Mood Disturbances and Regional Cerebral Metabolic Abnormalities in Recently Abstinent Methamphetamine Abusers

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Background: Mood disturbances in methamphetamine (MA) abusers likely influence drug use, but the neurobiological bases for these problems are poorly understood.

Objective: To assess regional brain function and its possible relationships with negative affect in newly abstinent MA abusers.

Design: Two groups were compared by measures of mood and cerebral glucose metabolism ([^{18}F]fluorodeoxyglucose positron emission tomography) during performance of a vigilance task.

Setting: Participants were recruited from the general community to a research center.

Participants: Seventeen abstaining (4-7 days) MA abusers (6 women) were compared with 18 control subjects (8 women).

Main Outcome Measures: Self-reports of depressive symptoms and anxiety were measured, as were global and relative glucose metabolism in the orbitofrontal, cingulate, lateral prefrontal, and insular cortices and the amygdala, striatum, and cerebellum.

Results: Abusers of MA provided higher self-ratings of depression and anxiety than control subjects and differed significantly in relative regional glucose metabolism: lower in the anterior cingulate and insula and higher in the lateral orbitofrontal area, middle and posterior cingulate, amygdala, ventral striatum, and cerebellum. In MA abusers, self-reports of depressive symptoms covaried positively with relative glucose metabolism in limbic regions (eg, perigenual anterior cingulate gyrus and amygdala) and ratings of state and trait anxiety covaried negatively with relative activity in the anterior cingulate cortex and left insula. Trait anxiety also covaried negatively with relative activity in the orbitofrontal cortex and positively with amygdala activity.

Conclusions: Abusers of MA have abnormalities in brain regions implicated in mood disorders. Relationships between relative glucose metabolism in limbic and paralimbic regions and self-reports of depression and anxiety in MA abusers suggest that these regions are involved in affective dysregulation and may be an important target of intervention for MA dependence.

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ABSTAINING METHAMPHETAMINE (MA) abusers have mood disturbances[1] that likely reflect neurochemical abnormalities. Animal studies indicate that MA alters dopaminergic, serotonergic, and nonmonoaminergic systems,[2-10] and postmortem tissue from human MA abusers exhibits deficits in striatal dopaminergic markers and in orbitofrontal cortical serotonin.[11] In vivo studies of abstinent MA abusers also indicate loss of striatal markers for dopaminergic systems.[12,13]

Effects of MA on cerebral metabolism have also been studied. Chronic treatment reduced subcortical glucose metabolism in rats.[14] In addition, compared with control subjects, abstinent human MA abusers (abstinent from 2 weeks to >2 years) had higher cerebral glucose metabolism,[15] lower levels of *N*-acetylaspartate in the basal ganglia and frontal white matter, lower total creatinine levels in the basal ganglia, and higher levels of choline-containing compounds and *myo*-inositol in the frontal gray matter.[16]

The present study aimed to clarify the nature of brain disorder in MA abusers by identifying brain regions whose dysfunction may underlie negative affect. Stimulant abusers often enter treatment within their first week of abstinence. For example, most participants (86/112) entering a research protocol for treatment of MA dependence provided MA-positive urine

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Table 1. Characteristics of Research Participants*

	SPM Analysis		Absolute CMRglc Analysis	
	Control Subjects (n = 18)	MA Abusers (n = 17)	Control Subjects (n = 13)	MA Abusers (n = 14)
Age, y, mean (SEM)	32.3 (1.91)	34.7 (1.87)	32.6 (2.48)	34.5 (2.14)
Women	8	6	5	4
Subject's education, y, mean (SEM)	14.6 (0.37)	12.9 (0.41)†	14.1 (0.45)	13.1 (0.48)
Mother's education, y, mean (SEM)	14.2 (0.54)	12.7 (0.78)	14.3 (0.61)	12.5 (0.76)
Race				
White (non-Hispanic)	12	9	9	7
White (Hispanic)	2	4	1	4
African American	3	2	2	1
Asian	1	2	1	2
Right-handed‡	14	14	10	11

Abbreviations: CMRglc, cerebral glucose metabolic rate; MA, methamphetamine; SPM, statistical parametric mapping.
*Values are expressed as number of subjects unless otherwise indicated.
†Significantly different from control group; $P = .006$ by t test.
‡Handedness was determined according to the Lateral Preference Pattern Assignment subtest of the Physical and Neurological Examination for Soft Signs.[22] To qualify as right-handed, a participant had to write and perform all or all but 1 of 11 items with the right hand.

samples, indicating MA use within 72 hours (R.R., unpublished data, September 2002). Because treatment for MA abuse almost exclusively involves outpatient methods,[1] the first week of abstinence is a crucial determinant of engagement and retention and, thus, of treatment outcome.[17] We therefore measured cerebral metabolism in MA abusers during early abstinence and in comparison subjects using the [^{18}F]fluorodeoxyglucose (FDG) positron emission tomographic (PET) method.[18,19]

METHODS

SUBJECTS

Twenty inpatient MA abusers and 22 control subjects gave informed consent and participated in this study, approved by the institutional review boards of the University of California, Los Angeles, and the Long Beach Department of Veterans Affairs Medical Center, Long Beach, Calif. Participants in both groups were healthy according to medical history, physical examination findings, and laboratory test results. Use of psychoactive medications and seropositive status for human immunodeficiency virus were exclusionary.

As established by the *Structured Clinical Interview for DSM-IV Axis I Disorders–Patient Edition (SCID-IP, version 2.0)*,[20] current Axis I diagnoses of dependencies on substances other than MA or nicotine and lifetime Axis I diagnoses unrelated to drug abuse were exclusionary for MA abusers. The same criteria applied for control subjects, but MA dependence was not allowed and restrictions on drug dependence included lifetime diagnoses. Personality disorders, other than antisocial personality disorder, which was evaluated using the *Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID II): User's Guide*,[21] were not exclusionary. Antisocial personality disorder was detected in 3 MA abusers.

Brain imaging data from 17 MA abusers and 18 control subjects were analyzed using statistical parametric mapping (SPM). Seven subjects were excluded for various reasons: motion artifact, no magnetic resonance (MR) image, sleeping after FDG injection, and an inconsistent drug history report. Fourteen MA abusers and 13 control subjects provided measures of absolute global cerebral glucose metabolic rate (CMRglc). Nine were excluded for technical reasons: no arterial catheter, plasma glucose levels higher than 150 mg/dL (8.3 mmol/L), and improper instrument calibration.

The groups did not differ significantly in age or mother's education, but MA abusers had fewer years of education than control subjects (group difference in SPM analysis, $t_{35} = 2.90$; $P = .006$; group difference in absolute CMRglc analysis, $t_{25} = 1.85$; $P = .08$) (**Table 1**). Although the groups were similar in handedness[22] and sex distribution, the control group included a larger proportion of non-Hispanic white individuals, whereas white MA abusers reported Hispanic ethnicity more frequently.

Both groups were allowed light alcohol use (equivalent to <7.5 drinks per week). For MA abusers, self-reports of spending $100 or more on MA during the month before screening and MA use within 3 days of enrollment (verified by urine sample) were required. Control subjects provided urine samples negative for illicit drugs.

Participants completed self-report questionnaires about drug use (intake questionnaire and drug use survey) and were administered the Addiction Severity Index[23] (**Table 2**). The MA abusers had used the drug, on average, for more than 8 years, consumed about 2 to 4 g/wk, and had used MA on most of the 30 days before entering the study. The MA and control groups reported similar alcohol and marijuana use and were generally matched on use of illicit drugs other than MA. Most of the MA abusers smoked cigarettes, but none of the control subjects did.

DRUG USE AND AFFECTIVE STATES

Participants completed the Addiction Severity Index when entering the study. Self-ratings of depressive symptoms (Beck Depression Inventory [BDI])[24] and anxiety (State-Trait Anxiety Inventory)[25] were obtained on the day of PET scanning. Abusers of MA rated their MA craving (visual analog scale)[26] within 48 hours of scanning.

MR SCANS

Structural MR images (3-T; GE Medical Systems, Waukesha, Wis) included T1-weighted volumetric scans (spoiled gradient-recalled acquisition, 256 × 256 matrix, echo time [TE] = 4 milliseconds, repetition time [TR] = 24 milliseconds, angle = 35°, 1.22-mm slice thickness) that were used for coregistration with PET data (see "PET Procedure" subsection). The findings from T2-weighted (spin echo) scans (256 × 256 matrix, TE = 34 mil-

Table 2. Self-reported Drug Use*

	SPM Analysis		Absolute CMRglc Analysis	
	Control Subjects (n = 18)	MA Abusers (n = 17)	Control Subjects (n = 13)	MA Abusers (n = 14)
MA use				
Duration, y	NA	10.1 (1.3)	NA	10.2 (1.46)
Average, g/wk	NA	4.0 (0.72)	NA	2.9 (0.50)
No. of days used in last 30	NA	18.85 (1.95)	NA	18.1 (2.25)
Age of first use, y	NA	24.3 (2.14)	NA	25.0 (2.34)
Tobacco smokers, No. of subjects†	0	14‡	0	11‡
Marijuana use, No. of days in last 30	1.44 (0.93)	2.7 (0.97)	1.83 (1.2)	2.8 (1.2)
Alcohol use, No. of days in last 30§	2.63 (0.76)	2.94 (1.04)	2.17 (0.6)	3.57 (1.2)

Abbreviations: CMRglc, cerebral glucose metabolic rate; MA, methamphetamine; NA, not applicable; SPM, statistical parametric mapping.

*Values are expressed as mean (SEM), unless otherwise indicated, of self-reported drug use from the intake questionnaire, drug use survey, and Addiction Severity Index.[23] In addition to the data regarding regular drug use (MA and marijuana), data were obtained on other illicit drugs. Control subjects provided 12 reports (n = 10) of having used an illicit drug (other than marijuana) fewer than 5 times and 8 reports (n = 8) of more than 5 instances of use. Methamphetamine abusers gave 29 reports (n = 13) of using an illicit drug (other than MA or marijuana) fewer than 5 times and 11 reports (n = 11) of more than 5 instances of use.

†Self-reported smoking of 5 or more cigarettes per day.

‡Significantly different from control subjects using χ^2 analysis ($\chi^2_1 = 24.71$; $P<.001$ for analysis of larger groups shown above [SPM analysis]; $\chi^2_1 = 17.23$; $P<.001$ for subgroups participating in absolute CMRglc measurement).

§None of the MA subjects had a lifetime history of alcohol abuse or dependence. One of the control subjects had a history of alcohol abuse but no current drug- or alcohol-related diagnosis.

liseconds, TR = 5500 seconds, 1 number of excitations, 2-mm slice thickness) from all subjects included were read as clinically normal.

PET PROCEDURE

Methamphetamine abusers were tested when abstinent for 4 to 7 days. Catheters were inserted into the antecubital vein and contralateral radial artery for infusing FDG and blood sampling, respectively. The participant was positioned in the scanner gantry and fitted with a plastic face mask (Scrypton Systems, Annapolis, Md) to minimize head motion. A 3-minute ^{68}Ge transmission scan verified proper positioning, and a 20-minute ^{68}Ge transmission scan provided data for attenuation correction.

After subjects were removed from the scanner, they performed a continuous performance task (CPT) (version 2.26; Sunrise Systems, Pembroke, Mass) using a laptop computer. The task required discrimination of a target tone (higher pitch) from a sequence (interstimulus interval = 2 seconds) of nontarget tones (lower pitch). Pressing the *X* signified hearing a target tone. With the CPT underway, FDG (≤5 mCi [≤185 MBq]) was administered intravenously. The CPT was stopped 30 minutes later, and the subject was repositioned in the scanner.

Arterial blood samples were taken at 10-minute intervals for 90 minutes after the FDG injection, and plasma from these samples was assayed for radioactivity (Cobra II Auto-Gamma; Packard Instruments, Downers Grove, Ill) and glucose. The plasma activity curve was fit according to an analytic procedure to determine the integral of plasma-specific activity[27] for use in an operational equation.[28]

Brain images were acquired in 3-dimensional mode (Siemens ECAT EXACT HR+ tomograph; CTI, Knoxville, Tenn) for 30 minutes, starting 50 minutes after the FDG injection. We reconstructed 128×128-pixel images using a Hann filter (cut-off frequency = 0.5 cycles per pixel). The average transverse resolutions at 1 and 10 cm from the center of the field of view (measured using an ^{18}F line source) were 6.52 and 7.16 mm (full width at half maximum), and the average axial resolutions were 3.72 and 5.64 mm at 0 cm and 10 cm from the center of the field of view, respectively.

The CMRglc was calculated from the modeled images using MEDx software (Sensor Systems, Sterling, Va). An edge-detection algorithm defined the brain contour in each transaxial plane. A 3-dimensional contour was then derived from the sum of the 2-dimensional slices, and mean CMRglc was calculated. Voxels exhibiting metabolic rates less than or equal to 4 mg of glucose per 100 g per minute were excluded to minimize contribution from cerebrospinal fluid.

STATISTICAL ANALYSIS

We conducted group comparisons of demographic variables and CMRglc using the *t* test. When a continuous measurement variable did not meet the assumption of homogeneity of variance, it was assessed using a separate variance *t* test (Statistical Package for the Social Sciences; SPSS Inc, Chicago, Ill). Pearson product moment correlation analyses tested relationships between CMRglc and MA use (duration, number of days in the last month, grams per week in the last month). We used d′ (discriminability statistic) to assess CPT performance and evaluated group differences in d′ using a *t* test. For these analyses, the statistical threshold was $P<.05$, uncorrected for multiple comparisons.

Group comparisons of self-reports of depressive symptoms and anxiety were performed by multivariate analysis of variance (SPSS). Post hoc *t* tests determined the contribution of each variable to the significant results of an omnibus test.

Group comparisons of brain activity, indicating relative regional cerebral glucose metabolism, were performed by SPM (SPM99; Wellcome Department of Cognitive Neurology, London, England).[29,30] The PET images (decay-corrected counts) were coregistered to the corresponding structural MR images using automated image registration,[31] and the MR images were used to normalize the PET data spatially by transformations that warped them into a standard coordinate system (MNI space; Montreal Neurological Institute, Toronto, Ontario).[29] Normalized images were smoothed with an 8-mm (full width at half maximum) isotropic Gaussian kernel, and effects of global activity were removed by proportional scaling.

In SPM, a parametric statistical model, assumed at each voxel, describes variability in the data in terms of experimental and confounding effects and residual variability. The model provides that

Table 3. Self-reports of Mood and Feeling State*

	Control Subjects	Methamphetamine Abusers
Beck Depression Inventory		
Sample size	18	17
Score	1.1 (0.5)	9.5 (2.1)†
State-Trait Anxiety Inventory		
Sample size	16	13
State anxiety, mean of all 20 items	1.4 (0.08)	1.9 (0.14)†
Trait anxiety, mean of all 20 items	1.5 (0.09)	2.2 (0.18)†

*Values are expressed as mean (SEM). Beck Depression Inventory scores range from 0 to 63. State-Trait Anxiety Inventory scores are on a scale of 1 to 4 for each item. State-Trait Anxiety Inventory was not administered to several subjects.

†Significantly different from control subjects using post hoc *t* test, $P<.01$.

for each group of subjects, the activity in each voxel is normally distributed with homogeneous variance about a group mean. The hypothesis that the group means for each voxel were homogeneous was assessed with a *t* test, giving an image SPM(*t*) whose voxel values were *t* statistics. The multiple comparisons problem of simultaneously assessing all the voxel statistics is addressed by modeling the image as a sample of a continuous Gaussian random field. For each voxel, the corrected *P* value is the probability of finding at least 1 voxel in the search volume with a greater or equal *t* value. For each cluster of contiguous voxels where *t* exceeds a preset threshold, the corrected *P* value is the probability of finding at least 1 cluster that is at least that large.

For whole-brain SPM analysis, the multiple comparisons correction is based on all gray matter voxels in the brain and the possibility of deviation from the null hypothesis. To test the effect of group, we set an initial voxel height threshold of $P=.05$ (uncorrected) for inclusion in clusters. We considered individual clusters to indicate a significant difference only when $P<.05$ (corrected) also for spatial extent.

Statistical parametric mapping allows for multiple comparisons correction on the basis of a restricted set of hypotheses, namely, consideration of limited contiguous regions within the cerebral gray matter. Such an analysis is appropriate when prior work identifies particular brain regions as relevant.

We tested certain regions of interest (ROIs) because of their implication in negative affective states: orbitofrontal cortex (OFC) (medial [gyrus rectus and medial orbital gyrus; Brodmann area (BA) 11] and lateral [lateral and posterior orbital gyri, orbital portion of the inferior frontal gyrus; BA 47 and 11]), cingulate gyrus (infragenual [BA 25 and 32], perigenual [BA 24, 32, and 33], and posterior [BA 31, 23, and 30]), lateral prefrontal cortex (middle frontal [BA 8, 9, and 46] and inferior frontal gyri [BA 44, 45, 46, and 47]), insula (BA 13), and amygdala. Other than the posterior cingulate gyrus, activities of these regions have been linked to depressive disorders, depressed mood, or sadness.[32-36] Activity of the posterior cingulate gyrus was increased during presentation of aversive and anxiogenic stimuli[37,38] and was related to the anxiety component of depressive symptoms.[39] In addition, activities of the OFC and insula have been related to anxiety,[40] and pharmacologically induced anxiety was associated with activation of the amygdala, insula, and anterior cingulate cortex (ACC).[41] Lastly, the ventral and dorsal striatum and cerebellar vermis were tested because their activities were increased or associated with drug craving.[26,42-46] The ROIs were drawn on the structural MR template provided in SPM99, using MEDx. Bilateral sampling, except for the cerebellar vermis, provided data on 23 ROIs and 46 comparisons (positive and negative contrasts). Statistical significance within each ROI was determined according to the SPM model described earlier, using a voxel height threshold of $P=.05$ (uncorrected) for inclusion in clusters. An ROI was considered to show a significant group difference if it contained a cluster with $P<.05$ for spatial extent (corrected). In each ROI that showed a significant group difference using these criteria, the probability associated with the peak voxel height (corrected for ROI search volume) was also noted. Further, we identified ROIs whose group differences maintained statistical significance ($P\leq.001$) after applying the Bonferroni correction for number of comparisons (46) and the correction for search volume.

Relationships between relative regional CMRglc (rCMRglc) and depressive symptoms (BDI) and anxiety (State-Trait Anxiety Inventory) were tested using covariate analysis. Statistical significance of the effect of each covariate was assessed within the 18 ROIs preselected because of their implication in negative affective states (9 bilateral regions). Separate SPM analyses were performed for each covariate, yielding SPM (*t*)s. The multiple comparisons correction within each ROI and the Bonferroni correction for number of ROIs were applied. An ROI was considered to show a significant covariate effect if it contained a cluster with $P<.05$ for spatial extent (corrected). In each ROI that showed significant covariance using these criteria, the probability associated with the peak voxel height (corrected for search volume) was also noted. Further, we identified those ROIs whose covariance maintained statistical significance ($P<.001$) after applying the Bonferroni correction for number of comparisons (ie, 18 ROIs × 2 = 36, testing positive and negative covariance) and the correction for search volume.

RESULTS

AFFECTIVE STATES

An omnibus multivariate analysis of variance of measures of depression and anxiety demonstrated a significant group difference ($F_{3,25}=7.60$; Wilks $\Lambda=0.52$; $P<.001$) (**Table 3**). The groups differed on each measure. Although only 1 MA abuser reported being depressed within the month before testing on the Addiction Severity Index (data not shown), MA abusers had higher BDI scores than control subjects ($t_{18}=-3.88$; $P=.001$; n = 35, degrees of freedom adjusted for separate variance test). As the BDI data did not meet the assumption of homogeneity of variance, separate variance *t* tests assessed this variable. Some MA abusers (4/17) but no control subjects reported anxiety symptoms on the Addiction Severity Index. The MA abusers also had higher scores of both state ($t_{27}=-2.91$; $P=.007$) and trait ($t_{27}=-3.82$; $P=.001$) anxiety on the State-Trait Anxiety Inventory. In tests of correlation between these scores and MA use (duration of use, number of days used in the past month, grams per week in the past month), the only significant finding was a positive correlation between BDI score and recent use (grams per week) ($r_{14}=0.70$; $P=.006$).

The MA abusers reported drug craving (mean ± SEM visual analog scale scores, 4.06 ± 0.94). Craving was correlated with frequency of MA use (number of days in the last 30) ($r_{17}=0.597$; $P=.01$).

CPT PERFORMANCE

We used CPT data from 15 control subjects and 16 MA abusers. Data from 5 subjects were excluded because of equipment failure (n = 1), lack of response for 20 to 40 seconds (n = 2), and responses to all stimuli (including

Table 4. Relative Regional Cerebral Glucose Metabolic Rates in Control and Methamphetamine Abuser Groups*

	Cluster-Level Analysis			Peak Voxel				
		No. of Voxels				Coordinates		
	Corrected *P* Value	Per Cluster	Search Volume	Corrected *P* Value	*z* Score	x	y	z
Higher Activity in Control Than MA Abuser Group								
Anterior cingulate								
Infragenual								
Left	<.001†	350	459	.03	3.13	−12	32	−10
Right	.001†	192	452	.07	2.71	2	24	−6
Perigenual								
Left	.03	147	1091	.10	2.84	0	22	−4
Insula								
Right	.006	310	1456	.11	2.91	34	−2	16
Higher Activity in MA Abuser Than Control Group								
Lateral orbitofrontal								
Left	.03	269	2206	.25	2.64	−30	40	−18
Right	.04	243	2099	.20	2.74	30	18	−20
Middle cingulate								
Right	.02	117	708	.001	4.23	4	−12	46
Posterior cingulate								
Left	.02	217	1003	.009	3.68	2	−16	48
Right	.01	282	973	<.001	4.81	8	−20	48
Amygdala								
Left	.04	24	160	.09	2.25	−22	2	−16
Right	.003	66	161	.003	3.58	22	2	−14
Ventral striatum								
Left	.001†	120	208	.04	2.79	−22	6	−12
Right	.001†	84	184	.005	3.45	16	6	−12
Cerebellar vermis	.02	156	720	.31	2.01	0	−56	−28

Abbreviations: MA, methamphetamine; ROI, region of interest.

*Cerebral glucose metabolism was measured in MA abusers (n = 17) and control subjects (n = 18) while they performed an auditory continuous performance task. Using SPM99 (Wellcome Department of Cognitive Neurology, London, England), planned comparisons of relative metabolism (normalized to global values) between groups were made in 11 ROIs of each hemisphere (medial and lateral orbitofrontal cortex, cingulate gyrus [infragenual, perigenual, and posterior], middle frontal gyrus, inferior frontal gyrus, ventral striatum, dorsal striatum [caudate], insula, and amygdala) and the midline cerebellar vermis, with the a priori hypothesis of group differences. Statistical parametric maps were generated for each ROI using a height threshold of $P<.05$ uncorrected. The heights and spatial extent of activated clusters of contiguous voxels were corrected for the search volume of the ROI. Corrected significant *P* values for cluster size (with cluster size and ROI size) and peak voxel height (with location and *z* score) are presented above. Locations for the peak voxels are given in MNI space (Montreal Neurological Institute, Toronto, Ontario) with the origin set at the anterior commissure. Positive x, y, and z values approximately represent millimeters to the right, anterior, and inferior to the origin, respectively.

†Clusters that exceeded the criterion of $P<.05$ after Bonferroni correction for number of comparisons (ie, 46 comparisons in 23 ROIs) as well as for the search volume of each region.

nontargets) during the first few minutes (not understanding the instructions) (n=2). Performance during the 15 minutes after FDG injection (when most of the brain uptake of FDG occurs) indicated no group differences in reaction time (means for the control and MA groups, 0.6257 and 0.6252 seconds, respectively) or percentage of correct responses (98.42 in the control group and 95.85 in the MA group). There was no group difference in d′ ($t_{33}=1.08$; $P=.29$; mean (SE) control d′ = 5.11 [0.21]; mean (SE) MA d′ = 4.80 [0.26]).

CEREBRAL GLUCOSE METABOLISM

Global glucose metabolism during performance of the CPT did not differ between the groups (mean ± SEM, 10.1 ± 0.52 and 10.2 ± 0.36 mg/100 g per minute in the control and MA groups, respectively [13 control subjects and 14 MA abusers]). Drug use measures were not significantly correlated with CMRglc in the MA abusers.

Whole-brain analysis revealed 1 cluster, extending from the middle to the posterior portions of the dorsal cingulate gyrus (4604 voxels; $P<.001$), with higher activity in MA abusers than control subjects. The peak voxel (6, −16, 46; MNI coordinates as defined in the legend for **Table 4**), which was in BA 24 or 31, also had significantly more activity in MA abusers by the criterion of peak height after correction for whole-brain search volume ($t=5.75$; $P=.02$). There were no clusters of significantly higher activity in control subjects than MA abusers.

All regions tested, except for those in the lateral OFC and lateral prefrontal cortex, exhibited clusters with group differences in relative rCMRglc (in 1 or both hemispheres) (Table 4 and **Figure 1**). Control subjects had greater activity than MA abusers bilaterally in the infragenual ACC, the left perigenual ACC, and the right insula. The MA abusers had higher activity bilaterally in the lateral OFC, right middle and posterior cingulate, amygdala, ventral striatum, and cerebellar vermis. After correction for the number of regions compared, MA abusers still had significantly lower relative rCMRglc than control subjects bilaterally in the infragenual ACC and higher activity in the bilateral ventral striatum.

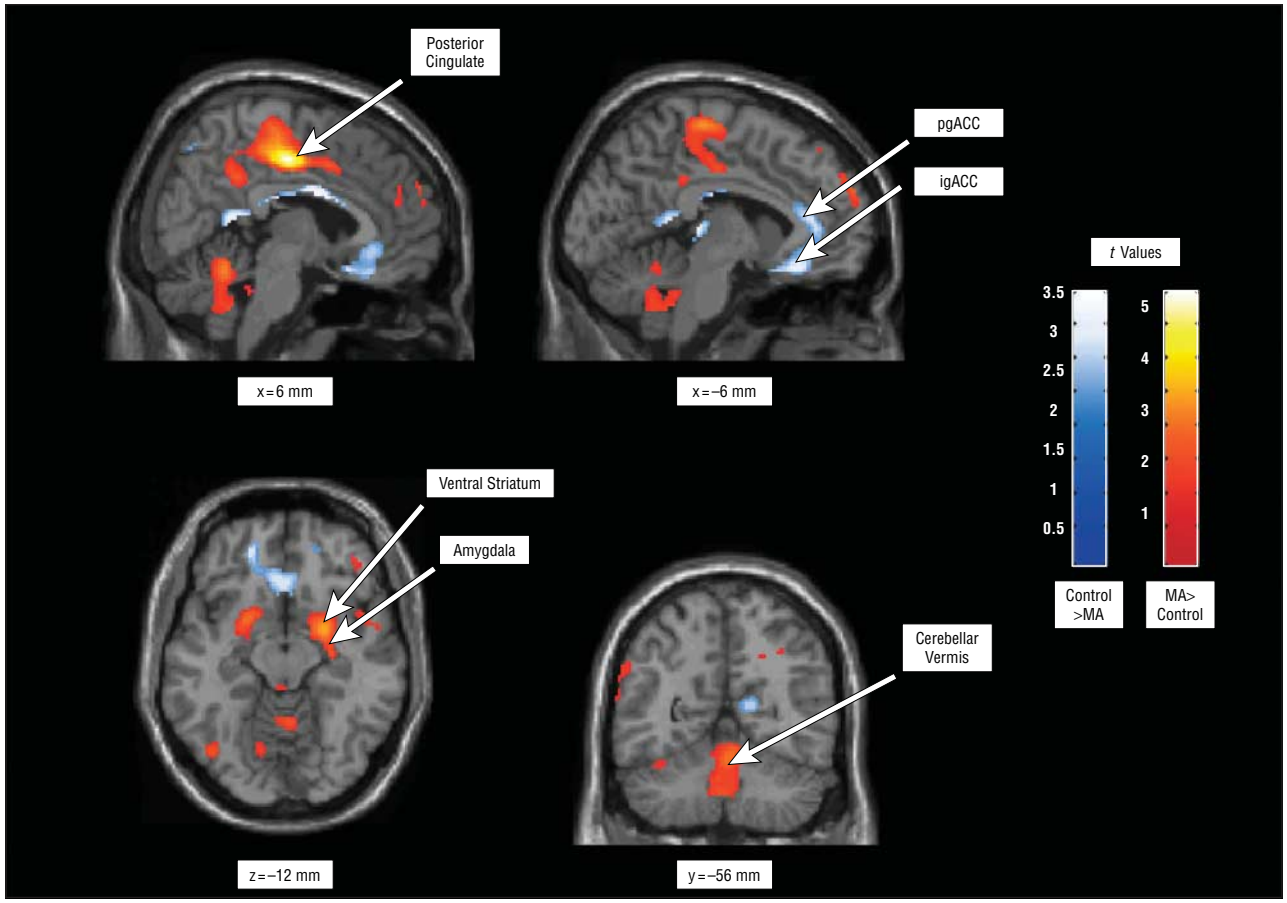

Figure 1. Locations of methamphetamine (MA) and control group differences in relative regional cerebral glucose metabolic rate (rCMRglc). Statistical parametric maps were generated using SPM99 (Wellcome Department of Cognitive Neurology, London, England) for the contrast of relative rCMRglc in the control group (n=18) greater than in the MA abuser group (n=17) and also for the contrast of relative rCMRglc in the MA abuser group greater than in the control group. Colors superimposed on the gray-scale structural magnetic resonance template indicate areas where the height threshold for the contrast (whole brain) was $t \geq 1.69$ ($P=.049$). Locations where clusters exhibited $P<.05$ for spatial extent (corrected for search volume of the relevant region of interest but not the number of regions) are noted (Table 4). Coordinates are in MNI space (Montreal Neurological Institute, Toronto, Ontario). igACC indicates infragenual anterior cingulate cortex; pgACC, perigenual anterior cingulate cortex.

Unlike absolute CMRglc, some relative rCMRglc measures showed relationships to recent MA use (which was related to measures of mood [see the "Affective States" subsection]). Activity in the left insula covaried negatively with MA use (grams per week) (cluster of 673 voxels; corrected $P<.001$), as did activity in the left infragenual ACC (cluster of 70 voxels; corrected $P=.02$). Activity in the cerebellar vermis (cluster of 267 voxels; corrected $P=.003$) covaried positively with this measure. In addition, activity in the right insula (cluster of 158 voxels; corrected $P=.03$) showed negative covariance with frequency of MA use (number of days in the past 30). Only the association of activity in the left insula with amount of intake retained statistical significance after correction for the number of brain regions tested.

The BDI score in the MA abusers covaried directly with relative rCMRglc in the bilateral infragenual and perigenual ACC and amygdala (**Table 5** and **Figure 2**). This relationship retained significance in the bilateral perigenual ACC and right amygdala after Bonferroni correction. Because the amount of MA consumption (grams per week) was correlated with BDI score, we reassessed the association of BDI score with relative rCMRglc after removing the effects of MA consumption by declaring it a nuisance variable. The BDI score activity retained a strong association with activity in the bilateral perigenual ACC as well as in the right amygdala ($P<.001$ for all). While BDI score for the control subjects also covaried with relative rCMRglc in 3 ROIs, none of these results retained significance after Bonferroni correction.

The relationship of anxiety to relative rCMRglc was assessed separately for state and trait anxiety measures (**Table 6**). There were no significant covariates of anxiety in control subjects. In MA abusers, state anxiety covaried negatively with rCMRglc in the left infragenual ACC and bilateral insula (**Figure 3**). The result in the left insula retained significance after Bonferroni correction. The pattern was more widespread for trait anxiety, which covaried negatively with activity in the OFC, infragenual and perigenual ACC, left posterior cingulate gyrus, and left insula. Negative covariance of trait anxiety with activity in the infragenual anterior cingulate gyrus (bilateral), medial (bilateral) and left lateral OFC, and left insula retained statistical significance after Bonferroni correction. Although there was evidence for the opposite pattern (high anxiety accompanied by high metabolism) in the bilateral amygdala and right insula, none of these results retained significance after Bonferroni correction.

Table 5. Covariance of Depressive Symptoms With Relative Regional Glucose Metabolic Rates*

	Cluster-Level Analysis			Peak Voxel				
		No. of Voxels				Coordinates		
	Corrected *P* Value	Per Cluster	Search Volume	Corrected *P* Value	*z* Score	x	y	z
Control Group								
Anterior cingulate								
Infragenual (+)								
Right	.005	132	452	.08	2.68	14	46	–6
Perigenual (+)								
Left	.04	128	1091	.40	2.10	–6	46	2
Right	.009	194	1086	.14	2.80	12	48	–4
Inferior frontal gyrus (+)								
Right	.006	496	2394	.08	3.26	50	26	14
MA Abuser Group								
Anterior cingulate								
Infragenual (+)								
Left	.03	62	459	.13	2.54	–12	42	–6
Right	.005	123	452	.03	3.15	8	32	–6
Perigenual (+)								
Left	.001†	379	1091	.09	3.04	2	22	20
Right	<.001†	598	1086	.09	3.93	10	30	–4
Amygdala (+)								
Left	.003	83	160	.03	2.84	–22	–2	–18
Right	<.001†	107	161	.008	3.76	34	4	–20

Abbreviation: MA, methamphetamine; +, positive covariance.

*Possible relationships between self-reports of depressive symptoms and relative regional cerebral glucose metabolic rate were assessed by testing whether the Beck Depression Inventory score was a significant covariate of the relative regional cerebral glucose metabolic rate in the following brain regions, which were selected a priori on the basis of literature accounts of their involvement in depressive disorders: orbitofrontal cortex (medial and lateral areas), lateral prefrontal cortex (middle and inferior frontal gyri), anterior cingulate gyrus (infragenual and perigenual portions), insula, and amygdala. These regions were tested with small-volume correction using SPM99 (Wellcome Department of Cognitive Neurology, London, England). Regions with clusters that exhibited *P* values <.05 corrected for search volume are listed.

†*P*<.05 after Bonferroni correction for number of comparisons (ie, 16 regions, 2 tests each), in addition to the search volume of each region.

COMMENT

This study identified regional brain dysfunction that may underlie affective deficits in MA abusers during early abstinence. Abnormalities were observed in limbic and paralimbic regions that have been implicated in emotional processing by many investigations. These include neuroimaging studies in which mood induction accompanied activation of the amygdala, insula, and ACC.[40,47-51] The most robust group differences in relative rCMRglc were in the infragenual ACC, where MA abusers showed relative hypoactivity compared with control subjects, and the ventral striatum, where MA abusers showed relative hyperactivity.

The BDI scores in MA abusers covaried positively with relative activity in regions that have been linked with negative affect. In line with previous evidence for dysfunction of the subgenual and perigenual portions of the ACC in clinical depression,[33,34,52] relative rCMRglc in the right perigenual ACC was robustly associated with BDI score in MA abusers. This association is also consistent with a report that this region was affected (activated) when autobiographical scripts induced sadness in healthy subjects.[40] Nonetheless, the positive associations appear to be paradoxical because higher ratings of depressive symptoms accompanied a lower relative rCMRglc in the infragenual and, less robustly, the perigenual ACC compared with control subjects. Thus, while the ACC appears dysfunctional in MA abusers, the relationship between depressive symptoms and ACC function may differ between MA users and healthy subjects.

After correction for multiple comparisons, the perigenual (not infragenual) ACC retained a significant positive correlation between BDI score and relative activity bilaterally, whereas the infragenual (not perigenual) ACC showed lower relative rCMRglc bilaterally in MA abusers than in control subjects. These subregions of the ACC are functionally distinct. While the infragenual region is part of BA 25 and functionally linked to the limbic system, the superior perigenual region has been linked to diverse functions including attention,[53] conflict resolution,[54] and analgesia.[55,56]

Another strong finding was the direct covariance of BDI score with relative rCMRglc in the amygdala in MA abusers. Along with the higher relative activity of the amygdala in MA abusers (vs control subjects), this effect suggested that amygdalar dysfunction contributes to depressed mood in abstinent MA abusers. Prior studies have shown elevated amygdalar blood flow or rCMRglc in depressed subjects with familial major depressive disorder or bipolar I and II disorders and have demonstrated elevated amygdalar metabolism rates during major depressive episodes (see Drevets[34]). One report noted that resting blood flow and relative rCMRglc were higher in the amygdala in subjects with depression than in control subjects and that relative activity in the left amygdala was correlated with the severity of depressive symptoms.[57] Similar associations in MA abusers but not in patients

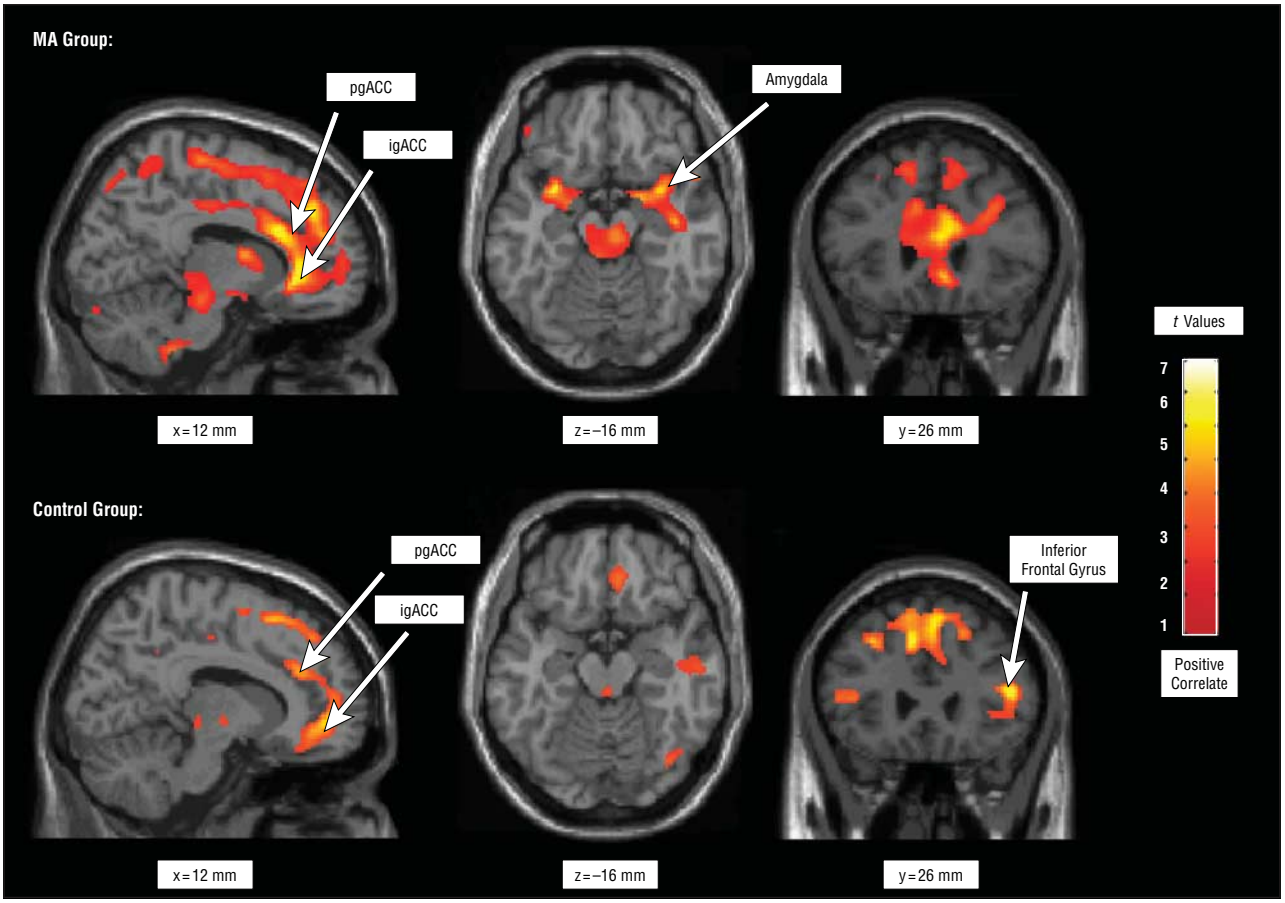

Figure 2. Locations of positive covariation between relative regional cerebral glucose metabolic rate (rCMRglc) and Beck Depression Inventory (BDI) score in the methamphetamine (MA) abuser group (n=18) (top row) and locations of positive covariation between relative rCMRglc and BDI score in the control group (n=17)(bottom row). Colors superimposed on the gray-scale structural magnetic resonance template indicate areas where the height threshold for the contrast (whole brain) was $t \geq 1.69$ ($P=.049$). Locations where clusters exhibited $P<.05$ for spatial extent (corrected for search volume of the relevant region of interest but not the number of regions) are noted (Table 5). There were no significant clusters with BDI score as a negative covariate of relative rCMRglc. Coordinates are in MNI space (Montreal Neurological Institute, Toronto, Ontario). igACC indicates infragenual anterior cingulate cortex; pgACC, perigenual anterior cingulate cortex.

with panic disorder, obsessive-compulsive disorder, phobic disorders, or schizophrenia[36] suggest a unique similarity between MA abusers and individuals with primary mood disorders.

Although the mechanism by which depressive symptoms may be linked to the activity of the amygdala in MA abusers or patients with primary mood disorders is not known, Drevets[36] discussed how this relationship might reflect a role of the amygdala being to organize emotional and stress responses. He noted that electrical stimulation of the amygdala in humans produces dysphoria (see Brothers[58]) and that excessive amygdalar transmission to the periaqueductal gray matter may produce depressive signs.

Although several regions had relative rCMRglc that covaried with anxiety measures (state or trait), only the left insula exhibited a significant association with both state and trait anxiety after Bonferroni correction. This inverse relationship is consistent with the negative correlation between anxiety scores of patients with depression with relative rCMRglc in the left but not the right insula.[51] Covariance of trait anxiety with relative activity of left infragenual ACC, left OFC, and medial OFC (bilaterally) also retained significance after correction. Our observations that the MA abusers had lower relative rCMRglc in the insula and infragenual ACC and higher anxiety self-ratings were also internally consistent. The negative association of trait anxiety with relative activity in the lateral OFC, where MA abusers had higher activity than control subjects, is less clear.

A report[59] on the relationships between cortical glucose metabolism rates, blood flow, and anxiety in control subjects is relevant to the present findings in the insula. That report indicated a linear inverse correlation between global anxiety score and cortical rCMRglc but an inverted U relationship between anxiety and cortical blood flow, measured by the less stressful xenon Xe 133 inhalation technique. Cortical blood flow increased with anxiety in subjects with low anxiety but decreased with anxiety in subjects with high anxiety. In light of these findings and a report of insular activation in healthy subjects by scripts that induce anxiety,[40] the negative associations between insular metabolism and anxiety measures in MA abusers may reflect a similar curvilinear relationship. Because MA abusers exhibited higher scores on the State-Trait Anxiety Inventory than the control group, it is feasible that their relationship between insular activity and anxiety are at the upper end (negative slope) of such a curvilinear function.

Sufficient data were not collected on the day of PET scanning to test relationships between relative rCMRglc and MA craving. In keeping with findings of individuals

Table 6. Correlations of Anxiety Measures With Relative Regional Cerebral Glucose Metabolic Rates in Methamphetamine Abusers*

Brain Regions Where Score Covaried With Relative rCMRglc	Cluster-Level Analysis			Peak Voxel				
	Corrected *P* Value	No. of Voxels		Corrected *P* Value	*z* Score	Coordinates		
		Per Cluster	Search Volume			x	y	z
State Anxiety, STAI								
Anterior cingulate								
Infragenual (–)								
Left	.04	50	459	.18	2.42	–6	52	–10
Insula (–)								
Left	<.001†	498	1535	.04	3.52	–34	–8	14
Right	.007	251	1456	.27	2.67	38	6	8
Trait Anxiety, STAI								
Amygdala (+)								
Left	.02	37	160	.08	2.40	–22	0	–16
Right	.006	48	161	.02	3.04	24	0	–14
Insula (+)								
Right	.04	134	1456	.23	2.77	48	16	–6
Anterior cingulate								
Infragenual (–)								
Left	<.001†	239	459	.90	2.77	–2	44	–12
Right	.001†	172	452	.11	2.70	0	44	–12
Perigenual (–)								
Left	.002	306	1091	.08	3.15	–8	50	12
Right	.01	150	1086	.30	2.51	4	60	14
Insula (–)								
Left	.001†	378	1535	.27	2.69	–36	24	0
Lateral orbitofrontal (–)								
Left	<.001†	1186	2206	.06	3.53	–26	26	–18
Right	.01	345	2099	.004	4.41	36	38	–18
Medial orbitofrontal (–)								
Left	<.001†	681	1597	.06	3.41	–26	28	–16
Right	<.001†	648	1552	.13	3.06	8	36	–20
Posterior cingulate (–)								
Left	.04	153	1003	.24	2.48	0	–44	36

Abbreviations: rCMRglc, regional cerebral glucose metabolic rate; STAI, State-Trait Anxiety Inventory; –, negative covariance; +, positive covariance.

*Relationships between self-reports of anxiety and relative rCMRglc were assessed by testing whether STAI score was a significant covariate of relative rCMRglc in the following brain regions, which were selected a priori on the basis of literature accounts of their involvement in anxiety states: orbitofrontal cortex (medial and lateral areas), anterior cingulate gyrus (infragenual and perigenual portions), posterior cingulate gyrus, insula, and amygdala. These regions were tested with small-volume correction using SPM99 (Wellcome Department of Cognitive Neurology, London, England). Regions with clusters that exhibited *P* values <.05 corrected for search volume are listed. There were no regions with significant clusters for the control group.

†*P*<.05 after Bonferroni correction for number of comparisons (ie, 14 regions, 2 tests each) in addition to the search volume of each region.

who abused drugs other than MA, MA abusers had a higher relative rCMRglc than control subjects in some regions (lateral OFC, posterior cingulate gyrus, amygdala, ventral striatum, and cerebellar vermis) whose activities were previously positively related to drug cravings.[26,42,46,60-64] They did not, however, show a higher relative rCMRglc of other regions (lateral prefrontal cortex, ACC, and insula), which also were positively associated with drug craving in previous studies.[26,45,46,60-67]

Some abnormalities in rCMRglc of MA abusers may be due to effects on dopaminergic systems. Of the regions selected for planned comparisons, the OFC, ACC, insula, amygdala, and dorsal and ventral striatum have dopaminergic innervation.[68-70] Each of these regions contained a cluster with a group difference in relative rCMRglc. The direction of the difference varied across the regions. To the extent that group differences may result from insult to dopaminergic systems, this variation may reflect differential effects of such deficits.

Notably, the infragenual ACC, which showed the most robust deficit of relative rCMRglc compared with the control group, receives a dense dopaminergic innervation.[71] A dopaminergic deficit in this region therefore may produce the local metabolic defect. Alternatively, defective rCMRglc in the OFC may reflect striatal dopaminergic deficiency as demonstrated by correlation between striatal dopamine D_2 receptor availability with orbitofrontal rCMRglc.[72] Orbitofrontal rCMRglc abnormalities in MA abusers may also reflect a serotonergic deficit because low levels of serotonin were measured in postmortem samples of OFC from MA abusers.[11]

Absolute CMRglc in MA abusers in early abstinence did not differ from CMRglc in control subjects. Because MA abusers who were abstinent for 2 weeks to 35 months previously exhibited higher CMRglc than in control subjects,[15] rCMRglc may change with sustained abstinence, unmasking a hypermetabolic condition. Longitudinal studies that include early abstinence may resolve this question.

This study has limitations, including the fact that although all of the regions tested have been shown to influence mood, they contribute to other behavioral states

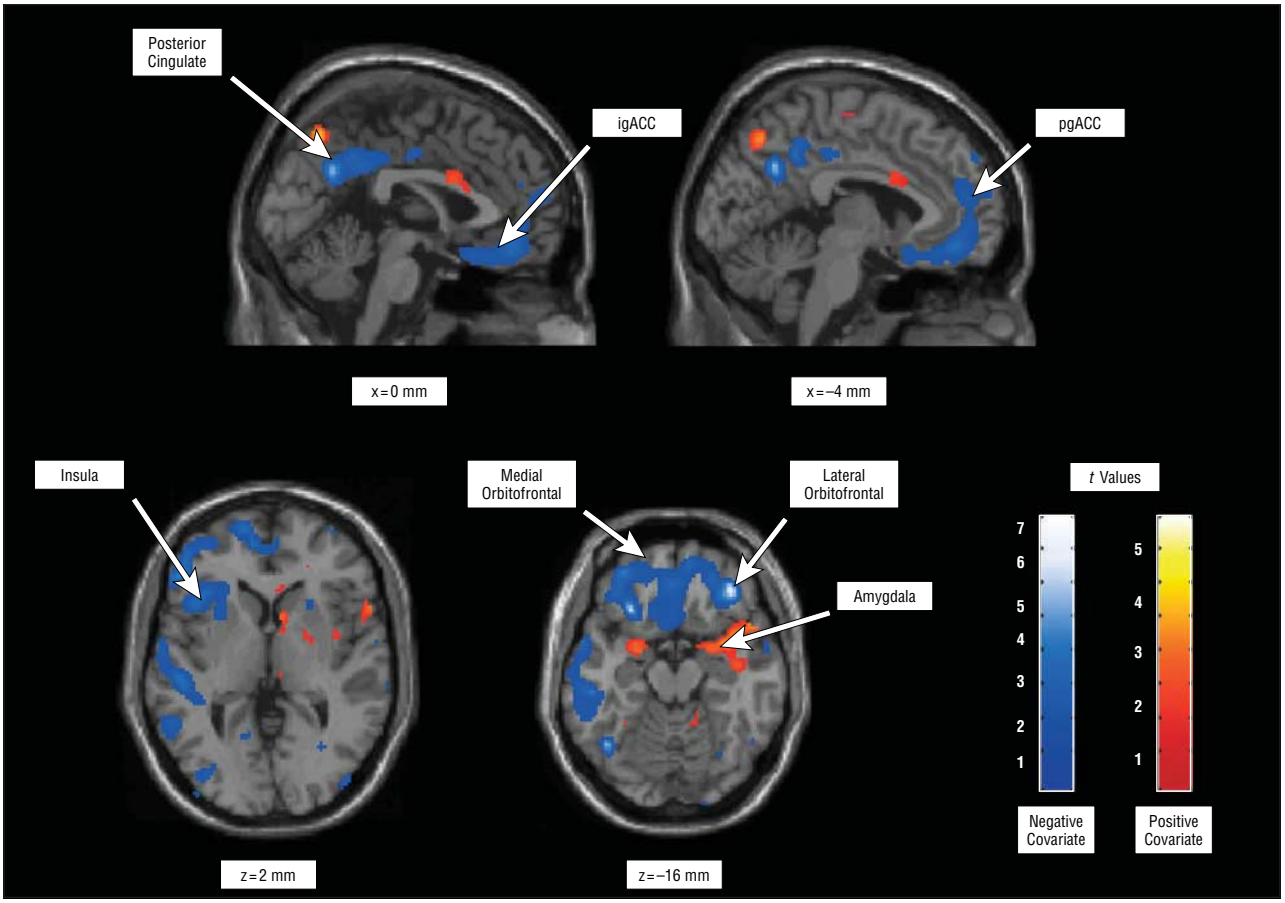

Figure 3. Locations of covariation between relative regional cerebral glucose metabolic rate (rCMRglc) and trait anxiety (State-Trait Anxiety Inventory score) in the methamphetamine abuser group (n=13). Colors superimposed on the gray-scale structural magnetic resonance template indicate areas where the height threshold for the contrast (whole brain) was $t \geq 1.69$ ($P=.049$). Locations where clusters exhibited $P<.05$ for spatial extent (corrected for search volume of the relevant region of interest but not the number of regions tested) are noted (Table 6). Coordinates are in MNI space (Montreal Neurological Institute, Toronto, Ontario). igACC indicates infragenual anterior cingulate cortex; pgACC, perigenual anterior cingulate cortex.

not addressed in the current study. Another limitation is that while the groups were similar in most categories, most of the MA abusers but none of the control subjects were tobacco smokers. Smoking status was not considered in prior studies of MA abusers, and differences in cerebral metabolism associated with nicotine dependence have not been described but warrant further study. One potentially confounding variable was craving associated with abstinence in nicotine-dependent smokers. Although craving for cigarettes can begin within minutes of smoking, and smokers were required to abstain from smoking for at most 2 hours before the PET measurement, the pattern of abnormalities observed in the MA abusers' relative rCMRglc compared with control subjects did not resemble relative rCMRglc findings in smokers during cigarette craving.[65]

Another issue was the subjects' state during relative rCMRglc measurement. The participants performed an auditory CPT, and this simple task may affect relative rCMRglc differently in MA abusers than in control subjects because subjects in the 2 groups may have had different levels of regional activation. The group differences, accordingly, may be state dependent. Finally, our study could not discriminate between effects of early abstinence, effects of chronic MA abuse that are unchanged by abstinence, and factors that predated MA abuse on relative rCMRglc and mood.

With these caveats, we conclude that MA abusers in early abstinence have dysfunction in the limbic and paralimbic regions that have been linked with negative affective states. Depressive symptoms showed positive covariance with perigenual ACC and amygdalar activity in MA abusers. In contrast, anxiety was negatively associated with activities in all of the regions, except for the dorsal striatum, where MA abusers exhibited CMRglc deficits compared with control subjects. The findings identified brain substrates of affective dysregulation as potential targets for therapeutic intervention during early abstinence and withdrawal in MA abusers.

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