

Activation of Orbital and Medial Prefrontal Cortex by Methylphenidate in Cocaine-Addicted Subjects But Not in Controls: Relevance to Addiction

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Drugs of abuse are rewarding to addicted and nonaddicted subjects, but they trigger craving and compulsive intake only in addicted subjects. Here, we used positron emission tomography (PET) and [¹⁸F]deoxyglucose to compare the brain metabolic responses (marker of brain function) of cocaine-addicted subjects ($n = 21$) and controls ($n = 15$) to identify brain regions that are uniquely activated in addicted subjects by intravenous methylphenidate (a drug that cocaine-addicted subjects report to be similar to cocaine). In parallel, we also measured the changes in dopamine (DA) induced by intravenous methylphenidate (using PET and [¹¹C]raclopride) in the striatum and in the thalamus. Metabolic responses between groups differed significantly only in the right medial orbital prefrontal cortex [Brodmann's area (BA) 25 and medial BA 11], where methylphenidate increased metabolism in addicted subjects but decreased metabolism in controls. These changes were associated in all subjects with increased "desire for methylphenidate" and in the addicted subjects with "cocaine craving." In addicted subjects, increases in BA 25 were also associated with mood elevation. Methylphenidate-induced increases in metabolism in the medial orbital prefrontal cortex were associated with its increase of DA in the thalamus but not in the striatum. These findings provide evidence that enhanced sensitivity of BA 25 (region involved with emotional reactivity) and BA 11 (region involved with salience attribution and motivation) in cocaine-addicted subjects may underlie the strong emotional response to the drug and the intense desire to procure it that results in craving and compulsive drug intake. It also suggests that the mesothalamic DA pathway may contribute to these processes.

Key words: thalamus; dopamine; motivation; orbitofrontal; cingulate gyrus; imaging

Introduction

The ability of cocaine to increase dopamine (DA) in the nucleus accumbens (NAc) seems to be crucial for the reinforcing effects of cocaine (Koob and Bloom, 1988). However, cocaine-induced DA increases in the NAc do not explain addiction, because this effect occurs in nonaddicted as well as addicted subjects (Volkow et al., 1997a). A reasonable hypothesis is that addiction results from adaptations triggered by intermittent cocaine-induced supraphysiological perturbations of the DA system, which could disrupt the circuits regulated by DA. Indeed, positron emission tomography (PET) reveals that DA brain function (assessed by DA D₂ receptors and DA release in the striatum), as well as activity in the orbitofrontal cortex (OFC) and anterior cingulate gyrus (CG) (assessed by brain glucose metabolism), is markedly de-

creased in cocaine-addicted subjects tested during withdrawal (Volkow et al., 1993). Reductions in OFC and CG metabolism were associated with decreases in striatal DA D₂ receptors, which suggested that these cortical changes reflect the consequences of disrupted DA activity. From these studies, a hypothesis emerged that abnormalities in the OFC and CG, which are regions involved with salience attribution and inhibitory control and implicated in compulsive behaviors, underlie craving and compulsive drug intake in addiction (Volkow and Fowler, 2000). This hypothesis was evaluated in this study by comparing the regional brain metabolic responses of cocaine-addicted subjects with controls after administration of the stimulant drug methylphenidate (MP). In parallel, we also measured the association between the metabolic changes and the DA changes induced by MP to assess whether the brain responses were linked to its dopaminergic effects.

For this purpose, detoxified cocaine-addicted subjects and controls were administered two sequential doses of intravenous MP. PET imaging of [¹⁸F]deoxyglucose (FDG) was used to measure the effects of MP in brain glucose metabolism (marker of brain function) (Sokoloff et al., 1977), and imaging of [¹¹C]ra-

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clopride was used to measure DA transmission (Volkow et al., 1994). We selected MP because it is similar pharmacologically to cocaine; both drugs increase DA by blocking DA transporters (DATs) with similar potencies (Volkow et al., 1995) and induce similar changes in regional brain activation (Dirckx et al., 2004). Moreover, cocaine-addicted subjects report that intravenous MP has similar effects to cocaine (Wang et al., 1997). We chose two sequential doses rather than a single dose because this mimics better the pattern of drug intake in cocaine abuse (multiple administrations). Previous publications have documented the effects of MP on brain metabolism in controls (Volkow et al., 1997b) and in cocaine-addicted subjects (Volkow et al., 1999) and have compared DA changes between controls and addicted subjects (Volkow et al., 1997a). Here, we compare for the first time the brain metabolic responses to MP between cocaine-addicted subjects and controls and evaluate the association between MP-induced metabolic and DA changes. We hypothesized that responses to MP of addicted subjects and controls would differ in the OFC and CG and that these differences would be associated with the “desire for the drug” and would be linked to the dopaminergic effects of MP.

Materials and Methods

Subjects. The cocaine-addicted subjects were 21 male right-handed subjects [age, 36 ± 5 years; education, 12 ± 2 years; intelligence quotient (IQ)-verbal, 103 ± 11] who were inpatients at Veterans Administration Hospital (Northport, NY). Subjects fulfilled *Diagnostic and Statistical Manual of Mental Disorders*, fourth revision (DSM-IV) criteria for cocaine dependence and had used cocaine (free-base or as crack) for at least the previous 6 months (at least “3 g” per week). Note that subjects were excluded who met DSM-IV criteria for cocaine abuse rather than dependence. The exclusion criteria were current or past psychiatric disease other than cocaine dependence; past or present history of neurological, cardiovascular, or endocrinological disease; history of head trauma leading to loss of consciousness >30 min; and current medical illness and dependence or abuse on any substance other than cocaine, nicotine, or caffeine. Care was taken to exclude subjects that abused or were addicted to alcohol or drugs other than cocaine and nicotine. Subjects were tested within 1 month of their last cocaine use (14 ± 7 d) and had an average history of 13 ± 5 years of cocaine use. Controls were 15 healthy right-handed male subjects (age, 35 ± 7 years; education, 15 ± 2 years; IQ-verbal, 115 ± 12), and although they had previous experience with recreational drug use, they were excluded if they met DSM-IV criteria for alcohol or drug abuse or dependence. The exclusion criteria were as for the addicted subjects, except for cocaine dependence. Cocaine-addicted subjects remained in the hospital after completion of the study and were not discharged unless craving for cocaine had subsided. The protocol was approved by the Institutional Review Boards at Veterans Administration Hospital and at Brookhaven National Laboratory. Written informed consent was obtained after complete description of the study to the subjects.

Scans. Each subject underwent two PET FDG and two PET [^{11}C]raclopride scans done on two separate days. On a given day, each subject was given an injection first of [^{11}C]raclopride and then 90 min later an injection of FDG. Before each radiotracer injection, the subjects were given injections of a placebo (3 cc of saline intravenously before [^{11}C]raclopride and 3 cc of saline intravenously before FDG) on the first day and injections of MP (0.5 mg/kg MP intravenously before [^{11}C]raclopride and 0.25 mg/kg MP intravenously before FDG) on the second day (Fig. 1). The order of administration was fixed (placebo was given on the first day, and MP was given on the second day) to avoid possible long-lasting effects of MP on brain metabolism. The study was a single blind design (subjects were blind to the drugs received). For [^{11}C]raclopride, dynamic scans were started immediately after injection of 4–10 mCi of [^{11}C]raclopride (specific activity, 0.5–1.5 Ci/ μM at end of bombardment) for a total of 60 min using procedures published previously (Volkow et al., 1994). For FDG, an emission scan was obtained for 20 min and was

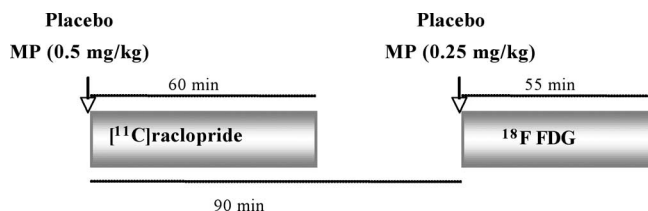


Figure 1. Diagram of experimental design. Subjects were tested on two separate days. On each day, they were scanned first with [^{11}C]raclopride, and this was followed by an FDG scan. On the first day of the study, subjects received intravenous placebo before each radiotracer injection, and on the second day, they received intravenous MP before each radiotracer injection.

started 35 min after injection of 4–6 mCi of FDG on a CTI 931 tomograph ($6.5 \times 5.9 \times 5.9$ mm full-width at half-maximum; 15 slices) using procedures described previously (Wang et al., 1993). FDG measures were completed in all subjects, but the [^{11}C]raclopride scans in one of the controls and in two of the cocaine-addicted subjects were lost because of technical errors.

Behavioral measures. Before and at 27 min after the first and the second MP (or placebo) dose, subjects rated drug effects (high, desire for MP, desire for cocaine, restlessness, and mood) on a 0–10 analog scale (Wang et al., 1997). When asked about the “desire for MP” subjects were asked to rate the desire to have the drug that they had just received (placebo or MP). MP concentration in plasma was measured using capillary gas chromatography/mass spectroscopy (Srinivas et al., 1991). A factorial repeated ANOVA was used to assess the effects of MP in the behavioral measures (drug main effect) and to assess whether the differences differed between controls and addicted subjects (drug by group interaction effect).

Analysis. The data for the metabolic images were analyzed using Statistical Parametric Mapping (SPM) (Friston et al., 1995), and the results were corroborated with region of interest (ROI) analysis. For the SPM analyses, the images were spatially normalized using the template provided in the SPM 99 package, then normalized to the mean metabolic activity for the entire brain (mean of all voxels within the brain) and subsequently smoothed with a 16 mm isotropic Gaussian kernel. Paired-samples *t* tests were performed to compare the images obtained in the placebo and MP conditions separately for the addicted subjects and the controls. Independent (unpaired) *t* tests were used to compare the difference images (placebo – MP) for the cocaine-addicted and control groups. Significance was set at $p < 0.005$ for clusters ≥ 100 voxels. The statistical maps were overlaid on a magnetic resonance imaging (MRI) structural image.

For the ROI analyses, an automated ROI extraction method was used based on the standard brain template of the Talairach atlas (Talairach and Tournoux, 1988). First, to eliminate variations across the brain of individuals, the PET FDG images were mapped into the Talairach brain using the spatial normalization package provided in SPM. The inverse mapping procedure was used to extract the Talairach coordinates of all voxels for a given anatomical region using the stereotaxic coordinates provided in the Talairach Daemon database (Collins et al., 1995; Lancaster et al., 1997, 2000). These anatomically defined ROI were overlapped voxel by voxel onto the normalized PET image (Volkow et al., 2002). This automated ROI method was validated by comparing the metabolic measures obtained with the manually drawn ROI and those obtained with the automated ROI from FDG images of 35 subjects (Ma et al., 2004). The correlations between the two methods were very high and ranged between $r = 0.86$ for head of caudate and $r = 0.99$ for the middle temporal gyrus. A factorial repeated ANOVA was used to assess the effects of MP in the metabolic measures (drug effect) and to assess whether the differences differed between controls and addicted subjects (drug by group interaction effect). Because controls and cocaine-addicted subjects differed in years of education and on their IQ scores, we performed a covariance analysis to assess whether these differences influenced the results.

For the [^{11}C]raclopride images, we obtained ROI in the striatum, thalamus, and cerebellum, from which we generated time-activity curves

as described previously (Volkow et al., 1994). The time-activity curves for tissue concentration and unchanged tracer in plasma were used to calculate the distribution volumes (DVs), using a graphical analysis technique for reversible systems (Logan et al., 1990), to estimate the equilibrium ratio of tissue concentration to plasma concentration in the striatum, thalamus, and cerebellum. The ratios of DVs in the striatum and in the thalamus to those in the cerebellum correspond to $(B_{\max}/K_d) + 1$ and are insensitive to changes in cerebral blood flow (Logan et al., 1994). The response to MP was quantified as the percentage of change in B_{\max}/K_d from placebo $(B_{\max}/K_{d\text{placebo}} - B_{\max}/K_{d\text{MP}}/B_{\max}/K_{d\text{placebo}} \times 100)$.

Pearson product moment correlations were used to assess the association between the regional metabolic changes induced by MP (expressed as the percentage of change from the metabolic measures obtained after placebo), which differed between controls and addicted subjects, and the changes in behavioral ratings induced by MP (difference between an individual's highest scores obtained during MP administration and the scores before MP administration). Correlations between the metabolic and behavioral measures were based on data from all subjects, except for the behavioral measure of cocaine craving when correlations were from just the cocaine abusers, because they were the only ones that experienced significant drug craving with MP. We also report the correlations with desire for MP and for "mood" separately for the cocaine abusers. In addition, correlations were obtained between the changes in DA (percentage of change in B_{\max}/K_d) and changes in metabolic activity for regions where the response differed between controls and addicted subjects.

Results

Behavioral effects of MP

MP induced significant changes in the behavioral measures in both groups of subjects for self-reports of "high" (ANOVA; drug effect; $F = 50$; $p < 0.0001$), desire for MP ($F = 39$; $p < 0.0001$), and "restlessness" ($F = 30$; $p < 0.0001$) (Table 1). The behavioral effects differed between the groups; in controls, MP induced significantly greater increases in self-reports of high (ANOVA; interaction effect; $F = 6.3$; $p < 0.003$) and restlessness ($F = 4.6$; $p < 0.05$) than in cocaine-addicted subjects, but MP-induced increases in desire for MP ($F = 3.8$; $p < 0.05$) was greater in the addicted subjects than in controls (Table 1). In addition, in cocaine abusers, MP increased "cocaine craving" ($p < 0.001$). Neither serum concentrations of MP nor cardiovascular effects differed between the groups (data not shown).

Effects of MP on regional brain metabolism

The SPM analysis conducted separately for each group revealed significant relative metabolic increases with MP in the cerebellum and occipital cortex and relative metabolic decreases in the caudate and temporal insula, both in controls and in addicted subjects (Fig. 2). In addition, in controls, MP increased metabolism in the precuneus and left thalamus and decreased metabolism in the NAc and in the right orbital and medial prefrontal cortices (including BA 25 and medial BA 11). Table 2 provides the Talairach coordinates for the regions that were significantly affected by MP in controls. In contrast, in cocaine-addicted subjects, MP increased metabolism in the right orbital medial prefrontal cortex (OMPFC) and decreased metabolism in the right frontal cortex (BA 8, BA 6, and BA 4) and parietal cortex (BA 40) (Fig. 1). Table 3 provides the Talairach coordinates of the regions that were significantly affected by MP in cocaine-addicted subjects.

Table 1. Behavioral effects of MP for the first (0.5 mg/kg, i.v.) and second (0.25 mg/kg, i.v.) doses in controls and in addicted subjects

	Control subjects (n = 15)			Cocaine-addicted subjects (n = 21)		
	Baseline	First MP (27 min)	Second MP (27 min)	Baseline	First MP (27 min)	Second MP (27 min)
High**	0 ± 1	7 ± 3	3 ± 3	0 ± 1	4 ± 3	2 ± 2
Desire cocaine**	0	1 ± 2	1 ± 2	3 ± 3	7 ± 4	6 ± 4
Desire MP**	0	3 ± 4	3 ± 3	1 ± 2	8 ± 3	5 ± 4
Restlessness*	1 ± 1	6 ± 2	5 ± 3	2 ± 2	5 ± 4	4 ± 4
Mood	6 ± 1	7 ± 2	7 ± 2	6 ± 2	6 ± 2	5 ± 2

MP significantly increased self-reports for high, desire for cocaine, desire for MP, and restlessness. Behavioral responses to MP were significantly larger in controls for restlessness and high, whereas responses were larger in cocaine-addicted subjects for desire for cocaine and desire for MP. ANOVA interaction effect (group by drug): * $p < 0.05$; ** $p < 0.001$.

Regional brain metabolic differences in response to MP between controls and addicted subjects

The SPM analysis of the difference image (placebo – MP) revealed that only two brain regions differed significantly at $p < 0.005$ between controls and addicted subjects: an area in the right OMPFC [as defined by Ongur and Price (2000)] that included BA 25 and middle BA 11 and an area in the left occipital gyrus (BA 19) (Fig. 3A, Table 4).

The ROI comparison of the response to MP corroborated that the response to MP in the OMPFC differed between the groups (ANOVA; interaction effect; $F = 31$; $p < 0.0001$) but did not corroborate the differences in BA 19. The difference in the right OMPFC remained significant after covarying for years of education (ANCOVA; $p < 0.0001$) or for IQ ($p < 0.0001$). MP significantly increased metabolism in the right OMPFC ($p < 0.05$), whereas in controls it decreased metabolism ($p < 0.0005$) (Fig. 3B). Separate analysis for subregions revealed that the differences were significant both for right BA 25 ($p < 0.0003$) and for right BA 11 ($p < 0.01$). At baseline (placebo scan), metabolism in the right OMPFC was also significantly lower in cocaine-addicted subjects than in controls ($F = 22$; 1.1 ± 0.09 vs 1.24 ± 0.09 ; $p < 0.0001$).

Correlations between brain metabolism and behavior

Correlations were significant between the changes in metabolism in right BA 25 and desire for MP (all subjects, $r = 0.55$, $p < 0.0005$; addicted subjects, $r = 0.46$, $p < 0.05$; control subjects, $r = 0.25$, NS) (Fig. 3C) and for "desire for cocaine" (all subjects, $r = 0.50$, $p < 0.002$; addicted subjects, $r = 0.50$, $p < 0.02$; control subjects, $r = 0.07$, NS). The correlations with changes in right BA 11 and desire for cocaine were not significant (all subjects, $r = 0.32$, $p = 0.06$; addicted subjects, $r = 0.31$, $p = 0.17$; control subjects, $r = 0.05$, NS). The correlations between changes in right BA 11 and desire for MP were not significant (all subjects, $r = 0.27$, $p = 0.11$; addicted subjects, $r = 0.17$, NS; control subjects, $r = 0.02$, NS). In addition, in cocaine abusers only but not in controls, changes in metabolism in BA 25 were associated with MP-induced changes in self-reports of mood ($r = 0.52$; $p < 0.02$); the greater the increases in BA 25, the higher the increases in ratings of mood.

Effects of MP on [¹¹C]raclopride binding and correlations with MP-induced change in metabolism

MP significantly decreased B_{\max}/K_d (measure of receptor availability) in the striatum in both controls (placebo, 2.86 ± 0.28 ; MP, 2.22 ± 0.38) and cocaine-addicted subjects (placebo, 2.61 ± 0.39 ; MP, 2.34 ± 0.41 ; ANOVA; drug effect; $F = 27$; $p < 0.0001$). Baseline measures of B_{\max}/K_d in the striatum were smaller in addicted subjects than in controls in the striatum (control subjects, 2.90 ± 0.34 ; addicted subjects, 2.59 ± 0.34 ; $F = 4.1$; $p < 0.05$).

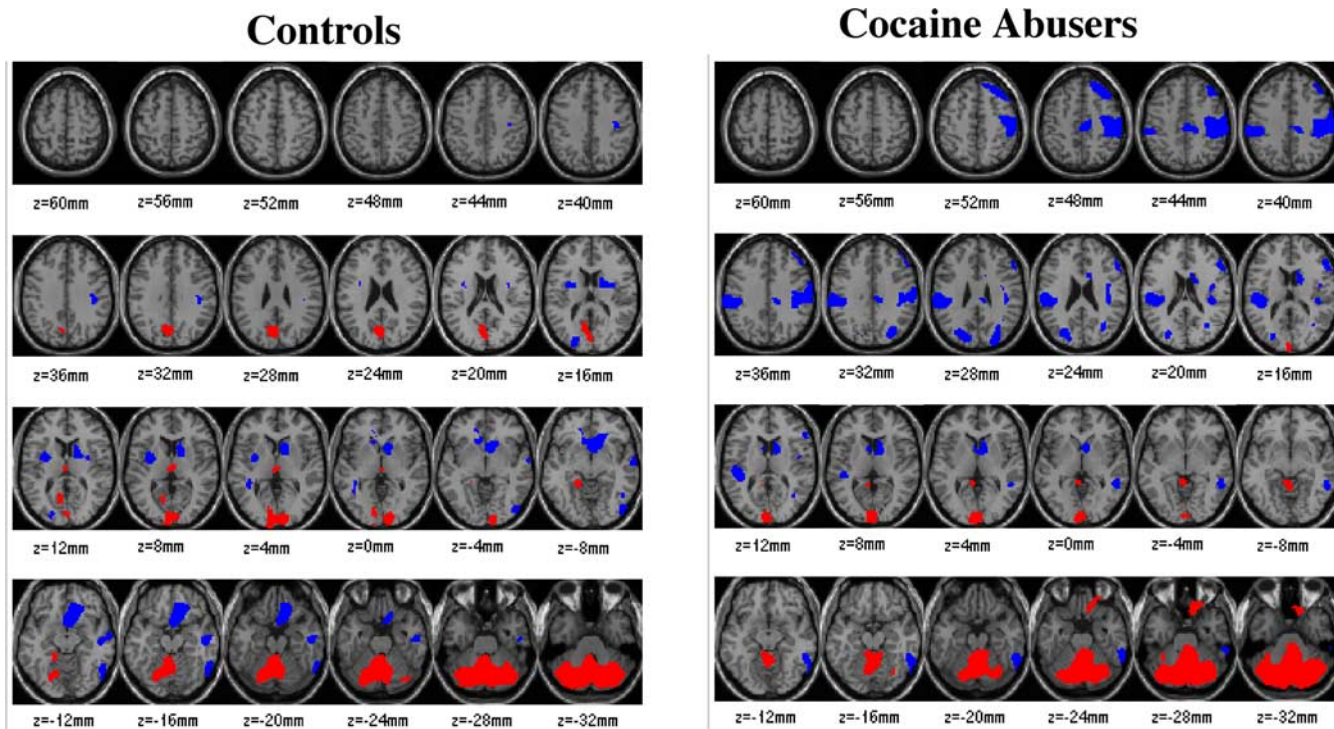


Figure 2. Brain regions where MP significantly ($p < 0.005$) increased (red) or decreased (blue) metabolism in controls and in cocaine-addicted subjects are shown.

Table 2. Location of regions where metabolism was increased or decreased significantly by MP in controls subjects ($p < 0.005$; volume, ≥ 100 voxels)

Region	Hemisphere	BA	x	y	z
Increases					
Occipital	Right	18	1	-93	4
	Left		-1	-93	5
Cerebellum	Right		1	-65	-28
	Left		-1	-65	-21
Precuneus	Left	31	-5	-63	27
Thalamus	Left		-1	-2	8
Decreases					
Caudate head	Right		10	15	5
Temporal insula	Left		-4	-1	8
NAc	Right		5	10	-8
Frontal medial	Right	11, 25	7	27	11

Table 3. Location of regions where metabolism was increased or decreased significantly by MP in cocaine-addicted subjects ($p < 0.005$; volume ≥ 100 voxels)

Region	Hemisphere	BA	x	y	z
Increases					
Occipital	Left	18	-3	-95	7
Cerebellum	Right		1	-77	-25
	Left		-1	-77	-25
Frontal medial	Right	11	11	37	-25
Decreases					
Caudate head	Right		5	10	8
Temporal superior	Left	22	-47	-30	-12
Frontal paracentrals	Right	4, 6	45	-15	44
	Left		-47	-17	40
Frontal superior	Right	8	30	35	48
Parietal inferior	Right	40	55	-30	36
	Left		-59	-33	37
Occipital gyrus	Right	19	20	-85	28
	Left		-25	-85	28

0.05) but did not differ in the thalamus (control subjects, 0.42 ± 0.10 ; addicted subjects, 0.43 ± 0.15 ; $F = 1.9$; $p = 0.17$). The responses in the striatum differed between the groups (ANOVA; interaction effect; $F = 5.1$; $p < 0.05$), indicating that the decrements were significantly smaller in addicted subjects ($-10 \pm 14\%$ change) than in controls ($-21 \pm 16\%$ change). In the thalamus, MP significantly changed B_{max}/K_d (ANOVA; drug effect; $F = 5.2$; $p < 0.05$), and the response also differed between groups (ANOVA; interaction effect; $F = 10$; $p < 0.004$). In addicted subjects but not in controls, MP significantly decreased B_{max}/K_d in the thalamus (control subjects, $16 \pm 34\%$ change; cocaine-addicted subjects, $-35 \pm 36\%$ change). The correlation between MP-induced changes in B_{max}/K_d and the changes in metabolism in the right OMPFC were significant in the thalamus ($r = 0.49$; $p < 0.005$) (Fig. 4). The correlations with MP-induced changes in DA in the striatum were not significant (data not shown).

Discussion

The main difference in the brain metabolic response to MP between the control and cocaine-addicted groups was in an area in the right OMPFC that included BA 25 (ventral region in the anterior CG) and medial BA 11 (medial region in the OFC). The qualitative difference in the response (in controls it decreased metabolism, and in cocaine-addicted subjects it increased metabolism) provides additional evidence of the involvement of the anterior CG and the OFC in cocaine addiction. Abnormalities in the OFC and anterior CG have been reported previously in cocaine-addicted (Modell et al., 1990; Volkow et al., 1991, 1993; Franklin et al., 2002; Bolla et al., 2003; Matochik et al., 2003; Myrick et al., 2004), methamphetamine-addicted (Volkow et al., 2001; Sekine et al., 2003), heroin-addicted (Sell et al., 2000), and marijuana-addicted (Volkow et al., 1996) subjects and in alcohol-

ics (Modell et al., 1990; Volkow et al., 1997c; Dao-Castellana et al., 1998; Myrick et al., 2004), suggesting that they reflect a common abnormality across various types of drug addictions.

Previous functional neuroimaging studies in cocaine abusers

Imaging studies have compared the response of cocaine abusers and controls to cocaine-related stimuli and to nondrug reinforcers. When presented with stimuli that are associated with cocaine (video of cocaine administration, imagery of previous drug experiences), various brain regions are activated in cocaine abusers, including the anterior CG (Maas et al., 1998; Childress et al., 1999; Garavan et al., 2000; Kilts et al., 2001; Wexler et al., 2001; Bonson et al., 2002) and OFC (Grant et al., 1996; Wang et al., 1999). In contrast, when cocaine abusers were exposed to nondrug reinforcers (i.e., erotic stimuli), they showed a blunted activation, compared with controls, in regions that are activated by cocaine cues (including anterior CG and medial frontal regions) (Garavan et al., 2000). This suggests that in the addicted subject, regions that process natural reinforcers become more sensitive to the drug than to the natural reinforcers (Garavan et al., 2000).

Acute intravenous cocaine given to cocaine abusers was shown to activate several regions (including BA 25, the insula, and the NAc) and deactivated others (amygdala and medial prefrontal cortex) (Breiter et al., 1997). Here, we compared the responses between cocaine-addicted and nonaddicted subjects for MP, which is pharmacologically similar to cocaine. As for intravenous cocaine, the response was not limited to prefrontal regions but included activation of the occipital cortex and cerebellum and deactivation of the amygdala, insula, and NAc. The decreases in the NAc and insula with MP contrasts with the increases reported with cocaine (Breiter et al., 1997). These discrepancies could reflect differences in subjects, drugs (cocaine vs MP; two doses vs one dose), and methods (PET vs functional MRI).

Imaging studies measuring DA increases in the striatum induced by amphetamine have also reported blunted responses in cocaine abusers compared with controls (Martinez et al., 2003). To our knowledge, such comparisons have not been made in the thalamus.

Role of BA 25 and BA 11 in addiction

The significant correlation between MP-induced activation of BA 25 and MP-induced desire for MP and cocaine craving suggests that its abnormal activation may underlie the intense desire to take the drug. Indeed, previous imaging studies in cocaine abusers have shown that activation of BA 25 after cocaine administration (Breiter et al., 1997) or after cocaine imagery (Kilts et al., 2001) was associated with cocaine craving.

BA 25 has been implicated in mediating the emotional responses to salient stimuli (rewarding as well as aversive). BA 25 is activated by natural and drug rewards (Breiter et al., 1997; Schlaepfer et al., 1998; Francis et al., 1999; Berns et al., 2001) and by positive and negative emotional stimuli (Elliott et al., 2000). The

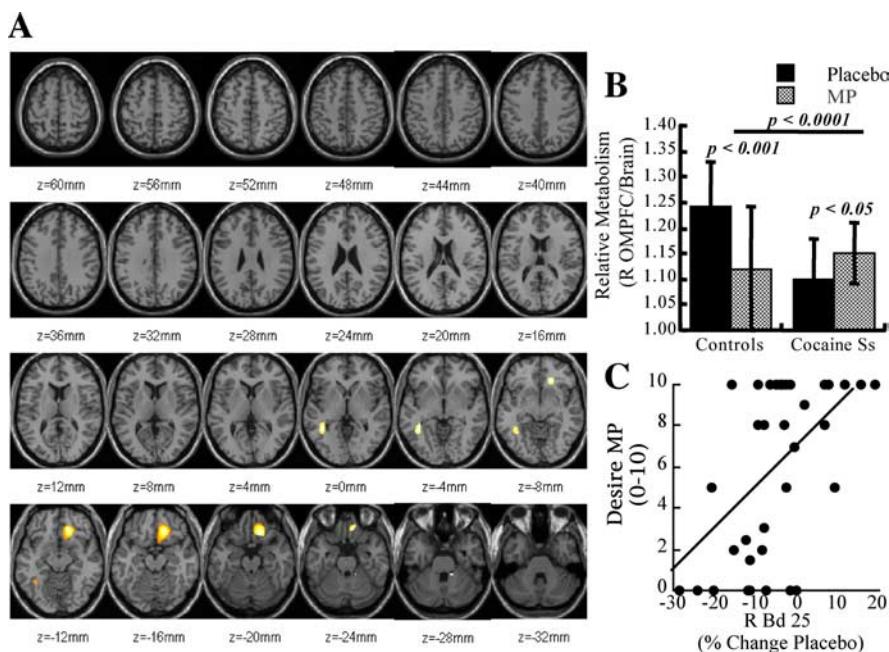


Figure 3. *A*, Brain regions where the response to MP differed between controls and cocaine-addicted subjects. The results are presented with respect to the controls. *B*, Relative metabolic measures in the right OMPFC in controls and in cocaine-addicted subjects for the placebo and for MP conditions. Metabolism was significantly lower in addicted subjects than in controls for the placebo condition. MP decreased metabolism in controls but increased metabolism in addicted subjects (values correspond to means and SDs). R OMPFC, Right OMPFC. *C*, Relationship between the changes in metabolism induced by MP and the self-reports for desire for MP ($r = 0.55$; $p < 0.0005$). R Bd 25, Right Brodmann area 25.

Table 4. Location of regions where increases in metabolism induced by MP were increased significantly in cocaine-addicted subjects compared with controls ($p < 0.005$; volume ≥ 100 voxels)

Region	Hemisphere	BA	x	y	z
Frontal medial	Right	11, 25	17	33	-16
Occipital gyrus	Right	19	-37	-47	-5

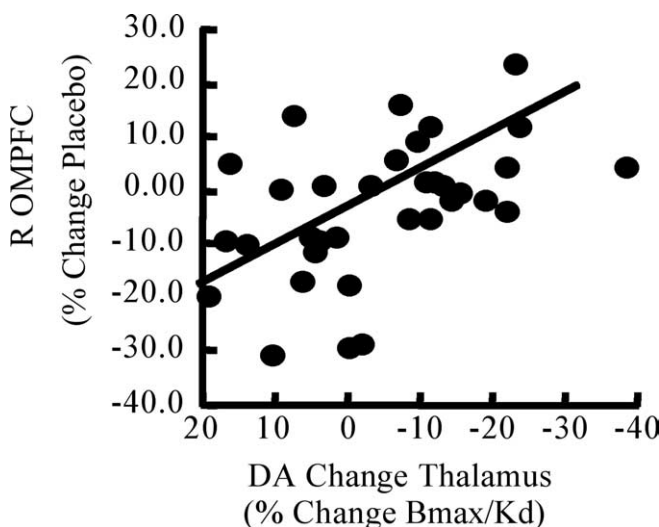


Figure 4. Correlation between MP-induced changes in OMPFC metabolism and the changes in thalamic DA. R OMPFC, Right OMPFC.

difference in the response of BA 25 between the groups is therefore consistent with an enhanced emotional response to MP in addicted subjects. Indeed, support for the role of BA 25 in emotional reactivity is its activation in cocaine abusers, not only by

cocaine imagery but also by anger imagery (Kilts et al., 2001). The current study provides additional support by documenting an association between MP-induced changes in BA 25 and its changes in mood in the cocaine abusers.

The responses between groups also differed in BA 11 (medial OFC), which is a region involved with processing the reward value of stimuli and motivating behavioral responding to reward (Arana et al., 2003). Indeed, in rodents, lesions of the medial OFC impair cocaine-primed reinstatement (Fuchs et al., 2004). Thus, the difference between the groups in BA 11 is likely to reflect the enhanced saliency value of MP in cocaine-addicted subjects. Abnormalities in the lateral OFC have also been documented in cocaine-addicted subjects and have been linked to poor impulse control (Goldstein et al., 2001). This suggests that both the medial and lateral orbitofrontal cortices are involved in cocaine addiction.

BA 25 and BA 11 are likely to play complementary roles in addiction, with BA 25 processing the emotional reactivity to the drug and BA 11 processing the saliency value of the drug to the subject and the motivation to procure it. However, from the current data it is not possible to dissociate whether emotional reactivity reflects the enhanced saliency value of the drug or whether it is the enhanced emotional reactivity to the drug that increases the saliency value of the drug to the subject.

BA 25 and BA 11 have also been found to be activated by symptom provocation in patients with obsessive compulsive disorders (Breiter et al., 1996; Mataix-Cols et al., 2004). Thus, disruption of BA 25 and BA 11 may be a common substrate underlying disorders that manifest compulsive behaviors.

Role of DA in the Thalamus and involvement in addiction

The thalamus receives direct dopaminergic innervation (Melchitzky and Lewis, 2000). Therefore, the decreases in thalamic [^{11}C]raclopride binding could reflect MP-induced blockade of DATs (Melchitzky and Lewis, 2000) or of norepinephrine transporters, because these transporters also participate in DA reuptake (Moron et al., 2002) and are densely concentrated in the thalamus (Melchitzky and Lewis, 2001).

The significant association between MP-induced thalamic DA changes and the OMPFC metabolic changes suggests that the mesothalamic DA projection regulates the responses of the OMPFC to MP. However, because the innervation is reciprocal, it is also possible that the OMPFC drives the MP-induced DA changes in the thalamus via direct (Cavada et al., 2000) or indirect (Rolls, 2004) projections. Indeed, in rodents, the prefrontal cortex can modulate the response of thalamic neurons to DA (Lavin and Grace, 1998; Cavada et al., 2000). Although there is limited information on the role of the thalamus in addiction, there is evidence of thalamic involvement in conditioned drug responses (McAlonan et al., 1993). For example, studies in rodents have shown differential involvement of the thalamus in contingent versus noncontingent administration of cocaine (Porrino et al., 2002) and on the responses to cocaine when given in a conditioned environment versus when given in the home cage (Knapp et al., 2002). Similarly, the thalamus was differentially activated by MP only when cocaine abusers expected to receive it but not when they did not expect to get it (Volkow et al., 2003). This expectation effect was also most likely attributable to conditioned responses.

Chronic cocaine can result in reorganization of DA input into the striatum and medial prefrontal cortex (for review, see Crombag et al., 2005). Adaptations in glutamatergic projection from the prefrontal cortex to the ventral striatum (including the NAc)

are also critical for drug seeking in animal models of addiction (Kalivas and Volkow, 2005). The findings from the present study suggest that the mesothalamic DA pathway may be an additional component in the mesocortico-striatal circuit thought to be critical for drug seeking (Kalivas and Volkow, 2005). Preclinical studies support a functional relationship between the medial thalamus and mesocortico-accumbens circuitry in regulating behavioral activation. For example, inhibition of medial thalamic output to the prefrontal cortex results in locomotor activation, and the behavioral activation is associated with activation of mesocorticolimbic DA projections (Jones et al., 1988; Klitenick and Kalivas, 1994; Churchill et al., 1996). Also, activation of the medial thalamus stimulates the prefrontal cortex, as measured by *c-fos* staining (Bubser et al., 1997). Interestingly, inhibition of medial thalamic projections to the medial prefrontal cortex in rats disrupts working memory (Romanides et al., 1999), and deficits in higher cognitive function are thought to contribute to the decreased ability of addicts to control drug seeking and relapse (Berke and Hyman, 2000; Kalivas and Volkow, 2005).

Limitations

FDG measurements reflect the average activity over 30 min and thus may not be sensitive to short-lasting effects of MP. The limited spatial resolution of our PET scanner did not allow us to quantify B_{max}/K_d changes in the NAc. The specific to nonspecific binding ratio for [^{11}C]raclopride in the thalamus is low, so we cannot exclude the possibility that it reflects nonspecific effects.

The placebo was given on the first day, and MP was given on the second day. Thus, we cannot rule out the contribution of an order effect. However, this is unlikely to account for the differences between addicted subjects and controls.

Cocaine-addicted subjects and controls had very different experiences with stimulants, and we cannot rule out the possibility that in the addicted subjects the decreased high could reflect tolerance (cross-tolerance from cocaine) and that the increased desire for MP could reflect learned responses from previous experiences with stimulants. We also acknowledge that correlations do not necessarily reflect causal associations. Finally, we cannot determine whether differences in addicted subjects are caused by drug abuse or whether they preceded drug consumption.

Summary

The differential response to MP in right BA 25 (region implicated in emotional reactivity) and BA 11 (region implicated in saliency attribution and motivation), for controls and addicted subjects, implicates these brain regions as a critical neural substrate of addiction. They also suggest that the meso-thalamo-cortical circuit contributes to these processes.

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