Proc. Natl. Acad. Sci. USA
Vol. 93, pp. 12040–12045, October 1996
Psychology

Activation of memory circuits during cue-elicited cocaine craving

STEVEN GRANT*, EDYTHE D. LONDON*†, DAVID B. NEWLIN*, VICTOR L. VILLEMAGNE*, XIANG LIU*, CARLO CONTOREGGI*, ROBERT L. PHILLIPS*, ALANE S. KIMES*, AND ARTHUR MARGOLIN‡

*Intramural Research Program, National Institute on Drug Abuse, P.O. Box 5180, Baltimore, MD 21224; and ‡Substance Abuse Center, Yale University School of Medicine, New Haven, CT 06510

Communicated by Endel Tulving, Rotman Institute of Baycrest Centre, Toronto, ON, Canada, August 5, 1996 (received for review May 30, 1996)

ABSTRACT **Evidence accumulated over more than 45 years has indicated that environmental stimuli can induce craving for drugs of abuse in individuals who have addictive disorders. However, the brain mechanisms that subserve such craving have not been elucidated. Here a positron emission tomographic study shows increased glucose metabolism in cortical and limbic regions implicated in several forms of memory when human volunteers who abuse cocaine are exposed to drug-related stimuli. Correlations of metabolic increases in the dorsolateral prefrontal cortex, medial temporal lobe (amygdala), and cerebellum with self-reports of craving suggest that a distributed neural network, which integrates emotional and cognitive aspects of memory, links environmental cues with cocaine craving.**

Most individuals who suffer from dependence on cocaine and other addictive drugs return to substance abuse within a year of initiating abstinence (1, 2). Addicts often attribute relapse to intense desire or "craving," which may arise in an environment associated with drug use (3–5). Moreover, drug-related cues can induce craving in laboratory settings (6–8). Substantial interest focuses on the mechanisms by which drug-related stimuli elicit craving (3, 5, 9–12) despite concerns that craving does not inevitably lead to drug taking (13). Little is known, however, about the biological basis of cue-elicited drug craving, except that cocaine users exposed to drug-related cues exhibit diffuse decreases in the power of the electroencephalogram (8). The purpose of the present study was to identify brain regions that mediate cue-elicited cocaine craving. To this end, regional cerebral metabolic rate for glucose (rCMRglc), an index of local brain function (14, 15), was measured in cocaine abusers and normal volunteers in a neutral test session and in another session during which cocaine-related stimuli were presented.

METHODS

Subjects. Thirteen cocaine abusers (COC group; 25–42 years old; 12 men, 1 woman; 12 Black, 1 White) and 5 normal volunteers (24–29 years old; 4 men, 1 woman; all Black) participated in the study. Evidence of physical disease, history of head trauma with loss of consciousness, or fulfillment of criteria for any axis I psychiatric diagnosis other than substance abuse or dependence or for any axis II disorder other than borderline or antisocial personality disorder were exclusionary criteria (16). Subjects in the COC group reported long-term cocaine use (median 8 years; range 2.5–20 years) with a current median use of 2.5 g/week (range 0.2–4.3 g/week). They also reported using opiates (5/13 subjects), marijuana (9/13), alcohol (13/13), and nicotine (11/13), but were not physically dependent on opiates or alcohol, nor were any of them receiving treatment for drug abuse. Some control subjects used nicotine (3/5), and alcohol (3/5); one reported a single use of marijuana more than a decade before the study. All volunteers in both groups had been abstinent from nicotine, alcohol, and caffeine for 12–15 h prior to each test session. Eight of the subjects in the COC group were right-handed, and 5 were ambidextrous; 3 control subjects were right-handed, and 2 were left-handed, as assessed by a questionnaire (17).

Experimental Design. After giving informed consent, volunteers participated in two test sessions, separated by at least 1 week. Volunteers in the COC group resided on a closed ward at the National Institute on Drug Abuse Addiction Research Center (ARC) for 2 nights before each test session, to avoid confounding effects of alcohol or illicit drugs of abuse on the test results. They did not stay on the ward during the time between the two sessions. Cocaine use was verified by urinalysis upon admission to the ward prior to each session. Control subjects resided at the ARC on the night before each session. To preclude drug-related associations with the experimental environment, the neutral stimulus complex was always presented during the first session and the cocaine-related stimulus complex was presented during the other session.

The neutral stimulus complex consisted of objects used for arts and crafts (leather punch, paint brush, paint bottles, clay) and a videotape of a person handling craft items (sea shells); no drug was present or offered. The cocaine-related stimulus complex consisted of drug-related paraphernalia (glass pipe, mirror, razor blade, straw, a $10 bill), 48 mg of *l*-cocaine hydrochloride (Research Technology Branch, National Institute on Drug Abuse) mixed with an equal mass of lactose, and a videotape showing cocaine self-administration (smoking and insufflation) and handling of white powder or crystals. To increase the likelihood of eliciting craving, exposure to drug-related cues was combined with anticipation of cocaine use. Subjects in the COC group were told that they would be allowed to self-administer (by insufflation) the cocaine that had been in view after all the experimental procedures (including acquisition of brain scans) had been completed.

During exposure to the stimulus complex, the subject was seated in a reclining chair, and white noise (75 decibels) was presented indirectly in the room and through headphones to mask extraneous sounds. Videotaped stimuli were presented on a monitor located 100 cm in front of and level with his or her face; the image on the monitor subtended a visual angle of 15°. Volunteers were instructed to keep their eyes focused on the monitor and the rest of the stimulus complex, and to refrain from unnecessary talking and movement, including eye blinks.

Two sets of psychometric measures were obtained during each session. A self-report questionnaire was administered before presentation of the stimulus complex and while the stimulus complex was present during uptake of the radiotracer (10, 20, and 30 min after radiotracer injection). This instrument consisted of the following five questions: "How good do you feel?", "Do you have a craving or urge for cocaine?", "Do you want cocaine?",

The publication costs of this article were defrayed in part by page charge payment. This article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. §1734 solely to indicate this fact.

Abbreviations: PET, positron-emission tomography; rCMRglc, regional cerebral metabolic rate for glucose; CMRglc, global cerebral metabolic rate for glucose; POMS, Profile of Mood States; FDG, 2-[^{18}F]fluoro-2-deoxy-D-glucose; ROI, region of interest; MRI, magnetic resonance imaging; COC group, cocaine abusers group.

†To whom reprint requests should be addressed.

"Do you need cocaine?", and "Are you turned off?". The subjects were instructed to respond verbally on a scale of 0–10, with "0" indicating "not at all" and "10" indicating "extremely." In addition, the Profile of Mood States (POMS) (18) was administered at the beginning of each session.

Measurement of rCMRglc. The rCMRglc was measured by positron-emission tomography (PET) (14, 15). 2-[^{18}F]Fluoro-2-deoxy-D-glucose (FDG; 5 mCi, 185 MBq) was infused intravenously about 1 min after initial exposure to the stimulus complex. Participants continued to view the stimulus complex for the next 30 min, following the time course over which most of the brain uptake of FDG presumably occurred (14). Approximately 34 arterial samples were drawn, and plasma was assayed for radioactivity and glucose to provide the input function to an operational equation for calculation of rCMRglc (15). PET scans were acquired using a three-ring tomograph (NeuroECAT, Computers and Technology in Imaging, Knoxville, TN), with a resolution of 8.6 mm (full width at half maximum) at the center of the field of view. Scanning began approximately 50 min after FDG injection. Four consecutive 15-min scans were performed, yielding images of 12 slices, each approximately 14 mm thick, parallel to the inferior orbitomeatal plane, and on 8-mm centers.

Values of rCMRglc were determined in 46 bilateral and 4 medial regions of interest (ROIs), which consisted of circles (12 pixels in diameter; 0.9 mm pixel size) and ellipses (minor axis length = 12 pixels, major axis length = 25 pixels). ROIs were named as in a published atlas of the human brain (19) and were placed on magnetic resonance imaging (MRI) slices corresponding to the PET slices, using the IMAGE version 1.55 (National Institutes of Health) program on a Macintosh computer. MRI images were acquired on a 1.5-T General Electric Signa scanner, using a spoiled GRASS (gradient radiofrequency at steady state) volumetric protocol, with the following parameters: echo time = 13 msec; repetition time = 38 msec; matrix = 256 × 192 lines; slice thickness = 1.5 mm; flip angle = 45°; field of view = 24 cm. MRI slices were selected by a semi-automated procedure using an edge-matching algorithm (ANALYZE version 7.0, Biomedical Imaging Resources, Mayo Foundation, Rochester, MN).

ROIs, placed on MRI slices by three independent raters without reference to PET images, were later transferred automatically to the PET slices. Before the transfer, each PET image was expanded with a bilinear interpolation algorithm to the same pixel size as the MRI (0.9 mm × 0.9 mm), and the MRI and PET slices were coregistered by using an automated procedure (20) in IMAGE version 1.55. Reliability between raters for each PET session was >0.85 (Pearson correlation coefficient between values of rCMRglc from all pairs of raters for all subjects). There were no significant differences between raters for measurements of individual ROIs using an intra-class correlation procedure (21); the mean intraclass correlation for individual ROIs across raters was 0.88 (SD = 0.03; range = 0.69–0.99). Therefore, a single value of rCMRglc was derived by averaging the rCMRglc values obtained by all raters. Normalized values of rCMRglc were taken as the quotients of absolute rCMRglc in each ROI divided by the global cerebral metabolic rate for glucose (CMRglc). CMRglc was estimated by segmenting the brain on each MRI slice, transferring the outline to the PET slice, calculating an area-weighted average across all pixels included within the contour, excluding the ventricles, and computing the mean for 12 PET slices.

Data Analysis. Values of rCMRglc in individual ROIs were averaged to form 18 composite regions (15 bilateral, 3 medial). The bilateral composite regions and their component ROIs were as follows: dorsolateral prefrontal cortex (dorsal superior frontal gyrus, dorsal middle frontal gyrus, dorsal inferior frontal gyrus); ventrolateral prefrontal cortex (ventral superior frontal gyrus, ventral middle frontal gyrus, ventral inferior frontal gyrus); medial orbitofrontal cortex (medial orbitofrontal gyrus, ventral frontal pole); lateral orbitofrontal cortex (basal inferior frontal gyrus, anterior orbitofrontal gyrus, posterior orbitofrontal gyrus, lateral orbitofrontal gyrus); anterior cingulate cortex (pregenual cingulate cortex, medial prefrontal cortex); paralimbic cortex (gyrus rectus, insula, temporal pole); medial temporal lobe (ventral amygdala, dorsal amygdala, hippocampus, parahippocampal gyrus); retrosplenium (posterior cingulate cortex, retrosplenial cortex, precuneus); temporal lobe (superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus); striate/extrastriate cortex (inferior fusiform gyrus, cuneus, lingual gyrus); peristriate cortex (middle occipital cortex, lateral occipital gyrus); superior parietal cortex (dorsal superior parietal cortex, ventral superior parietal cortex, lateral parietal cortex); temporal/parietal cortex (inferior parietal gyrus, angular gyrus, supramarginal gyrus); rolandic cortex (pre-central gyrus, postcentral gyrus, paracentral gyrus); and basal ganglia (ventral striatum, dorsal striatum, putamen). The medial composite regions and their component ROIs were as follows: thalamus (medial, left, and right posterior nuclei), brainstem (midbrain, pons), and cerebellum (vermis, left and right cerebellar cortex).

Data were analyzed using analysis of variance (ANOVA), Pearson product moment correlation, and Student's paired *t* test. Differences in rCMRglc were initially evaluated in two separate mixed-model ANOVAs with a single between-subjects factor (Group) and two or three within-subject factors. In the first ANOVA, the 15 bilateral composite regions were analyzed as a single set with Session, Region, and Hemisphere taken as repeated measures. The three midline composite regions were analyzed in a second ANOVA without the Hemisphere factor. In both analyses, the three-way interaction of Group × Session × Region was used to test the primary hypothesis that the COC and control groups differed in rCMRglc responses to cocaine-related stimuli. To identify the specific regions that exhibited group differences in rCMRglc across sessions, each composite region was evaluated in a separate ANOVA, with Group, Session, and Hemisphere (if appropriate) as factors. Those composite regions exhibiting a significant Group × Session interaction were then evaluated for simple main effects of Session in a separate ANOVA for each of the groups, with Session and Hemisphere as repeated measures. Differences in CMRglc were analyzed with a mixed-model ANOVA, with Group and Session as the factors. After testing for the Group × Session interaction, the Newman–Keuls multiple-comparisons test was used to evaluate changes across sessions within each group. Differences in the self-report items were also analyzed in a mixed-model ANOVA, with Session and Time as repeated measures, and Group as a between-subjects factor. A significant Group × Session interaction was followed by separate ANOVAs for each group, with Session and Time as repeated measures. Relationships between the change in craving and change in rCMRglc in each of the 18 composite regions across the two test sessions were tested with Pearson product moment correlation. The number of tests was reduced by averaging rCMRglc from both hemispheres for each pair of bilateral ROIs. Differences between sessions in the POMS were evaluated with Student's paired *t* test. In all analyses, the criterion for statistical significance was $P < 0.05$ (uncorrected for the total number of tests). Reported significance levels of ANOVAs reflect Greenhouse–Geiser adjustments for repeated measures. Statistical analysis was performed using a commercial package (SAS for Windows version 6.10, SAS Institute, Cary, NC).

RESULTS

Means of rCMRglc and CMRglc are shown in Table 1. There was a significant three-way interaction of Group, Session, and Region among the 15 bilateral composite regions [$F(14, 224) = 1.86, P < 0.05$], but not among the 3 midline composite regions [$F(2, 32) = 0.74$, not significant]. Analysis of individual regions revealed significant Group × Session interactions in the following cortical areas: dorsolateral prefrontal [$F(1, 16) = 11.45, P < 0.005$], ventrolateral prefrontal [$F(1, 16) = 5.23, P < 0.04$], medial

Table 1. Effects of cocaine-related cues on cerebral glucose metabolism

	rCMRglc, mg/100 g per min							
	COC group				Control group			
	Neutral cues		Cocaine cues		Neutral cues		Cocaine cues	
Composite region	Left	Right	Left	Right	Left	Right	Left	Right
Prefrontal cortex								
Dorsolateral**	8.32 ± 0.20	8.66 ± 0.28	9.06 ± 0.24	9.14 ± 0.30	8.56 ± 0.61	8.72 ± 0.66	8.12 ± 0.27	8.01 ± 0.46
Ventrolateral	8.84 ± 0.29	8.92 ± 0.32	9.22 ± 0.23	9.07 ± 0.26	8.84 ± 0.36	8.86 ± 0.41	8.03 ± 0.21	8.15 ± 0.22
Medial orbitofrontal*	7.83 ± 0.25	7.98 ± 0.27	8.30 ± 0.28	8.28 ± 0.26	8.73 ± 0.44	8.27 ± 0.46	7.88 ± 0.33	7.52 ± 0.45
Lateral orbitofrontal	7.91 ± 0.26	7.55 ± 0.24	8.00 ± 0.27	7.66 ± 0.26	8.36 ± 0.33	7.71 ± 0.46	7.49 ± 0.43	7.59 ± 0.28
Limbic cortex								
Anterior cingulate	7.84 ± 0.17	8.12 ± 0.24	8.07 ± 0.21	8.24 ± 0.24	8.09 ± 0.43	8.33 ± 0.50	7.93 ± 0.49	7.68 ± 0.42
Paralimbic	7.47 ± 0.25	7.27 ± 0.23	7.38 ± 0.28	7.30 ± 0.25	7.73 ± 0.32	7.70 ± 0.38	7.28 ± 0.31	7.31 ± 0.22
Medial temporal lobe	5.73 ± 0.17	5.80 ± 0.18	5.99 ± 0.17	5.97 ± 0.17	5.84 ± 0.13	5.98 ± 0.25	5.29 ± 0.21	5.63 ± 0.14
Retrosplenial*	9.43 ± 0.38	9.22 ± 0.42	9.82 ± 0.34	9.66 ± 0.45	9.81 ± 0.41	10.28 ± 0.57	9.08 ± 0.67	9.95 ± 0.25
Temporal cortex								
Temporal lobe*†	8.31 ± 0.29	7.94 ± 0.28	8.80 ± 0.29	8.26 ± 0.25	8.45 ± 0.24	8.35 ± 0.37	7.45 ± 0.17	7.89 ± 0.24
Visual cortex								
Striate/extrastriate	9.62 ± 0.31	9.59 ± 0.40	9.92 ± 0.37	10.06 ± 0.40	9.71 ± 0.41	9.58 ± 0.41	9.00 ± 0.42	9.27 ± 0.35
Peristriate*	7.89 ± 0.26	8.19 ± 0.30	8.53 ± 0.39	8.71 ± 0.35	8.06 ± 0.43	8.47 ± 0.59	7.11 ± 0.51	7.50 ± 0.35
Parietal cortex								
Superior parietal	8.45 ± 0.29	8.26 ± 0.27	8.70 ± 0.42	8.79 ± 0.37	8.03 ± 0.66	8.30 ± 0.52	7.61 ± 0.21	7.66 ± 0.24
Temporal/parietal*	8.16 ± 0.31	8.21 ± 0.28	8.57 ± 0.36	8.64 ± 0.27	8.43 ± 0.52	8.22 ± 0.30	7.15 ± 0.16	7.70 ± 0.22
Sensory/motor cortex								
Rolandic	8.34 ± 0.22	8.24 ± 0.24	8.57 ± 0.29	8.52 ± 0.34	8.57 ± 0.53	8.39 ± 0.27	8.02 ± 0.26	7.99 ± 0.35
Subcortical								
Basal ganglia	8.98 ± 0.34	9.01 ± 0.31	8.88 ± 0.28	8.90 ± 0.29	9.69 ± 0.55	9.68 ± 0.56	9.05 ± 0.56	8.82 ± 0.55
Brain stem	5.83 ± 0.18		6.00 ± 0.34		5.92 ± 0.27		5.48 ± 0.25	
Thalamus	7.97 ± 0.15		7.80 ± 0.30		8.19 ± 0.22		7.72 ± 0.28	
Cerebellum	6.75 ± 0.19		6.81 ± 0.22		6.63 ± 0.23		6.08 ± 0.33	
Global (CMRglc)‡	6.68 ± 0.16		6.89 ± 0.18		7.48 ± 0.36		7.01 ± 0.26	

Each value is the mean ± SEM for the 13 subjects in the COC group and the 5 subjects in the Control group. Significant effect of Session by two-way ANOVA in the COC group: *, $P < 0.05$; **, $P < 0.01$. Significant effect of Hemisphere by two-way ANOVA in the COC group: †, $P < 0.05$. Significant difference between sessions in the Control group by Newman–Keuls test: ‡, $P < 0.01$.

orbitofrontal [$F(1, 16) = 18.84, P < 0.001$], medial temporal lobe [$F(1, 16) = 8.72, P < 0.01$], retrosplenial [$F(1, 16) = 4.74, P < 0.05$], temporal lobe [$F(1, 16) = 15.66, P < 0.001$], temporal/parietal [$F(1, 16) = 10.85, P < 0.005$], striate/extrastriate [$F(1, 16) = 5.15, P < 0.05$], and peristriate [$F(1, 16) = 7.87, P < 0.001$]. The COC group showed a significant increase in rCMRglc during presentation of drug-related cues compared with rCMRglc in the neutral cues session in the following six composite cortical regions: dorsolateral prefrontal (7% increase relative to neutral cues session), medial orbitofrontal (5%), retrosplenial (5%), temporal lobe (5%), peristriate (7%), and temporal/parietal (5%) (Fig. 1, Table 1). Although there was no main effect of Session on rCMRglc in ventrolateral prefrontal cortex, medial temporal lobe, or striate/extrastriate cortex, the means of rCMRglc indicated a trend toward increases during presentation of cocaine-related cues in the COC group and a decrease or no change in the control group. No significant decreases in rCMRglc were seen in response to the drug-related stimuli in the COC group. None of the regions exhibited statistically significant changes in the control subjects, although there was a trend toward decreased rCMRglc in some composite regions. A significant Group × Session interaction in CMRglc [$F(1, 16) = 12.73, P < 0.005$] was due to a 6.5% reduction in CMRglc during the second test session in the control subjects (Newman–Keuls test, $P < 0.01$) (Fig. 1, Table 1); a 3% increase in CMRglc during the second session in the COC group was not statistically significant ($P < 0.10$).

Increases in rCMRglc in the COC group were bilateral, with no significant Hemisphere × Session interactions. Only the temporal lobe showed a main effect of Hemisphere ($P < 0.01$), indicating that rCMRglc was greater on the left than on the right in both sessions. Although the COC group included non-right-handed subjects, the overall pattern of significance for the Session and Hemisphere factors was unchanged when these subjects were excluded from analysis (data not shown). Increases in rCMRglc in the dorsolateral prefrontal and peristriate cortices remained significant after the data were normalized, but changes in the temporal lobe, temporal/parietal, retrosplenial, and medial orbitofrontal cortices did not (data not shown). Normalization did not produce statistically significant changes that had not been previously observed in absolute rCMRglc.

In the COC group, exposure to the drug-related stimuli increased self-reports of cocaine craving compared both to scores obtained before presentation of the cocaine-related cues and to those taken during presentation of the neutral cues (Fig. 2*A*). All control subjects reported a score of "0" in response to cocaine-related questions before and during presentation of both sets of stimuli. The lack of variance in the control subjects precluded inclusion of a between-subjects group factor in the ANOVA; therefore, only data from the COC group were analyzed. The greatest change in the COC group was in response to the question "Do you have a craving or urge for cocaine?", with a statistically significant difference in the score between sessions [$F(1, 12) = 22.81, P < 0.001$]. There was also a Session × Time interaction due to the increases over baseline in the cocaine cues session but not the neutral cues session [$F(3, 36) = 8.17, P < 0.001$]. Responses to other cocaine-related questions exhibited similar, but less marked, changes ["Do you want cocaine?": Session, $F(1, 12) = 9.12, P < 0.01$; Session × Time, $F(3, 36) = 4.25, P < 0.05$; "Do you need cocaine?": Session, $F(1, 12) = 8.45, P < 0.05$; Session × Time, $F(3, 36) = 0.075$, not significant]. Neither group manifested pronounced differences in mood at the beginning of

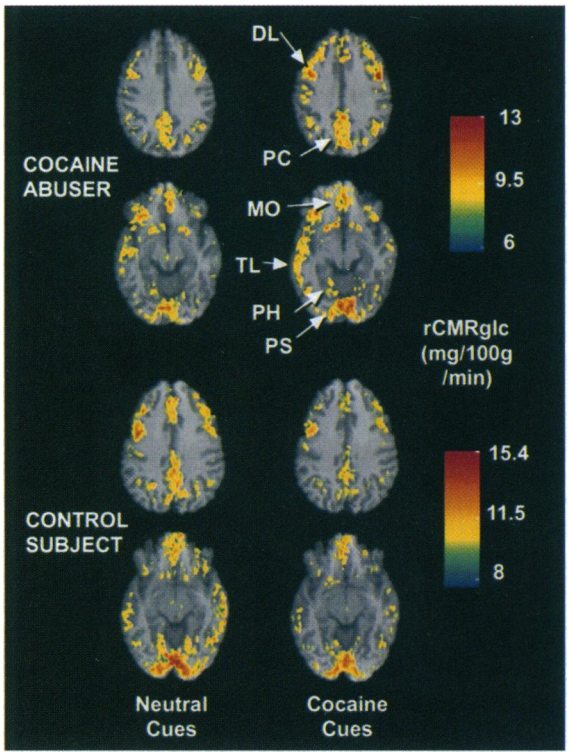

FIG. 1. Representative images of rCMRglc in selected subjects from the COC group (*Upper*) and the control group (*Lower*) during the neutral (*Left*) and cocaine-related (*Right*) stimulus sessions. Two levels of brain in each subject are displayed. In each case a pseudocolored metabolic (PET) image was superimposed on a structural (MRI) image. Arrows indicate regions which exhibited significant increases in rCMRglc in the COC group: DL, dorsolateral prefrontal cortex; PC, precuneus; PS, peristriate cortex; MO, medial orbitofrontal cortex; TL, temporal lobe; PH, parahippocampal gyrus. Other areas that exhibited metabolic increases in the subject shown, however, did not manifest increases in other subjects of the COC group. In contrast to the metabolic increases in the COC group, control subjects exhibited a tendency for a decrease in rCMRglc.

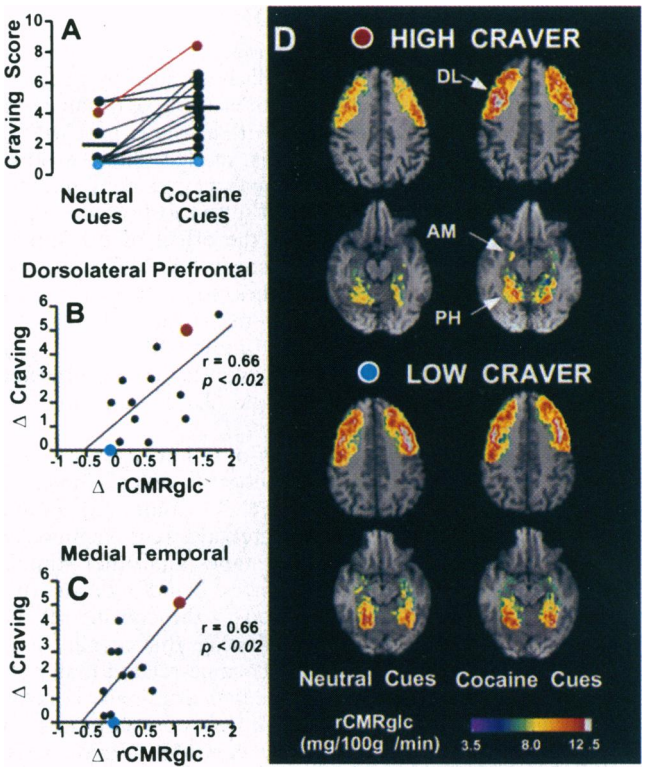

FIG. 2. Self-reports of craving induced by cocaine-related cues and correlations of rCMRglc with cocaine craving. (*A*) Self-report responses of individual subjects in the COC group to the question "Do you have a craving or urge for cocaine?" during exposure to neutral and to cocaine-related stimuli. The mean score (horizontal bar) was significantly increased during exposure to the cocaine-related stimulus complex compared with the neutral stimulus, and the magnitude of the response across individuals varied considerably. PET scans from two subjects, marked with red and blue dots, are shown in *D*. (*B*) Correlation of change (Δ) in self-reported craving with change (Δ) in rCMRglc in dorsolateral prefrontal cortex in the COC group. (*C*) Correlation of change (Δ) in self-reported craving with change (Δ) in rCMRglc in medial temporal lobe in the COC group. In both *B* and *C* the ordinate represents the difference (Δ) between the average of the responses to the question "Do you have a craving or urge for cocaine?" taken at three times during the 30-min presentation of the neutral and cocaine-related stimulus complexes. The abscissa represents the difference (Δ) in rCMRglc between the two sessions (cocaine cues minus neutral cues). (*D*) Pseudocolored PET images of metabolic activity in the dorsolateral prefrontal cortex and medial temporal lobe superimposed on structural (MRI) images, illustrating increases of rCMRglc associated with self-reports of craving (metabolic activity outside the dorsolateral prefrontal cortex and medial temporal lobe is not shown). One subject, who reported a large increase in self-reported craving during presentation of cocaine-related cues (*Upper*—red dot in *A–C*), exhibited a marked increase in rCMRglc in the amygdala (AM) and parahippocampal gyrus (PH). This effect was not evident in a subject who reported no increase in craving due to the cocaine-related cues (*Lower*—blue dot in *A–C*).

the two sessions, as indexed by the POMS. In addition, there were no differences between sessions or across time within the sessions in response to items on the self-report questionnaire that related to mood ("How good do you feel?" and "Are you turned off ?").

The relationship in the COC group between changes in rCMRglc and self-reports of craving for cocaine across sessions was examined by correlation analysis. Among the 18 composite regions, only the dorsolateral prefrontal cortex ($r = 0.66$, $P < 0.025$, $n = 13$; Fig. 2 *B* and *D*), medial temporal lobe ($r = 0.66$, $P < 0.025$, $n = 13$; Fig. 2 *C* and *D*), and cerebellum ($r = 0.66$, $P < 0.025$, $n = 13$) exhibited statistically significant correlations. Unlike the dorsolateral prefrontal cortex, where ANOVA revealed a significant main effect of Session on rCMRglc, neither the medial temporal lobe ($P < 0.10$) nor the cerebellum ($P < 0.80$) showed significant rCMRglc changes because of the smaller magnitudes and larger individual differences in the effects of drug-related cues (Table 1). A more detailed regression analysis of changes in craving with the changes in rCMRglc in the medial temporal lobe was performed by calculating correlations using data from the individual ROIs comprising this composite region. This finer analysis was performed because the medial temporal lobe is anatomically heterogeneous, containing cortical (parahippocampal gyrus), allocortical (hippocampus), and noncortical (amygdala) structures, and also because these components subserve distinct functions—e.g., cognition (parahippocampal gyrus and hippocampus) and emotion (amygdala) (22, 23). While the amygdala is a complex of individual nuclei with distinct patterns of connectivity and function (23), it was treated as a single structure, given the limited resolution of the PET scanner. A single measure of rCMRglc in the amygdala was derived by averaging rCMRglc in the ventral and dorsal ROIs. The change in craving was correlated significantly with the changes in rCMRglc in the amygdala ($r = 0.64$, $P < 0.01$, $n = 13$; Fig. 2*B*) but not in the parahippocampal gyrus ($r = 0.52$, $P < 0.07$, $n = 13$) or the hippocampus ($r = 0.10$, not significant, $n = 13$). Although ANOVAs revealed no significant effects of Session on rCMRglc in two of the individual component ROIs of the medial temporal lobe (amygdala and hippocampus), rCMRglc increased significantly across sessions in the parahippocampal gyrus [$F(1, 12) = 5.96$, $P < 0.05$].

DISCUSSION

The present study demonstrates regional increases in cortical and medial temporal lobe metabolism elicited by cocaine-related cues in human volunteers with histories of cocaine use. Cue-elicited craving was correlated with increases in rCMRglc in the dorsolateral prefrontal cortex, medial temporal lobe, and cerebellum. In contrast, cocaine-related cues did not significantly affect rCMRglc or elicit self-reports of craving in normal volunteers, suggesting that the effect of the stimuli depended on prior experience with cocaine use. The decrease in CMRglc from the first (neutral cues) to the second session (cocaine cues) in the control group may reflect an effect of habituation, as a similar small reduction in CMRglc was seen in a previous study in which human volunteers were subjected to repeated measurement of CMRglc (J. M. Stapleton and E.D.L., unpublished observations).

The lack of significant changes in occipital regions during exposure to cocaine-related cues in control subjects indicated that the increases of rCMRglc in the COC group were not due to differences in the physical characteristics (e.g., luminosity, color mix, motion) of the two videotapes and other stimuli. The increase in the peristriate cortex could indicate that greater visual attention was directed to the cocaine-related stimuli. This view is consistent with findings that cocaine users spend more time visually scanning cocaine-related than neutral stimuli (24), and they are less able than drug-naïve controls to maintain vigilance toward stimuli unrelated to cocaine (25). It is unlikely, however, that increases in rCMRglc in the COC group can be attributed solely to nonspecific arousal. In a recent study, transition from a relaxed state to a high level of vigilance in humans was accompanied by increased subcortical blood flow in the reticular formation, but not in the cortical regions that were activated in the present study (26).

Although increased attention or arousal could have contributed to elevations in rCMRglc in the COC group, it is notable that all of the regions that exhibited responses to drug-related stimuli are activated by cognitive tasks that involve one or more types of memory (22, 27–29). Cognitive operations that require working memory (i.e., short-term, limited-capacity memory of task-relevant stimuli) activate the dorsolateral prefrontal cortex and, in some cases, the temporal–parietal junction (supramarginal and angular gyri) (28, 29). When tasks require explicit episodic memory (i.e., conscious recall of autobiographical events), retrosplenial regions (including precuneus), the medial orbitofrontal, and the dorsolateral prefrontal cortex are activated (22, 28, 29). Although activation of the hippocampus and parahippocampal gyrus has not been observed consistently using tasks sensitive to medial temporal lobe damage (30, 31), lesion studies have demonstrated an essential contribution of the parahippocampal gyrus to explicit memory (22). At a more perceptual level, the temporal cortex, especially its inferior portion, is important for object recognition and memory (30, 32).

Craving for cocaine was correlated not only with increases of rCMRglc in the dorsolateral prefrontal cortex and the medial temporal lobe, regions involved in explicit memory, but also with activation in the amygdala and cerebellum, whose roles in memory have only recently been recognized. The classic role of the amygdala in mediating behavioral and physiological aspects of emotional expression (23) suggests that this region may be critical to the incentive-motivational and autonomic responses that accompany cue-elicited craving (6–8). There is increasing evidence, however, that the contribution of the amygdala in conditioned emotional responses also involves implicit, nonconscious memory and control of attention (22, 23, 33, 34). Furthermore, recent studies have suggested that emotional arousal, mediated by the amygdala, can facilitate explicit memory (35, 36). This view is congruent with the hypothesis that the amygdala plays a critical role in learned stimulus–reward associations, as demonstrated by the fact that lesions of the amygdala impair responses to stimuli associated with drug administration (37–39) or to the availability of biological reinforcers (e.g., food, water, footshock, sexual activity) (33, 39–41). Correlation of craving with rCMRglc in the amygdala is consistent with the finding that c-fos-like immunoreactivity, a marker for cellular activation, is increased in the rat amygdala by both cocaine administration and exposure to an environment in which cocaine had been administered (42).

The correlation of craving with increased rCMRglc in the cerebellum is intriguing in light of recent data linking cerebellar function to cognition (43, 44). Although the cerebellum had once been viewed solely as a mediator of motor functions, cerebellar activation has been observed during performance of cognitive tasks that require explicit, episodic memory while motor activity is controlled (27, 43–45). In fact, a recent study reported as strong a correlation of performance on a recognition memory task with cerebellar activation as with activation of the medial temporal lobe (31). Much of the interest in the role of the cerebellum in cognition is based on the presence of anatomical pathways connecting the cerebellum and dorsolateral prefrontal cortex (46, 47), another region whose activation exhibits a significant correlation with cocaine craving.

Our findings contrast with hypotheses positing that the same brain regions that mediate the direct pharmacological effects of a drug also generate responses to stimuli associated with administration of the drug (9–12). Although the amygdala and other limbic regions are activated both by administration of cocaine and by placement of a rat in an environment associated with cocaine administration (42), the present findings indicate that cerebral responses to drug-related cues are not simply equivalent to the reaction to the drug itself or to a conditioned withdrawal state (3, 5, 9, 11, 12, 48). The discrete distribution of activation produced by cocaine-related stimuli differs markedly from the response to acute cocaine administration, which involves widespread decreases in rCMRglc in human volunteers (49). Interpretation of the discordance between the direction and topography of the response to acute cocaine administration and the response to cocaine-related cues must be tempered, however, by the fact that although rCMRglc measurement is weighted toward the first 10–15 min after radiotracer injection, it is influenced by metabolic activity over a longer period. In the present study, the level of craving reported was relatively constant during the first 30 min after the injection of FDG, whereas subjective responses to an acute administration of cocaine change rapidly during the same period of time (49).

The cerebral activation observed here also differs from findings in cocaine abusers who were studied in the absence of overt drug-relevant cues during the first week of drug abstinence (50). Those subjects showed elevated rCMRglc in the basal ganglia and the medial orbitofrontal cortex, and a correlation between rCMRglc in medial prefrontal regions and self-reports of craving during the preceding week. In the present study, cocaine cues did not elicit changes in the basal ganglia. This lack of effect is consistent with the failure to find increased numbers of cells staining for c-fos in the dorsal striatum or nucleus accumbens in rats which had been placed in an environment associated with repeated cocaine administration (42), even though these structures mediate the direct locomotor and reinforcing effects of the drug (51).

The significance of the increased rCMRglc in the medial orbitofrontal cortex both in the volunteers exposed to the cocaine-related stimuli in the present study and in individuals undergoing cocaine withdrawal is less apparent (50). It is unlikely that the increased rCMRglc in the present study reflects cocaine withdrawal *per se*, as subjects in the COC group had been abstinent from cocaine for approximately the same amount of time before both test sessions. Another possibility is that cocaine-related cues acted as classically conditioned stimuli that evoked a change in rCMRglc that normally accompanies cocaine abstinence. Nonetheless, al-

though rCMRglc in medial orbitofrontal cortex was correlated with retrospective reports of cocaine craving in patients undergoing cocaine withdrawal (50), the change in rCMRglc in the medial orbitofrontal cortex elicited by cocaine-related cues was not related to the magnitude of cue-elicited craving (r = 0.31, not significant). This discrepancy suggests that the neuroanatomical substrates engaged when craving arises spontaneously are different from those involved in craving elicited by drug-related cues. On the other hand, the increase in rCMRglc in the medial orbitofrontal cortex could reflect the operation of a similar cognitive process, such as intrusive thoughts about drug self-administration, in both conditions. Normal volunteers as well as patients with obsessive-compulsive disorder manifest increased perfusion of the medial orbitofrontal cortex during the presentation of stimuli that trigger intrusive ideation (43), and it is plausible that the cocaine-related cues had an analogous effect on participants in of the COC group.

The present findings indicate that activation of brain regions implicated in several forms of memory (working, episodic, and emotional) is directly related to the intensity of cue-elicited craving. It has been previously suggested that drug craving may be mediated by brain systems involved in memory, but no evidence in support of this view has been available to date (10). The correlations of craving with increases in rCMRglc in the dorsolateral prefrontal cortex, amygdala, and cerebellum, nonetheless, suggest the outlines of an information processing circuit in which perceptions of drug-related stimuli lead to the experience of craving. An interplay between these regions is consistent with suggestions that emotional arousal, mediated by the amygdala, serves not only to prioritize behavioral goals (52) but also to enhance explicit memory (35, 36). It also is congruent with the view that brain circuits that participate in explicit memory support goal-directed behavior by sensitizing sensory processing to environmental stimuli that are relevant to those goals (32, 53). In this manner, activation of brain regions integrating the emotional and cognitive components of memory by drug-related stimuli could contribute to one of the hallmarks of addiction–i.e., the excessive focus on activities that lead to further drug use.

Although memory was not directly tested in this study, the present research suggests that mechanisms mediating memory processing are as germane to the understanding of cocaine craving as are the neural substrates of the direct effects of cocaine. Identification of a specific pattern of brain activation correlated with cocaine craving can direct future investigations into the mechanism of and therapeutic interventions for craving in drug addiction, and possibly in other appetitive disorders that involve powerful urges.

We thank A. Leshner, J. Metcalfe, T. Shippenberg, R. Soria-Heidbreder, and especially S. R. Zukin for discussion and comments on the manuscript; W. Eckelman and his staff at the Clinical Center, National Institutes of Health, for supplying FDG; L. Weyl for nuclear medicine technology support; D. Coats, R. Stauffer, J. Eber, J. Kivet, and K. Demuth for nursing services; D. B. Vaupel for assistance in electrophysiological measurements; and G. Wood for computer support. This work was supported by funding from the Counterdrug Technology Assessment Center, Office of National Drug Control Policy, Office of the President.

1. Hunt, W. A., Barnett, L. W. & Branch, L. G. (1971) *J. Clin. Psychol.* **27,** 455–456.
2. Harrison, P. A., Hoffman, N. G. & Streed, S. G. (1991) in *Comprehensive Handbook of Drug and Alcohol Addiction,* ed. Miller, N. S. (Dekker, New York), pp. 1163–1200.
3. Childress, A. R., Ehrman, R., Rohsenow, D. J., Robbins, S. J. & O'Brien, C. P. (1992) in *Substance Abuse: A Comprehensive Textbook,* eds. Lowinson, J. H., Ruiz, P., Millman, R. B. & Langrod, J. G. (Williams & Wilkins, Baltimore), pp. 56–69.
4. Wikler, A. (1948) *Am. J. Psychiatry* **105,** 329–338.
5. Drummond, D. C., Tiffany, S. T., Glautier, S. & Remington, B. (1995) *Addictive Behavior: Cue Exposure Theory and Practice* (Wiley, Chichester, U.K.).
6. Avants, S. K., Margolin, A., Kosten, T. R. & Singer, J. L. (1993) *J. Subst. Abuse Treat.* **10,** 577–583.
7. Ehrman, R. N., Robbins, S. J., Childress, A. R. & O'Brien, C. P. (1992) *Psychopharmacology (Berlin)* **107,** 523–529.
8. Bauer, L. O. & Kranzler, H. R. (1994) *Biol. Psychiatry* **36,** 189–197.
9. Stewart, J., de Wit, H. & Eikelboom, R. (1984) *Psychol. Rev.* **91,** 251–268.
10. Wise, R. A. (1987) *Pharmacol. Ther.* **35,** 227–263.
11. Robinson, T. E. & Berridge, K. C. (1993) *Brain Res. Rev.* **18,** 247–291.
12. Siegel, S. (1991) in *Perspectives in Cognitive Neuroscience,* eds. Lister, R. G. & Weingartner, L. H. G. (Oxford Univ. Press, New York), pp. 405–416.
13. Fischman, M. W., Foltin, R. W., Nestadt, G. & Pearlson, G. D. (1990) *J. Pharmacol. Exp. Ther.* **253,** 760–770.
14. Reivich, M., Kuhl, D., Wolf, A., Greenberg, J., Phelps, M., Ido, T., Casella, V., Fowler, J., Hoffman, E., Alavi, A., Som, P. & Sokoloff, L. (1979) *Circ. Res.* **44,** 127–137.
15. Phelps, M. E., Huang, S. C., Hoffman, E. J., Selin, C., Sokoloff, L. & Kuhl, D. E. (1979) *Ann. Neurol.* **6,** 371–388.
16. American Psychiatric Association (1987) *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, Washington, DC), 3rd. Ed., revised.
17. Annett, M. (1970) *Br. J. Psychol.* **61,** 303–321.
18. McNair, D., Lorr, M. & Droppleman, L. (1971) *Profile of Mood States (Manual)* (Educational and Industrial Testing Service, San Diego).
19. Damasio, H. (1995) *Human Brain Anatomy in Computerized Images* (Oxford Univ. Press, New York).
20. Wood, G. (1993) M.S. thesis (Univ. Texas Southwest Graduate School for Biomedical Sciences, Dallas).
21. Semple, W. E., Johnson, J. L. & Cohen, R. (1993) in *Imaging Drug Action in the Brain,* ed. London, E. D. (CRC, Boca Raton, FL), pp. 297–316.
22. Squire, L. R. & Knowlton, B. J. (1995) in *The Cognitive Neurosciences,* ed. Gazzaniga, M. S. (MIT Press, Cambridge, MA), pp. 825-837.
23. Aggleton, J. P. (1992) *The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction* (Wiley-Liss, New York).
24. Rosse, R. B., Miller, M. W., Hess, A. L., Alim, T. N. & Deutsch, S. I. (1993) *Biol. Psychiatry* **33,** 554–556.
25. Bauer, L. O. (1994) *Addict. Behav.* **16,** 599–607.
26. Kinomura, S., Larsson, J., Gulyas, B. & Roland, P. E. (1996) *Science* **271,** 512–515.
27. Andreasen, N. C., O'Leary, D. S., Cizadlo, T., Arndt, S., Rezai, K. & Watkins, G. L. (1995) *Am. J. Psychiatry* **152,** 1576–1585.
28. Buckner, R. L. & Tulving, E. (1995) in *Handbook of Neuropsychology,* eds. Boller, F. & Grafman, J. (Elsevier, Amsterdam), Vol. 10, pp. 439–466.
29. Grafton, S. T. (1995) *Semin. Neurosci.* **7,** 157–163.
30. Ungerleider, L. G. (1995) *Science* **270,** 769–775.
31. Nyberg, L., McIntosh, A. R., Houle, S., Nilsson, L.-G. & Tulving, E. (1996) *Nature (London)* **380,** 715–717.
32. Desimone, R., Miller, E. K., Chelazzi, L. & Lueschow, A. (1995) in *The Cognitive Neurosciences,* ed. Gazzaniga, M. S. (MIT Press, Cambridge, MA), pp. 475–490.
33. LeDoux, J. E. (1993) *Behav. Brain Res.* **58,** 69–79.
34. Gallagher, M. & Holland, P. C. (1994) *Proc. Natl. Acad. Sci. USA* **91,** 11771–11776.
35. Cahill, L., Prins, B., Weber, M. & McGaugh, J. L. (1994) *Nature (London)* **371,** 702–704.
36. Cahill, L., Bablinsky, R., Markowitsch, H. J. & McGaugh, J. L. (1995) *Nature (London)* **377,** 295–296.
37. Hiroi, N. & White, N. M. (1991) *J. Neurosci.* **11,** 2107–2116.
38. Brown, E. E. & Fibiger, H. C. (1993) *Psychopharmacology (Berlin)* **113,** 123–130.
39. Burns, L. H., Robbins, T. W. & Everitt, B. J. (1993) *Behav. Brain Res.* **55,** 167–183.
40. Robbins, T. W., Cador, M., Taylor, J. R. & Everitt, B. J. (1989) *Neurosci. Biobehav. Rev.* **13,** 155–162.
41. Gaffan, D. & Liang, K. C. (1992) in *The Amygdala: Neurobiological Aspects of Emotion, Memory, and Mental Dysfunction,* ed. Aggleton, J. P. (Wiley–Liss, New York), pp. 471–484.
42. Brown, E. E., Robertson, G. S. & Fibiger, H. C. (1992) *J. Neurosci.* **12,** 4112–4121.
43. Fiez, J. A. (1996) *Neuron* **16,** 13–15.
44. Roland, P. E. (1993) *Can. J. Neurol. Sci.* **20,** S75–S77.
45. Gao, J.-H., Parsons, L. M., Bower, J. M., Xiong, J., Li, J. & Fox, P. T. (1996) *Science* **272,** 545–547.
46. Schmahmann, J. D. & Pandya, D. N. (1995) *Neurosci. Lett.* **199,** 175–178.
47. Middleton, F. A. & Strick, P. L. (1994) *Science* **266,** 458–461.
48. Wise, R. A. (1988) *J. Abnorm. Psychol.* **97,** 118–132.
49. London, E. D., Cascella, N. G., Wong, D. F., Phillips, R. L., Dannals, R. F., Links, J. M., Herning, R., Grayson, R., Jaffe, J. H. & Wagner, H. N., Jr. (1990) *Arch. Gen. Psychiatry* **47,** 567–574.
50. Volkow, N. D., Fowler, J. S., Wolf, A. P., Hitzemann, R., Dewey, S., Bendriem, B., Alpert, R. & Hoff, A. (1991) *Am. J. Psychiatry* **148,** 621–626.
51. London, E. D., Grant, S. J., Morgan, M. J. & Zukin, S. R. (1996) in *Handbook of Neuropsychiatry,* eds. Fogel, B. & Schiffer, R. (Williams & Wilkins, Baltimore), pp. 635–678.
52. Kosslyn, S. M. & Koenig, O. (1995) *Wet Mind: The New Cognitive Neuroscience* (Free Press, New York).
53. Tulving, E. (1995) in *The Cognitive Neurosciences,* ed. Gazzaniga, M. S. (MIT Press, Cambridge, MA), pp. 839-847.