measured. Mean effect sizes (in Z score units, reflecting the number of standard deviations below the comparison group means) ranged from -0.49 to -1.2 in the cocaine group and from -0.49 to -0.89 in the alcohol group (see Table 3 and Fig. 1) with an overall profile mean for the cocaine group of -0.72 (± 0.81) and for the alcohol group -0.74 (± 0.69), indicating a generalized deficit of less than one standard deviation ($F_{d.f.=2, 151} = 17.7$, $P < 0.0001$) for both drug groups. Restricting the analyses to the most severe users (>50‰) in

Table 3
Scores on neuropsychological scales and respective tests for all non-missing study subjects, Brookhaven National Laboratory 1988–1996

Scale and test	Comparison group			Cocaine group			Alcohol group		
	Mean[a]	S.D.	N	Mean[a]	S.D.	N	Mean[a]	S.D.	N
Visual Memory	0	1	72	−0.61	1.04	42	−0.88	1.20	39
BVRT, number of errors	3.4	3.0	72	4.8	3.3	41	6.2	4.7	39
WMS, visual reproduction II	10.1	4.0	71	8.4	4.1	41	7.9	4.1	37
WMS, visual reproduction I	11.2	3.2	71	10.1	3.3	40	9.8	3.3	39
BVRT, correct	7.7	1.8	72	6.5	2.6	42	6.1	2.4	39
Booklet Categories Test, number of errors	36	22.6	71	49.5	21.8	41	53.5	20.8	38
Verbal Knowledge	0	1	72	−1.2	1.22	42	−0.67	0.86	40
Boston Naming Test	56.7	5.1	71	51.2	7.0	42	54.7	3.9	40
WAIS-R, vocabulary	11.3	3.3	72	9.9	3.2	42	10.4	2.7	40
WRAT-R, reading	104.1	11.4	72	92.7	14.3	42	97.8	10.5	39
WAIS-R, information	13.2	3.3	72	10.8	3.4	42	11.7	3.2	40
WAIS-R, similarities	12.8	3.7	72	10.7	3.6	42	11.0	3.1	40
Verbal Memory	0	1	72	−0.62	1.25	42	−0.49	1.03	40
CVLT, total trials 1–5	52.9	9.5	71	45.3	14.8	42	49.0	9.5	40
CVLT, delay free recall	11.3	2.7	71	9.6	3.3	42	9.7	2.9	40
CVLT, recognition	14.4	1.7	71	14.0	2.0	42	14.1	2.0	40
WMS, verbal paired associates	24.3	4.2	71	22.0	5.3	42	23.3	3.8	38
WMS, logical memory I	9.1	2.7	72	8.4	2.9	42	8.4	2.8	40
Attention/Executive functioning	0	1	72	−0.49	1.07	42	−0.89	1.33	39
Cancellation Test	46.7	11.0	72	47.9	11.3	36	53.2	14.0	39
Trail Making Test, part A	26.1	9.3	72	28.0	7.8	42	33.6	14.5	39
Trail Making Test, part B	66.7	27.2	72	81.4	41.3	42	85.9	61.2	39
Symbol Digit Modality Test	54.3	11.2	68	47.7	9.1	40	46.5	13.6	38
WCST, preservative errors	13.9	13.9	69	13.7	10.3	27	18.1	16.8	35

Abbreviations: BVRT is Benton Visual Retention Test; WMS is Wechsler Memory Scale; CVLT is California Verbal Learning Test; WAIS-R is Wechsler Adult Intelligence Scale-Revised; WRAT-R is Wide-Range Achievement Test-Revised; WCST is Wisconsin Card Sorting Test.

[a] Mean (S.D.) values for scales are in standard score (Z score) units; values for individual test variables are in the original metric of each instrument (raw scores, before correction for outliers, see text), except for subtests of the WAIS-R and WRAT-R, which are age-corrected scaled or standard scores.

the cocaine group (≥ 2 g per day, $N = 22$) did not increase effect sizes for most NP scales (except for a slight increase on Verbal Memory, $Z = −0.73$ instead of $−0.62$) or for the mean NP profile ($Z = −0.73$). In contrast, restricting the analyses to the most severe users (>50‰) in the alcohol group (≥ 17 drinks per day, $N = 20$), slightly increased severity of impairment across all NP scales (Visual Memory $Z = −1.08$; Premorbid function $Z = −0.87$; Verbal Mem-
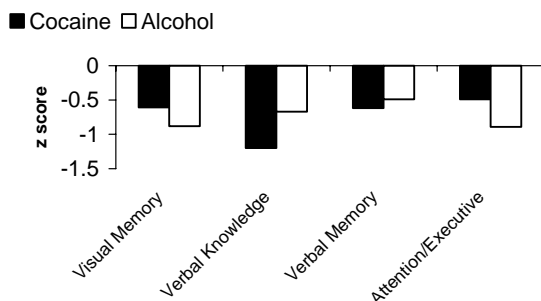

Fig. 1. Deficits in scores for neuropsychological scales of cocaine and alcohol dependent subjects (relative to scores for comparison subjects; by definition, the comparison group had a mean score of zero on each scale; see text), Brookhaven National Laboratory 1988–1996.

ory $Z = −0.87$; Attention/Executive function $Z = −1.1$) and for the mean NP profile ($−0.98$ instead of $−0.74$). In addition, the Attention/Executive scale was significantly ($P < 0.05$) more impaired for the cocaine users who reported current or past alcohol use ($N = 23$, $M = −0.78$, S.D. $= 1.1$) than for the cocaine subjects who denied regular alcohol use ($N = 15$, $M = −0.01$, S.D. $= 0.9$). Such an effect was not observed for the other NP scales or for the mean NP profile.

Univariate ANOVAs with post hoc tests (with Bonferroni correction) revealed that both drug groups differed significantly from the comparison group on Verbal Knowledge and that the alcohol group also differed significantly from the comparison group on Visual Memory and Attention/Executive scale (all $P < 0.01$). The Verbal Knowledge scale showed significantly more impairment compared with the Attention/Executive scale for the cocaine group (paired $t = −3.3$, d.f. $= 41$, $P < 0.01$). There were no other deviations from flatness, that is, no other scale was significantly more impaired than any of the other scales for any of the subject groups. When we removed the variance in the Visual Memory and Attention/Executive functioning scales due to Verbal Knowledge (by using regression analyses), the differences between the alcohol group and controls on

Table 4
Significant associations between the neuropsychological factors and demographics and PET ^{18}FDG relative metabolism in reward ROIs for the comparison subjects (first row), both drug groups (second row, italics), and all subjects (bottom row, bold), Brookhaven National Laboratory 1988–1996

Variables/neuropsychological scale	F1	F2	F3	F4
Age	−0.54 (N = 72)		−0.44 (N = 72)	−0.59 (N = 72)
	−0.29 (N = 81)			*−0.38 (N = 81)*
	−0.35 (N = 153)		**−0.30 (N = 154)**	**−0.41 (N = 153)**
Education		0.36 (N = 72)		
	0.31 (N = 153)	**0.42 (N = 154)**	**0.22 (N = 154)**	**0.34 (N = 153)**
Anterior cingulate				0.42 (N = 70)
				0.36 (N = 80)
	0.26 (N = 150)			**0.43 (N = 150)**
Dorsolateral prefrontal cortex	0.31 (N = 70)		0.35 (N = 70)	0.33 (N = 70)
	0.34 (N = 150)		**0.32 (N = 151)**	**0.30 (N = 150)**

F1, Visual Memory; F2, Verbal Knowledge; F3, Verbal Memory; F4, Attention/Executive functioning. All $P < 0.01$, two-tailed.

the Visual Memory and Attention/Executive functioning scales remained significant ($P < 0.01$). Group differences in overall profile mean also remained significant.

Because there were no significant differences between the cocaine and alcohol groups in any of the NP scales (all $P > 0.09$), the two groups were combined into a single "drug addicted" group in all subsequent analyses. Student's independent t-tests demonstrated that this group was significantly impaired compared to controls on all NP scales (all $P < 0.01$). When we removed the variance in all the NP

scales due to age and education (by using regression analyses), the differences between the drug addicted group and comparison group were still significant (all $P < 0.01$). This drug addicted group was also significantly different than the comparison group ($P < 0.05$) on all four NP scales even when restricting analyses to right-handed males (59 drug addicted subjects and 56 comparison subjects). Please note that the differences in demographics (age and education) between these smaller groups were unchanged from those reported for the complete study sample (see Table 1).

Table 5
Results of forward regression analyses of variables significantly predicting the four neuropsychological scales in all study subjects, Brookhaven National Laboratory 1988–1996

|	Standardized B	F	d.f.	P	R	R^2
F1: Visual Memory						
Step 1: Age	−0.35	20.47	1, 148	<0.0001	0.35	0.12
Step 2: Education	−0.35					
	0.32	21.03	2, 147	<0.0001	0.47	0.22
Step 3: Dorsolateral prefrontal cortex	−0.29					
	0.28					
	0.20	16.87	3, 146	<0.0001	0.51	0.26
F2: Verbal Knowledge						
Step 1: Education	0.42	31.32	1, 149	<0.0001	0.42	0.17
F3: Verbal Memory						
Step 1: Dorsolateral prefrontal cortex	0.32	17.17	1, 149	<0.0001	0.32	0.10
Step 2: Age	0.25					
	−0.22	12.88	2, 148	<0.0001	0.39	0.15
Step 3: Education	0.22					
	−0.24					
	0.19	10.84	3, 147	<0.0001	0.43	0.18
F4: Attention/Executive functioning						
Step 1: Anterior cingulate	0.43	33.23	1, 148	<0.0001	0.43	0.18
Step 2: Education	0.39					
	0.29	26.88	2, 147	<0.0001	0.52	0.27
Step 3: Age	0.26					
	0.31					
	−0.30	25.31	3, 146	<0.0001	0.59	0.34

3.4. Association of the neuropsychological model with glucose metabolism in the reward circuit

See Table 4 for the results of the correlation analyses between the four NP scales and the 12 selected demographic, metabolism, and drug use variables (see statistical analysis, in Section 2.4). Correlations not reaching the nominal significance level ($P = 0.01$) are not shown. Age negatively correlated with all NP scales except for Verbal Knowledge for all study participants. Education positively correlated with all scales, again most reliably demonstrated across all subjects. Its strongest correlation was with the Verbal Knowledge scale. Relative metabolism in the anterior cingulate was associated with Attention/Executive functioning within each study group and with Visual Memory across all subjects. Relative metabolism in the dorsolateral prefrontal cortex positively correlated with all scales except for Verbal Knowledge for all study participants. For the cocaine group,
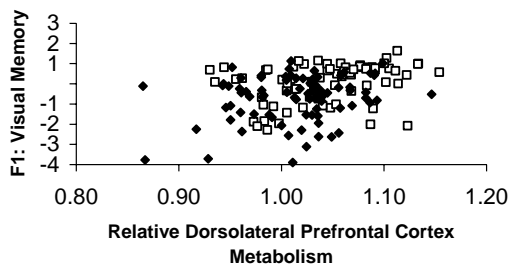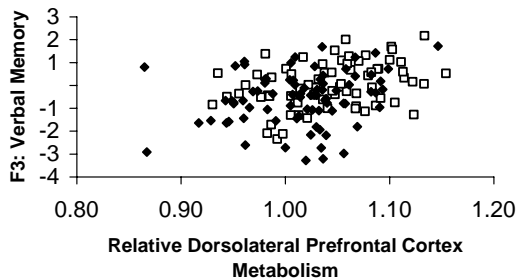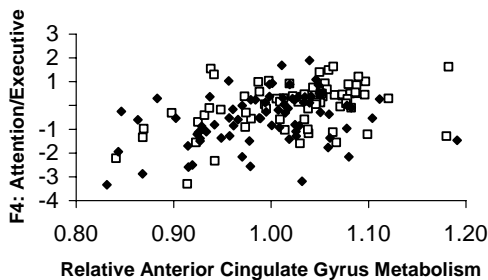

Fig. 2. Scatterplots between PET ^{18}FDG relative prefrontal metabolism and neuropsychological functioning across all study subjects, Brookhaven National Laboratory 1988–1996.

increased age at onset was associated with decreased Attention/Executive function ($r = -0.32$, $P = 0.044$); for the alcohol group, increased amount of last use was associated with decreased Verbal Memory ($r = -0.33$, $P = 0.038$). These correlations, however, did not reach nominal level of statistical significance and were not included in the subsequent regression analyses.

All four variables in Table 4 were then entered into four separate stepwise forward regression analyses with the NP scales as dependent variables (Table 5). Results revealed that, controlling for age and education, relative metabolism in the dorsolateral prefrontal cortex significantly predicted Visual Memory and Verbal Memory and relative metabolism in the anterior cingulate significantly predicted Attention/Executive functioning (see Fig. 2 for scatterplots between these dependent variables). Education was the sole predictor of Verbal Knowledge (Table 5). Including the test interval variable (number of days between the NP and PET studies) did not change these results: this variable was excluded from the final equation in all four regression analyses, the order of entry for the other variables remained unchanged as well as their exact contribution to the explained variance, R^2. Because there were significant handedness differences in Visual Memory (mean $Z \pm$ S.D. for right-handers versus non right-handers $= -0.30 \pm 1.1$ versus -1.26 ± 0.86, $t = 3.1$, d.f. $= 151$, $P < 0.01$) and Attention/Executive functioning (mean $Z \pm$ S.D. for right-handers versus non right-handers $= -0.26 \pm 1.1$ versus -1.38 ± 1.2, $t = 3.6$, d.f. $= 151$, $P < 0.001$), the regression analyses were repeated excluding non right-handers ($N = 14$). The order of predictors was now reversed for Attention/Executive functioning. No other significant differences were noted.

4. Discussion

The main objective of this study was to characterize the nature of the NP impairment in crack/cocaine addicted subjects using a group of alcoholics and non-addicted subjects for comparison. The present study: (1) developed a four-dimensional model of neurocognitive functioning from multiple standard NP test indices in 42 crack/cocaine addicted subjects, 40 alcoholics, and 72 comparison subjects participating in PET neuroimaging studies at Brookhaven National Laboratory between 1988 and 1996; and (2) examined the association of this neurocognitive model with the brain regions most frequently implicated in drug addiction.

4.1. Modeling neuropsychological functioning: severity of impairment

A reliability analysis followed by an exploratory factor analysis reduced 27 NP indices to four dimensions/scales assessing (a) Visual Memory; (b) Verbal Knowledge; (c) Verbal Memory; and (d) Attention/Executive functioning. The

combined group of drug addicted subjects showed a generalized deficit of less than one standard deviation ($Z = -0.7$ which increased to -0.85 when restricting analyses to the subjects who reported the heaviest drug use) relative to the comparison subjects. This effect was statistically significant. However, relative to individuals with other psychopathological disorders such as schizophrenia, where a generalized deficit of approximately 1.5 standard deviations relative to a comparison group has been reported (Bilder et al., 2000), the severity of impairment documented in the current report is modest. This relatively small size of the neurocognitive impairment in drug addicted individuals might partly account for the variability in the literature addressing NP functioning in cocaine addiction.

In this context of a relatively mild generalized deficit, the only deviation from flatness in the NP profile was for the Verbal Knowledge scale that was most severely impaired in the cocaine group in our study. These results are consistent with a finding that cocaine dependent subjects performed poorly on tasks tapping into overlearned verbal skills (WAIS-R Information, Vocabulary and Similarities scales), possibly representing a demographic bias (Gillen et al., 1998) or a compromised premorbid level of functioning (the Verbal Knowledge scale represents premorbid functioning in as much as it reflects language functions acquired before addiction could be fully diagnosed). To examine whether the generalized NP impairment in the current study could be explained on purely these demographic grounds/premorbid level of functioning we performed all analyses controlling for the Verbal Knowledge scale and also for other demographics (age, education, handedness) as described in the results section. Our results indicated that the NP differences between the drug addicted group and comparison subjects were still significant and could not be attributed to differences in premorbid achievement or the effects of individual variables.

Two other studies provided estimates of severity of neurocognitive impairment in cocaine addiction. A global clinical impairment scale was calculated mostly based on the MicroCog computerized assessment in a recent study comparing 20 crack dependent subjects and 37 crack and alcohol dependent subjects at 6 weeks abstinence to 29 normal controls (Di Sclafani et al., 2002). Although this global scale pointed to a higher level of impairment (equivalent to approximately 1.5 standard deviations below controls for both drug groups), a closer inspection revealed that the Z scores for the individual cognitive domains ranged from -0.15 to -0.91 for the crack dependent subjects and -0.39 to -0.78 for the crack and alcohol dependent subjects, consistent with a generally mild cognitive dysfunction. Moreover, the Z scores on five of the nine cognitive domains would have been even smaller were the study's control group norms used and not the test's published norms. A global deficit score was also calculated based on an expanded Halstead-Reitan NP Test Battery in 30 cocaine abusers, 30 co-dependent cocaine and alcohol users, and 30 controls (Robinson et al., 1999).

Using a cutoff point equivalent to a one standard deviation, the differences in percentage of the three groups that were classified as impaired were not significant, again consistent with a mild NP deficit.

Our results are thus consistent with these previous studies that pointed to a generalized mild neurocognitive impairment in cocaine subjects. Several explanations for the relatively small size of this generalized neurocognitive impairment in the drug-addicted group seem plausible. First, our strict selection criteria ensured that only "pure" and relatively young cocaine abusers were included; subjects co-dependent on other drugs such as alcohol (except nicotine) and cocaine subjects >48 years of age were excluded. Care was also taken to exclude cocaine abusers or alcoholics with psychiatric or neurological co-morbidities, which may have excluded subjects at the more severe range of functional impairment (i.e., where toxic effects of these drugs may have resulted in neurological or psychiatric impairment). Second, our statistical approach was conservative, so as to minimize chance findings. This approach may have reduced statistical power and contributed to the non-significant differences between the cocaine group and comparison subjects. Third, it is possible that tasks that simulate real-life decision-making would offer greater sensitivity in documenting the cognitive-behavioral and motivational-emotional changes accompanying drug addiction. Indeed, compared to recently abstinent (more than 4 days) cocaine-dependent subjects, active cocaine users achieved significantly lower scores on a gambling task that quantifies the inability to make advantageous decisions (Bechara, Damasio, Damasio, & Anderson, 1994) while performing indistinguishably from the former group on the WCST and CVLT, standard NP tests of concept formation, set shifting, and working memory (Bartzokis et al., 2000) that were also included in the current study. Sub-optimal decisions and longer deliberation times were also documented using another decision-making task in which subjects make choices between well-defined and clearly visible response-reinforcement contingencies in amphetamine abusers (Rogers et al., 1999). Overall, the use of tasks that are specifically sensitive to risk assessment, delay discounting, planning, attribution of salience and inhibitory control, all prerequisite to advantageous decision making, may offer greater insight into the neurocognitive sequel of drug addiction.

4.2. Association of the neuropsychological model with reward brain regions

Controlling for age and education, relative metabolism in the dorsolateral prefrontal cortex significantly predicted the Visual Memory and Verbal Memory scales. Relative metabolism in the anterior cingulate gyrus significantly predicted the Attention/Executive functioning scale, independently explaining 18% of variance in this scale. Education significantly predicted Verbal Knowledge, explaining 17% of variance in this scale. Thus, although we used traditional

NP tests whose reliability may be quite variable (see Rogers and Robbins, 2001), our statistical approach has been successful in creating cognitive scales that demonstrate sensitivity and specificity for neural function. The results of another study confirm our findings; performance on executive-type tasks, but not education or WAIS IQ, correlated significantly with PET [18]FDG metabolism in frontal regions (including the anterior cingulate and dorsolateral prefrontal cortex) in 17 chronic alcoholics (Dao-Castellana et al., 1998).

The dorsolateral prefrontal cortex has been most frequently implicated in the representation, manipulation, and active maintenance of attentional demands of a task (see for example review by Cabeza & Nyberg, 2000; and by Fletcher & Henson, 2001; see also MacDonald, Cohen, Stenger, & Carter, 2000). The association in our study of the two memory scales with relative metabolism in the dorsolateral prefrontal cortex, points to the role of working memory in these two NP scales. This evaluative component is possibly shared by all the tests that defined the Visual and Verbal Memory scales, including the tests that assess long-term memory.

The anterior cingulate cortex has been most frequently implicated in response competition, response selection, suppression of prepotent response tendencies, and error detection (Carter et al., 1998, 2000; Casey et al., 1997; Elliott, Rubinsztein, Sahakian, & Dolan, 2000; Krams, Rushworth, Deiber, Frackowiak, & Passingham, 1998; Kiehl, Liddle, & Hopfinger, 2000; Rubia et al., 2000). The association of the Attention/Executive functioning scale with relative metabolism in the anterior cingulate, points to the role of attentional and self-monitoring processes in this scale. The lack of association between the Attention/Executive functioning scale and the Stroop interference effect indicates this scale did not tap into inhibitory control.

The anterior cingulate gyrus and dorsolateral prefrontal cortex are both regions in the mesocortical dopamine circuit, which has been implicated in the core behavioral and motivational changes accompanying drug addiction including the conscious experience of drug intoxication, drug incentive salience, drug expectation/craving, and compulsive drug administration (for review see Goldstein & Volkow, 2002 and Volkow & Fowler, 2000). The association of these same regions with the cognitive changes accompanying drug addiction (see also Goldstein, Volkow, Wang, Fowler, & Rajaram, 2001), points to the importance of studying the role of dopamine in higher-order cognitive functions in drug addicted individuals. Indeed, we previously reported that striatal dopamine transporter was correlated with verbal memory and motor function in 15 detoxified methamphetamine abusers (Volkow et al., 2001) and we recently reviewed the role of dopamine pathways in learning and memory in addiction (Volkow et al., 2002). However, this issue deserves further exploration (see Jentsch & Taylor, 1999; Jentsch et al., 2002).

No significant associations were documented between the NP scales and the orbitofrontal cortex, hippocampus, thalamus, and basal ganglia. Several explanations for the absence of significant correlations with these regions seem likely. First, we controlled for age and education and for the total number of associations examined (to reduce Type I error); these stricter than usual statistical criteria might have reduced our power to detect smaller effects sizes. Second, some of the NP tests specifically tapping the functions subserved by these regions may have been lacking or removed (e.g., sensorimotor tests for the subcortical regions, gambling/higher-order decision-making tasks and the Stroop task for the orbitofrontal cortex). It is also possible that glucose metabolism during activation would be more reliably associated with NP measures than metabolism at rest, as implicated in a recent PET study where metabolism in the visual and auditory regions was correlated with neurocognitive function (dementia severity) during stimulation but not at rest in 15 Alzheimer's disease patients (Pietrini et al., 1999). Therefore, it remains to be determined whether metabolic changes in the reward circuit are associated with addiction. Finally, we pre-selected small ROIs (Wang et al., 1993), possibly contributing to a Type II error. The lack of an association between the two NP memory scales and the hippocampus is a case in point. A closer inspection of larger regions indeed revealed interesting associations (e.g., a positive correlation between Verbal Memory and the medial temporal gyrus in the control group). However, such an exploration is beyond the scope of this article as we targeted the regions of the brain that have been previously associated with the reward network.

4.3. General discussion and limitations

In the current study, we did not document significant differences in the NP profile between the cocaine addicted subjects and alcoholics, and both groups were combined to increase statistical power for all subsequent analyses. When interpreting the lack of significant differences between these groups it is important to keep in mind that the NP scales were created based on the performance of the comparison group. This methodology emphasized differences of both drug groups from the control subjects, probably precluding our ability to document more subtle differences between the cocaine addicted subjects and alcoholics in either cognitive functioning or in the correlations with glucose metabolism. Thus, while combining these groups allowed us to explore the association between neurocognitive function and glucose metabolism, we were not able to investigate the differential effect of cocaine versus alcohol on neurocognitive function. Nevertheless, our results suggest that alcohol has a more detrimental effect on Attention/Executive functioning than cocaine: this NP scale was more impaired in the alcohol group than the cocaine group, and the cocaine subjects who reported regular alcohol use had significantly worse scores on this scale than the cocaine subjects who denied alcohol use. In general, this undoubtedly multifaceted effect deserves further study.

We also did not document significant correlations between drug use variables and NP functioning, which may be attributed not only to our strict statistical criteria but also to difficulties with collecting these self-report data in a retrospective manner. For example, age at onset was defined as age at first use for some subjects but age at onset of abuse symptoms for others. Consequently, this variable as well as duration of use may represent somewhat different factors for different subjects. Also, amount of last daily use, although mostly representing the amount used immediately before detoxification, denoted the maximum amount used for some subjects. Finally, the range of length of abstinence was restricted in this study where most subjects were scanned within several weeks of detoxification. Moreover, this variable represented length of abstinence before the PET study, before the NP study, or before both if continuous abstinence was documented between the studies but not if it could not be quantified. In summary, dose dependent neurocognitive decrements should be further investigated using a priori hypotheses and prospective study designs, in as much as they have been previously documented in chronic cocaine use (Bolla et al., 1999).

A further limitation of this study is our inability to match the comparison subjects to the drug groups on the demographic variables that are known to affect neurocognitive functioning. Although our results were not accounted for by differences in sex, handedness, age, and education, future validation of results in groups matched for these and other demographic variables is needed. Another major limitation of this study is our inability to control for the time period between the NP and PET studies. Although our regression analyses indicated that this time interval did not impact the reported associations between NP function and regional brain metabolism, and although abstinence between PET and NP was mandatory for inclusion, the effect of factors such as length of abstinence, severity of relapse, neurological and health complications, learned compensatory mechanisms, and age differences, on the severity of cognitive impairment remains unclear. For example, it is quite likely that the effect of drug use on cognition differs as a function of length of abstinence (e.g., Selby & Azrin, 1998) and that severity of impairment is significantly more pronounced immediately after detoxification especially for the heavy drug users or for the polysubstance users.

To summarize, difficulties in controlling for the numerous possible confounding variables in this type of a clinical retrospective study abound. Nevertheless, in the current analyses we have addressed many of the possible confounds, and demonstrated mild deficits in NP functioning in cocaine subjects; although it remains to be determined whether metabolic changes in the reward circuit are associated with addiction, the correlations between the NP scales and metabolism in the dorsolateral prefrontal cortex and anterior cingulate cortex attest to the sensitivity of our NP measures. The impact of such small differences in perfor-

mance, however, on quality of life, and possibly on craving and relapse, may be substantial.

5. Conclusions

In conclusion, this study documented a relatively mild NP impairment in cocaine addiction which should not be misinterpreted as indicative of the absence of neurocognitive dysfunction in this group. Demonstrating clear associations between cognitive functioning as assessed by NP testing and neuronal functioning as estimated by PET ^{18}FDG, we furthered the fledgling research on the brain–behavior relationship in drug addiction.

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