Title

Cerebral metabolic dysfunction and impaired vigilance in recently abstinent methamphetamine abusers

Journal

Biological Psychiatry, 58(10)

ISSN

0006-3223

Authors

London, E D
Berman, S M
Voytek, B
et al.

Publication Date

2005-11-01

Peer reviewed

Cerebral Metabolic Dysfunction and Impaired Vigilance in Recently Abstinent Methamphetamine Abusers

Edythe D. London, Steven M. Berman, Bradley Voytek, Sara L. Simon, Mark A. Mandelkern, John Monterosso, Paul M. Thompson, Arthur L. Brody, Jennifer A. Geaga, Michael S. Hong, Kiralee M. Hayashi, Richard A. Rawson, and Walter Ling

Background: *Methamphetamine (MA) abusers have cognitive deficits, abnormal metabolic activity and structural deficits in limbic and paralimbic cortices, and reduced hippocampal volume. The links between cognitive impairment and these cerebral abnormalities are not established.*

Methods: *We assessed cerebral glucose metabolism with [F-18]fluorodeoxyglucose positron emission tomography in 17 abstinent (4 to 7 days) methamphetamine users and 16 control subjects performing an auditory vigilance task and obtained structural magnetic resonance brain scans. Regional brain radioactivity served as a marker for relative glucose metabolism. Error rates on the task were related to regional radioactivity and hippocampal morphology.*

Results: *Methamphetamine users had higher error rates than control subjects on the vigilance task. The groups showed different relationships between error rates and relative activity in the anterior and middle cingulate gyrus and the insula. Whereas the MA user group showed negative correlations involving these regions, the control group showed positive correlations involving the cingulate cortex. Across groups, hippocampal metabolic and structural measures were negatively correlated with error rates.*

Conclusions: *Dysfunction in the cingulate and insular cortices of recently abstinent MA abusers contribute to impaired vigilance and other cognitive functions requiring sustained attention. Hippocampal integrity predicts task performance in methamphetamine users as well as control subjects.*

Key Words: Methamphetamine, drug abuse, brain imaging, sustained attention, continuous performance test

Individuals who abuse methamphetamine (MA) have cognitive deficits that may influence their success in treatment. Active users show impairments in mental flexibility, response inhibition, problem solving, abstract thinking, and manipulation of information (Sim et al 2002; Simon et al 2002). Impairments of inhibitory control (Kalechstein et al 2003; Salo et al 2002), verbal learning (Volkow et al 2001c), and decision making (Paulus et al 2002, 2003) are observed during abstinence (Nordahl et al 2003).

Positron emission tomography (PET) reveals losses of cerebral dopamine transporters (McCann et al 1998; Sekine et al 2001, 2003; Volkow et al 2001c) and abnormalities of global and regional cerebral glucose metabolism (rCMRglc) in MA abusers (London et al 2004; Volkow et al 2001a; Wang et al 2004). Compared with control subjects, MA abusers in early abstinence exhibit lower relative rCMRglc in the anterior cingulate gyrus and insula but higher activity in lateral orbitofrontal and posterior cingulate cortices and subcortical limbic structures; their symptoms of depression and anxiety vary with relative rCMRglc in cortical and subcortical limbic regions (London et al 2004). Methamphetamine abusers also exhibit hippocampal and cortical structural deficits (Thompson et al 2004a). Furthermore, functional magnetic resonance imaging (fMRI) indicates that abstaining MA abusers performing a decision-making task have impaired activation of dorsolateral and ventromedial prefrontal cortex (Paulus et al 2002). Current findings suggest that recovery is slow and incomplete (Volkow et al 2001b; Wang et al 2004).

To help clarify the cognitive deficits in MA abusers, we examined relationships of relative rCMRglc, indexed by uptake of [F18]fluorodeoxyglucose (FDG), and hippocampal morphology with performance on an auditory continuous performance task (CPT), a vigilance test of sustained attention (Bush et al 2000; Riccio et al 2002). Performance in the intensity aspects of alertness and sustained attention is likely a prerequisite for the more demanding selective aspects of attention (Salo et al 2002) and other cognitive functions. The CPT activates a complex network involving cortical regions (Riccio et al 2002). Whereas most neuroimaging studies of attention have focused on the visual modality (Corbetta et al 1993; Heinze et al 1994; La Berge and Buchsbaum 1990; Pardo et al 1990, 1991), some tested auditory vigilance (Benedict et al 1998, 2002; Cohen et al 1987, 1992; Seidman et al 1998; Sturm et al 2004). Control subjects exhibited lower midcingulate rCMRglc during performance of tasks similar to the one used here compared with rest (Cohen et al 1987, 1992), and smaller midcingulate and hippocampal fMRI signals but greater signals in the insula have been associated with greater auditory CPT task difficulty (Seidman et al 1998).

We hypothesized that newly abstinent MA users would differ from control subjects in how their cognitive performance on an auditory vigilance task was related to concomitant relative rCMRglc in cognitive and affective brain networks and to hippocampal structural defects. The rCMRglc data from most of the subjects has been reported (London et al 2004). Because CPT performance was the focus of the current analysis, we excluded data from two subjects whose performance on the CPT during the 30-minute FDG uptake period differed by >3 SD of the mean from all subjects.

From the Departments of Psychiatry and Biobehavioral Sciences (EDL, SMB, BV, SLS, JM, ALB, RAR, WL), Molecular and Medical Pharmacology (EDL), Neurology (PMT, JAG, MSH, KMH), and the Brain Research Institute (EDL, SMB), David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California; and the Department of Physics (MAM), University of California Irvine, Irvine, California.

Address reprint requests to Edythe D. London, Ph.D., Neuropsychiatric Institute, David Geffen School of Medicine, UCLA, 760 Westwood Plaza, Room C8-528, Los Angeles, CA 90024-1759; E-mail: elondon@mednet.ucla.edu.

Received October 19, 2004; revised April 7, 2005; accepted April 21, 2005.

0006-3223/05/$30.00
doi:10.1016/j.biopsych.2005.04.039

Methods and Materials

Subjects

Written informed consent was obtained from all participants after a detailed description of the study, which was approved by the institutional review boards of University of California Los Angeles (UCLA) and the Long Beach Veterans Administration Medical Center. They were generally healthy by physical examination, medical history, and laboratory tests. Exclusion criteria included use of medications that affect the central nervous system; cardiovascular, pulmonary or systemic disease; claustrophobia; pregnancy; and seropositive status for human immunodeficiency virus infection. Psychiatric diagnoses were determined using the *Structured Clinical Interview for DSM-IV* (First et al 1996, 1997) to exclude participants with current psychotic disorders and to determine diagnoses of drug abuse disorders (also see below).

Participants completed questionnaires related to drug use (an intake questionnaire, a drug use survey, and the Addiction Severity Index) (McLellan et al 1992). Light use of alcohol (<7.5 drinks per week) was not exclusionary, but a diagnosis of current drug or alcohol dependence (other than MA dependence for the MA abuser group and nicotine dependence for both groups) was exclusionary. Recent use of MA was indicated by self-report of spending ≥$100 on MA during the month before screening, and MA use was verified by urine drug screen. A urine drug screen that was positive for any other illegal drug of abuse other than marijuana, at intake, was exclusionary. Control subjects provided urine samples negative for illicit drugs of abuse at the time of screening.

Handedness was determined according to the Lateral Preference Pattern Assignment subtest of the Physical and Neurological Examination for Soft Signs (Denckla 1985). The criterion for right-handedness was a self-report of writing and performing all or all but 1 of 11 items with the right hand.

General Experimental Design

Methamphetamine-abusing subjects were inpatients (at the UCLA General Clinical Research Center or the UCLA Neuropsychiatric Institute and Hospital) during their participation. Cerebral glucose metabolism was assayed by the FDG PET method (Reivich et al 1979; Phelps et al 1979) when the MA abusers were abstinent for 4 to 7 days. About 90% of MA administered orally is excreted within 4 days (Caldwell et al 1972). Control subjects participated on a nonresidential basis. Urine drug screens on the test day were negative for all illegal drugs of abuse in all participants.

PET Procedure

Before injection of FDG, the subject was positioned on the scanner gantry. A germanium (^{68}Ge) transmission scan was performed to verify the position of the brain, and a ^{68}Ge transmission scan was performed for attenuation correction. The subject was then removed from the scanner and began performing a CPT. The task, similar to one used by Cabeza and Nyberg (2000), presented tones every 2 seconds and required discrimination of a target tone (higher pitch) presented within a sequence of distracting tones (lower pitch) and responding with a button press.

[F18]fluorodeoxyglucose (≤5 mCi, ≤185 MBq) was injected intravenously 5 minutes after the CPT was started. Thirty minutes later, the CPT was stopped, and the subject was repositioned in the scanner. Brain images, acquired for 30 minutes (six 5-minute frames), beginning 50 minutes after the FDG injection, were reconstructed using attenuation correction data from the transmission scan.

Magnetic Resonance Imaging Scans and Analysis

A single 3-Tesla superconducting magnet (GE Medical Systems, Waukesha, Wisconsin) was used to obtain structural magnetic resonance imaging (MRI) scans as three-dimensional (3-D), T1-weighted spoiled gradient (SPGR) volumes (SPGR recalled acquisition, 256 × 256 matrix, echo time [TE] = 4 milliseconds, repetition time [TR] = 24 milliseconds, flip angle = 35 degrees, 1.22-mm slice thickness). They were used for co-registration with PET data (see below) to facilitate correct anatomical labeling and for hippocampal structural analysis.

For structural analysis, each magnetic resonance (MR) image volume was resliced into a standard orientation, and 20 standardized anatomical landmarks in each subject's image data set were "tagged" (Thompson et al 2003). A least squares, linear transformation spatially matched each individual to an average brain in the standardized coordinate space developed by the International Consortium for Brain Mapping (ICBM-305 space) (Mazziotta et al 2001), maintaining regional differences in brain size and shape.

We created 3-D surface models of the hippocampus in each scan, as previously described (Narr et al 2002), and measured the volumes of these models. A medial 3-D curve was derived from each individual hippocampus, threading down its central axis (Thompson et al 2004b), and the distance of each surface point from this centerline measured the hippocampal radius. Regressions were run at each surface point to map linkages between radial size and a log-transformed measure of CPT performance [log (1+ percent errors)]. The p value describing the significance of this linkage was plotted at each point on the surface to produce a statistical map showing the spatial patterns of correlations between hippocampal structure and performance. Permutation methods (Thompson et al 2003) were applied to assess the significance of the statistical maps and to correct for multiple comparisons. To do this, the covariate [log (1+ percent errors)] was permuted 1,000,000 times on an SGI Reality Monster supercomputer with 32 internal R10000 processors (Silicon Graphics Inc., California), and a null distribution was developed for the area of the average hippocampus with performance-structure correlation statistics above a fixed threshold in the significance maps. The overall linkage between performance and hippocampal structure was then reported after this correction for multiple comparisons.

Statistical Analysis

Group comparisons of demographic variables were conducted using t tests or chi-square analysis. As the number of days in the last 30 during which MA was used did not meet the assumption of homogeneity of variance, a separate variance t test was performed in the Statistical Package for the Social Sciences (SPSS, Illinois) and the degrees of freedom adjusted accordingly. A d′ statistic, which considers both correct responses and false alarms to overcome the problem of response bias (Green and Swets 1966), was used to evaluate CPT accuracy, and a t test compared the mean values of d′ between groups. For these analyses, the statistical threshold was set at $p < .05$, uncorrected for multiple comparisons. The d′ statistic calculation requires determination of individual z-scores for each subject's false alarms and hits separately. Since z-scores are infinite in the absence of errors, .001 errors were added to perfect scores.

Group comparisons of relative regional brain activity, indicating relative rCMRglc, were performed by statistical parametric mapping (SPM99; Wellcome Department of Cognitive Neurology, London, United Kingdom; http://www.fil.ion.ucl.ac.uk/spm/) (Friston et al 1995a, 1995b). Each PET image (decay-corrected raw counts of radioactivity) was co-registered to the corresponding structural MR image using Automated Image Registration (Woods et al 1992). These co-registered MR images were then used to normalize each subject's PET data spatially by linear and nonlinear transformations (Friston et al 1995a) that warped the images into ICBM-305 space (Mazziotta et al 2001). The hippocampal MRI data were mapped only linearly into standard space, so that hippocampal shape differences remained intact and could be analyzed for correlations with performance. For the PET image analyses, however, additional nonlinear anatomical normalization was applied to improve the spatial alignment of anatomy across subjects. Normalized images were then smoothed with an 8-mm (full width half maximum) isotropic Gaussian kernel, and the images were scaled to a fixed mean. A stationary random Gaussian field was used to model the data and to calculate the probability of one or more voxels having all possible values of t (or z) greater than a predefined height threshold. The probability associated with the spatial extent (size) of obtaining a cluster as large as or larger than all clusters of contiguous suprathreshold voxels that passed the predefined height threshold was also calculated. Group differences were assessed by two-sample, one-tailed t tests; the results were displayed as statistical parametric maps (SPMs).

For PET analyses, we sampled the following seven regions of interest (ROIs) in each hemisphere: lateral orbitofrontal cortex (lateral and posterior orbital gyri, Brodmann area [BA] 47, 11); cingulate gyrus (infragenual [BA 25, 24], perigenual [BA 24, 32, 33], middle [BA 23, 24, and small portions of 32, 31], and posterior [BA 23, 29, 30, 31]); insula (BA 13); and hippocampus. The cortical ROIs had exhibited differences in relative rCMRglc between MA users and control subjects during performance of the CPT in our previous investigation of mood disturbance (London et al 2004). While the hippocampus was not studied in that report, we added it here because structural imaging of MA abusers compared with control subjects (including the current subjects) found a deficit in hippocampal volume in MA abusers (Thompson et al 2004a).

Bilateral sampling provided data on 14 ROIs and 28 tests (MA abusers > control subjects, control subjects > MA abusers). Statistical significance within each ROI was determined according to the SPM model described above, using a voxel height threshold of $p = .05$ (uncorrected) for inclusion in clusters. Region of interest effects listed in the tables represent clusters with $p < .05$ for spatial extent (number of contiguous voxels) after correction for the ROI search volume. Although we used this spatial extent threshold as the statistical criterion, we also noted the probability associated with the peak voxel height (corrected for ROI search volume). Further, we indicated which clusters maintained spatial extent significance when applying the Bonferroni correction for the number of tests (e.g., 28 t tests for a two-tailed hypothesis of group differences in 14 ROIs). Nonetheless, the Bonferroni method is unduly conservative, as it assumes independence across tests while brain activities in the ROIs sampled are unlikely to be independent.

Relationships between relative rCMRglc in the 14 selected regions and CPT errors [log (1+ percent errors)] were evaluated with covariate analysis in SPM99. The Bonferroni correction was applied for 28 one-tailed tests (14 regions, positive and negative covariance). We examined the main effect of covariation (CPT errors and relative rCMRglc) and the interaction between group and covariation (slope tests).

Table 1. Characteristics of Research Participants

	Control Subjects	MA Abusers
Age (Years)[a]	33.3 (1.98)	34.7 (1.87)
Gender (Male Subjects/Total Number)	10/16	11/17
Education (Years)[a]	14.6 (0.47)	12.8 (0.50)[c]
Mother's Education (Years)[a]	14.1 (0.63)	12.7 (0.78)
Race		
Caucasian (non-Hispanic)	11/16	9/17
Caucasian (Hispanic)	2/16	4/17
African American	3/16	2/17
Asian	0/16	2/17
Handedness (Right-Handed)[b]	12/16	14/17

MA, methamphetamine.

[a]Data shown are mean values (standard errors of the means), $n = 16$ Control subjects, $n = 17$ MA abusers.

[b]Handedness was determined according to the Lateral Preference Pattern Assignment subtest of the Physical and Neurological Examination for Soft Signs. (Denckla 1985). To qualify as right-handed, a participant had to write and to perform all or all but 1 of 11 items in addition to writing with the right hand.

[c]Significantly different from control group, $p < .05$ by Student t test.

Results

Description of Subjects

The groups did not differ significantly in gender, handedness, race, age, or mother's education (Table 1). The MA abusers, however, had fewer years of education than the control subjects [$t(31) = 2.61$, $p = .014$]. One of the control participants had a history of a manic episode and two each had a past depressive episode. In addition, one MA abuser had a current diagnosis of social phobia and three met criteria for marijuana abuse but not dependence; three participants in the MA abuse group but no control subjects met criteria for antisocial personality disorder.

Drug Use

On average, participants in the MA abuser group reported MA use for more than 9 years, beginning in their early to mid twenties (Table 2). They used about 3.6 g MA per week, and they used MA on 19 of the 30 days before entering the study. For all subjects, the primary route of administration was smoking. The two groups reported similar alcohol use but differed significantly in frequency of marijuana use during the month before study [$t(31) = -2.23$, $p = .033$]; nine MA abusers and three control subjects reported use within the 30 days before study. Fourteen of the MA abusers and none of the control participants were also cigarette smokers.

CPT Performance

The CPT responses were equally fast in the two groups [$t(31) = -.314$, $p = .756$], and both groups exhibited a high degree of accuracy, consistent with findings in simple CPTs (Nuechterlein 1991) (Table 3). The distribution of percent errors was significantly positively skewed (skew = 1.35 ± .41). We therefore normalized the data by log transformation (log [1 + percent errors]), reducing the skew to .06 ± .41. Although our prior assessment of CPT performance between MA users and control subjects found no statistical significance during the first 15 minutes after FDG injection (London et al 2004), the current

Table 2. Self-Reported Drug Use

	Control Subjects	MA Abuser
Methamphetamine Use		
Duration (Years)	—	9.29 (1.13)
Average (g/week)	—	3.60 (.78)
Days Used in Last 30	—	19.24 (2.14)
Age of First Use (Years)	—	25.3 (1.84)
Tobacco Smokers		
(>5 Cigarettes/Day)	0/16	14/17[a]
Marijuana Use		
Days in Last 30	0.25 (.14)	2.82 (1.11)[b]
Alcohol Use		
Days in Last 30	1.96 (.59)	2.94 (1.04)

No subject (either group) had a diagnosis of current drug or alcohol dependence (other than MA dependence and nicotine dependence for MA abusers). Data shown are mean values (SEM) of self-reported drug use recorded on an intake questionnaire, a drug use survey, and the Addiction Severity Index (McLellan et al 1992). In addition to the tabulated data on regular drug use, control subjects provided 12 reports (10 subjects) of having used an illicit drug (other than marijuana) <5 times ever and 8 reports (8 subjects) of >5 instances of use. Methamphetamine abusers gave 29 reports (13 subjects) of using an illicit drug (other than MA or marijuana) <5 times and 11 reports (11 subjects) of >5 instances of such use.

MA, methamphetamine.

[a]Significantly different from control subjects by Pearson chi-square analysis ($\chi^2_1 = 22.89$, $p < .001$).

[b]Significantly different from control subjects by post hoc Student *t* test, $p \leq .05$.

analysis of normalized data over the entire 30-minute FDG uptake period indicated that MA users made significantly more errors than control subjects [$t(31) = 3.77$, $p < .001$]. They also did not discriminate as well between targets and nontargets, as assessed by the signal detection measure d′ [$t(31) = 3.39$, $p = .002$]. Log transformed [1 + percent errors] and d′ were highly correlated ($r = .89$). Since computing d′ required adjusting error rates when subjects had either no omissions or no commissions, we used log transformed [1 + percent errors] for all further analyses.

Cerebral Metabolism

As reported (London et al 2004), relative rCMRglc in the bilateral infragenual cingulate gyrus and right insula were lower in MA abusers than in control subjects. The deficit in the left infragenual anterior cingulate gyrus of the MA abusers remained significant after Bonferroni correction. In contrast, MA abusers had higher relative rCMRglc than control subjects in the right lateral orbitofrontal area and the right middle and posterior cingulate gyri. The group difference at the peak voxel in the right posterior cingulate gyrus remained significant after Bonferroni correction.

Table 3. CPT Performance in Early Abstinence from MA

	Control Subjects	MA Abuser
Reaction Time (milliseconds)	606 (191)	625 (152)
Percent Errors	1.6 (2.01)	5.5 (4.19)[a]
Normalized Errors (log [1 + %errors])	.32 (.072)	.72 (.077)[b]
d′	5.99 (.34)	4.57 (.25)[a]

Data are mean values (SEM) for 16 control subjects and 17 MA abusers.

CPT, continuous performance task; MA, methamphetamine.

[a]Significantly different from control subjects by post hoc Student *t* test, $p < .01$.

[b]Significantly different from control subjects by post hoc Student *t* test, $p < .001$.

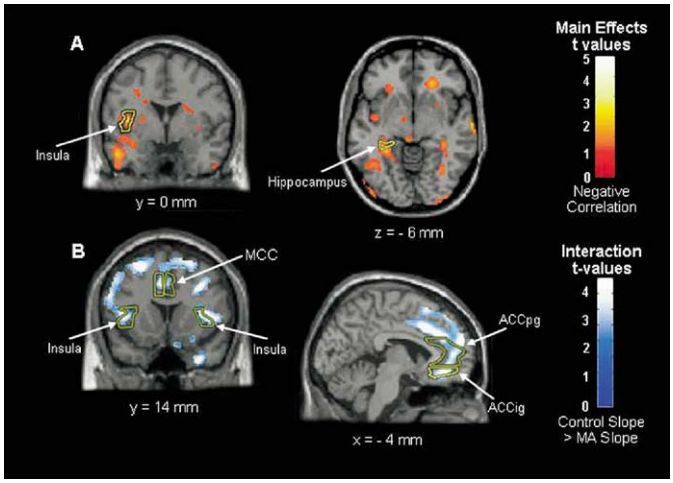

Figure 1. Relative rCMRglc is related to CPT error rate. **(A)** Main effects. Negative covariation between relative rCMRglc and CPT error rate (log [1 + percent errors]) across all subjects ($n = 33$) is shown by colored voxels in the gray-scale structural image representing ICBM space. Negative covariation indicates that higher relative rCMRglc was correlated with smaller error rates. Voxels are colored to indicate locations where the height threshold of $t \geq 1.69$ ($p < .05$) was reached. Arrows indicate clusters exhibiting $p < .05$ for spatial extent (corrected for the ROI volume, outlined in yellow). **(B)** Relationships between relative rCMRglc and CPT rate varies with the subject group. Slope differences between MA ($n = 17$) and control subjects ($n = 16$) in the covariation of relative rCMRglc and CPT error rate (log [1 + percent errors]). More positive covariation in the control group (= more negative covariation in MA group) is shown in blue. No ROI tested showed more positive covariation in the MA group. Coloration of voxels in the gray-scale structural image representing ICBM-space indicates areas where the height threshold of $t \geq 1.69$ ($p < .05$) was exceeded. Arrows indicate clusters exhibiting $p < .05$ for spatial extent (corrected for the ROI volume, outlined in yellow, see Table 4). ACCpg, perigenual region of anterior cingulate cortex; ACCig, infragenual region of anterior cingulate cortex; MCC, middle cingulate cortex; MA, methamphetamine; rCMRglc, regional cerebral glucose metabolism; CPT, continuous performance task; ROI, region of interest; ICBM, International Consortium for Brain Mapping.

Cerebral Metabolism and CPT Performance

Combining groups, higher relative rCMRglc in the left insula and bilateral hippocampus was associated with fewer errors (negative association) (Figure 1A). These effects in the left insula ($p < .001$) and left hippocampus ($p < .0005$), but not the right hippocampus ($p < .03$), remained significant after Bonferroni correction. In addition, a significant interaction indicated group differences in the relationship of relative rCMRglc in the left insula to performance. This interaction was also significant in the right insula, bilateral infragenual and perigenual regions of the anterior cingulate gyrus, and the midcingulate region of the left hemisphere (Table 4, Figure 1B).

The interactions in Table 4 and main effects in the hippocampus were clarified through examination of the relationship between relative rCMRglc and CPT performance within the individual groups (Table 5). While the significant main effect in the left hippocampus derives from significant direct relationships between relative rCMRglc and CPT performance in both groups, neither group showed an independently significant relationship involving the right hippocampus.

The interaction between group and covariation of error rate

Table 4. Interactions Between Group and the Relationships of CPT Error Rates to Relative rCMRglc

	Cluster-Level			Voxel-Level		
	Corrected *p* Value	Voxels/Cluster	Voxels/Search Volume	Corrected *p* Value	*z*-Score	Coordinates (x, y, z)
Anterior Cingulate Infragenual						
Left	< .0005[a]	240	459	.043	2.97	−4, 42, −10
Right	.013	91	452	.085	2.68	0, 42, −10
Anterior Cingulate Perigenual						
Left	.001[a]	415	1091	.141	2.74	−2, 44, −4
Right	.004	237	1086	.241	2.50	4, 34, 24
Middle Cingulate						
Left	.020	156	733	.052	3.00	−4, 16, 38
Insula						
Left	.020	197	1535	.225	2.64	−40, 12, 4
Right	.007	264	1456	.115	2.93	42, 10, 6

The measure of error rate entered into covariate analysis was log (1 + percent errors). In each case of a significant interaction, the slope was more positive in the control group (more negative in the MA abusers group).

CPT, continuous performance task; rCMRglc, regional cerebral glucose metabolism; MA, methamphetamine.

[a]After correction for search volume, the indicated clusters also exceeded the criterion of the Bonferroni correction for 14 comparisons.

with rCMRglc in the anterior cingulate gyrus resulted both from an association of higher relative rCMRglc with lower error rates in MA abusers and of higher relative rCMRglc with higher error rates in control subjects. In the right infragenual and perigenual cingulate gyrus, this association attained significance only in the MA group, and in the left perigenual and middle cingulate, the relationship attained significance only in the control group. The same relationship between errors and relative rCMRglc was found among MA users in the insula bilaterally but was strongest in the left hemisphere, with no evidence for any effect in control subjects.

Hippocampal Anatomical Deficits

The estimated mean hippocampal volume reduction in MA users was 6% to 8% in the present sample. Combining data from the current MA and control groups, the log transformation of CPT errors was strongly negatively correlated with hippocampal volume (left hippocampus: $p < .009$, right hippocampus: $p < .026$) after adjusting for differences in whole brain volume. The correlation was also significant without adjusting for brain volume (i.e., before scaling data into standard space; left hippocampus: $p < .016$, right hippocampus: $p < .025$). After further adjustment for experimental group (i.e., control subjects or MA), the number of CPT errors, after log transformation, was still associated with hippocampal volume in the left hemisphere ($p < .035$) and at trend level in the right hemisphere ($p < .061$). There was no significant interaction between group and CPT performance as predictors of hippocampal volume.

Given the main effect of CPT error rate as a predictor of hippocampal volume, statistical maps were also made to determine whether the association was localized or distributed over the hippocampal surface (Figure 2). Regions were identified that were associated with CPT error rate in the right hippocampus ($p = .048$, corrected; permutation test) and at trend level in the left hippocampus ($p = .059$, corrected; permutation test). In a post hoc exploratory test, the regions where left hippocampal atrophy was linked with CPT error rate were more sensitively detected when a primary threshold of $p = .1$ was used ($p = .040$, corrected, left hemisphere). This situation is unusual but occurs when a weak atrophy of low effect size is consistently found over the hippocampal surface and is pervasive enough to be significant by permutation when the entire surface is taken into account.

Discussion

Methamphetamine abusers differed from control subjects in the relationships between auditory CPT performance (normalized errors, i.e., log [1 + % errors]) and relative rCMRglc of the infragenual, perigenual, and midcingulate cortices and the insula. These cortical regions, as well as the lateral orbitofrontal gyrus, previously showed abnormalities in rCMRglc (London et al 2004). Although MA abusers also had a deficit in hippocampal structure (Thompson et al 2004a), both groups showed a negative association of hippocampal rCMRglc and CPT error rate, indicating that participants with more activity in their hippocampi had better performance irrespective of MA abuse.

Anterior Cingulate Cortex and Error Detection

Those control subjects who made the most errors had the highest relative rCMRglc in the anterior cingulate cortex. This relationship may reflect recruitment of activity in this region during error detection (Bush et al 2000). Given the rCMRglc and structural deficits in the anterior cingulate gyrus in MA abusers (London et al 2004; Thompson et al 2004a), however, low rCMRglc here may be an index of pathology that impairs performance. In this case, higher anterior cingulate activity may be associated with better performance because lower relative rCMRglc indexes the severity of MA-induced deficiency. Notably, relative rCMRglc in the anterior cingulate cortex (left infragenual) covaried negatively with recent MA use (g/week) (London et al 2004). While increase in relative rCMRglc associated with error monitoring may occur in the MA users, this effect may account for less variance than the severity of the drug abuse associated deficit.

Connections of the Anterior Cingulate Cortex

Given the complexity of connections of the cingulate gyrus, metabolic and structural abnormalities here could impair cognitive control functions (Cabeza and Nyberg 2000; Carter et al 1998; George et al 1994; Ito et al 2003) that are relevant to CPT performance. Whereas a dorsal cognitive subdivision maintains connections with the lateral prefrontal and parietal cortices and

Table 5. Significant Covariance Between Error Rates on Auditory CPT and Relative rCMRglc: Separate Groups

	Cluster-Level			Voxel-Level		
	Corrected *p* Value	Voxels/Cluster	Voxels/Search Volume	Corrected *p* Value	*z*-Score	Coordinates (x, y, z)
Anterior Cingulate Infragenual						
Left						
Control Group (+)	.008	110	459	.245	2.19	−4, 40, −14
MA (−)	.003	147	459	.228	4.11	0, 28, −16
Right						
MA (−)	.007	108	452	.223	2.23	2, 28, −18
Anterior Cingulate Perigenual						
Left						
Control Group (+)	.003	308	1091	.204	2.65	−2, 52, 8
Right						
MA (−)	.036	111	1086	.195	2.69	2, 22, 24
Middle Cingulate						
Left						
Control Group (+)	.006	224	733	.031	3.32	−2, −4, 44
Right						
Control Group (+)	.022	108	708	.117	2.77	2, −6, 44
MA (−)	.035	89	708	.077	2.93	2, 20, 28
Insula						
Left						
MA (−)	<.0005[a]	882	1535	.011	3.90	−44, 16, 12
Right						
MA (−)	.019	194	1456	.176	2.82	42, 10, 6
Hippocampus						
Left						
Control Group (−)	<.0005[a]	107	247	.148	2.39	−32, −20, −14
MA (−)	.009	29	247	.104	2.55	−36, −34, −8

Significant associations (individual groups) between relative rCMRglc and errors (log of [1 + percent errors]) on the auditory complex CPT. Each score was assessed as a covariate of relative rCMRglc in those regions that showed a significant relationship between performance and relative rCMRglc across groups or an interaction between group and the covariance between performance and relative rCMRglc (slope test). Tests were performed with small volume correction using SPM99 in the regions of interest (ROIs) where either an interaction (the seven regions in Table 4) or main effect without interaction (right and left hippocampus) was observed. Positive associations (+) indicate that higher relative rCMRglc accompanied more errors, whereas negative associations (−) indicate that higher relative rCMRglc accompanied fewer errors.

CPT, continuous performance task; rCMRglc, regional cerebral glucose metabolism; MA, methamphetamine.

[a]In addition to the correction for search volume, the indicated clusters also exceeded the criterion of the Bonferroni correction for 18 comparisons (i.e., for each of 2 groups, 9 ROIs).

premotor and supplementary motor areas, a rostroventral affective subdivision (where relatively low rCMRglc in MA users is related to negative affect [London et al 2004]) connects with the orbitofrontal cortex, insula, and subcortical limbic regions (Bush et al 2000; Devinsky et al 1995).

Divergent Effects Within the Cingulate Gyrus

While the area of the cingulate gyrus that showed relative rCMRglc below control levels in MA abusers was centered in the anterior portion (perigenual region), MA users had relative rCMRglc above control levels in an area centered in the posterior cingulate in BA 31, extending into the posterior part of the middle cingulate gyrus at the border between BA 31 and 24. The interactions produced by a more negative relationship between rCMRglc and CPT error rate in MA users than in control subjects were similarly centered in the anterior cingulate (Figure 1B) but extended into the anterior part of the middle cingulate gyrus in BA 32. Therefore, the midcingulate ROI contains parts of both anterior and posterior cingulate gyrus networks that functionally deviate from normality in opposite directions in MA users.

Effects Involving the Hippocampus and Insula

The association between errors and relative rCMRglc of the hippocampus and left insula implies that the best task performers had the highest rCMRglc in these regions. In light of the prior observations that task difficulty is inversely related to activity, the present finding suggests that participants who made more errors found the CPT task relatively more difficult and experienced greater hippocampal deactivation.

Also of interest is the link between hippocampal structure and CPT errors, with those subjects (in each group) who had smaller hippocampal volumes performing less well than those with larger hippocampi. Hippocampal volume has been positively associated with navigation skills in normal subjects (Maguire et al 2000), and deficits in hippocampal structure, including local volume reductions, have been correlated to poorer performance on the Mini-Mental State Exam in studies of aging and dementia (e.g., Thompson et al 2003). Given a structural hippocampal deficit in MA users and the correlation of hippocampal radius with memory performance (Thompson et al 2004b), the relationship between hippocampal structure and performance on a simple vigilance task suggests that hippocampal integrity is required to perform a broad range of cognitive functions in MA users and healthy subjects.

Unlike the consistent relationship across groups between relative hippocampal rCMRglc and CPT error rate, there was a negative correlation between relative insular rCMRglc and CPT

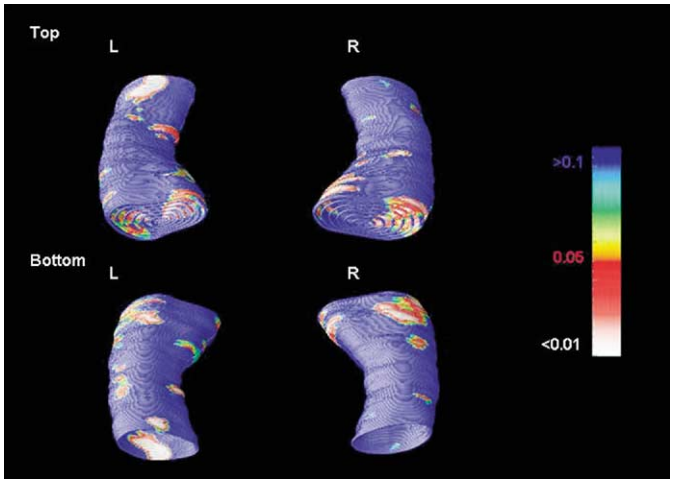

Figure 2. Hippocampal atrophy in MA abusers is linked with poorer auditory vigilance performance. Each hippocampus was traced in coronal MRI sections and converted to a mesh surface representation in which the radial size of the hippocampus was measured from a centerline and plotted on the surface. These meshes were averaged across MA subjects, and atrophy relative to the control mean was computed at each surface grid point as described before (Thompson et al 2004b). Hippocampal regions (in ICBM space) where CPT error rate [log (1+ percent errors)] was significantly associated with radial atrophy in the MA abuser group are shown in red. The "Top" section is viewed from the anterior and superior position while the view from "Bottom" is from the posterior and inferior position. MA, methamphetamine; MRI, magnetic resonance imaging; ICBM, International Consortium for Brain Mapping; CPT, continuous performance task.

error rate only in MA abusers. The insula, like the anterior cingulate cortex, is relatively hypometabolic in MA abusers performing this task, and relative rCMRglc in the insula covaries negatively with measures of MA use (left insula rCMRglc with amount used [g/week]; right insula rCMRglc with frequency of use [days in past 30]) (London et al 2004). Higher insular activity may therefore accompany better performance because it indexes less drug-related impairment, as we also suggested for the anterior cingulate cortex. However, since activation of the insula is greater when subjects perform a more demanding (vs. less demanding) CPT (Seidman et al 1998), the interaction may indicate that in more impaired MA abusers, activity does not increase to meet the demands of the task. Our data are consistent with results from a study using a visual CPT task, where healthy control subjects also showed poorer performance associated with greater local cortical activity, but euthymic patients with bipolar disorder had performance that was positively associated with the activity of several frontotemporal cortical gyri, including the anterior inferior insula (Strakowski et al 2004).

Possible Role of Negative Affect

The anterior cingulate and insular cortices have both been implicated in processing negative affect as well as cognition (Rémy et al 2003). We have observed (London et al 2004) that rCMRglc of both structures in a group of MA abusers, which included most of the current subjects, was indirectly associated with trait anxiety (State-Trait Anxiety Inventory) (Spielberger 1983). As higher activity in these structures reflected lower anxiety, it may be that anxiety influenced the relationship between rCMRglc and vigilance performance and contributed to the negative correlation between CPT error rates and relative rCMRglc in these structures of MA abusers but not control subjects.

Possible Effects of Group Differences in Tissue Composition

The interaction between group and relationship of CPT errors to relative rCMRglc in the anterior cingulate cortex may be related to an effect of MA on tissue composition, as indicated by loss of gray matter volume in the cingulate cortex (Thompson et al 2004a). Nonetheless, it appears that other factors are involved, as the interactions described were manifested in both hemispheres and were more robust on the left. In contrast, the deficits in cingulate gray matter were severe in the right hemisphere and nonsignificant on the left. In addition, no significant difference in volume of the cingulate gyrus was noted, unlike the situation with the hippocampus, where the average volume was 7.8% smaller in the MA group (Thompson et al 2004a). Therefore, PET measurements of the anterior cingulate gyrus were probably not influenced by partial volume effects that would include adjacent regions (e.g., corpus callosum, adjacent gyrus).

Caveats and Conclusion

These results should be considered with some caveats. First, while comparable to other imaging studies, the study sample was small. In addition, the FDG method does not distinguish between neuronal systems within an area. Finally, although the groups matched well on most categories, most of the MA abusers but none of the control subjects were tobacco smokers. One concern is the potential for effects of smoking abstinence on the day of the PET scan, when participants abstained from smoking for 2 to 4 hours before testing. Nonetheless, no significant effects on performance of a vigilance task by smokers were observed at 2, 4, and 8 hours of smoking deprivation, although an increase in errors of commission occurred after 24 hours (Hatsukami et al 1989). It therefore appears unlikely that nicotine withdrawal effects produced the effects that we now report, but there still may be group differences unrelated to withdrawal.

Our findings support the view that previously shown functional deficits in the anterior cingulate gyrus and insula of chronic MA abusers during early abstinence, as well as structural deficits in their hippocampi, also underlie cognitive vigilance deficits in these individuals. Given the importance of sustained attention in behavioral treatment for MA dependence, the present findings clarify a clinical challenge and underscore the need for pharmacological treatment for MA users in the early stages of abstinence, when retention in treatment is critical.

We gratefully acknowledge support from the National Institutes of Health (Grants RO1 DA 15179 [to EDL], RR12169, RR08655, and MOI RR 00865 and contract 1 Y01 DA 50038 [to EDL, WL]) and contributions by Leila Khenissi to image analysis. The Ahmanson-Lovelace Brain Mapping Center, where imaging data were collected, is supported by the Brain Mapping Medical Research Organization, the Brain Mapping Support Foundation, the Pierson-Lovelace Foundation, the Ahmanson Foundation, the Tamkin Foundation, the Jennifer Jones-Simon Foundation, the Capital Group Companies Charitable Foundation, the Robson Family, and the Northstar Fund.

Benedict RH, Shucard DW, Santa Maria MP, Shucard JL, Abara JP, Coad ML, et al (2002): Covert auditory attention generates activation in the rostral/dorsal anterior cingulate cortex. *J Cogn Neurosci* 14:637–645.

Benedict RHB, Lockwood AH, Shucard JL, Shucard DW, Wack D, Murphy BW (1998): Functional neuroimaging of attention in the auditory modality. *Neuroreport* 9:121–126.

Bush G, Luu P, Posner MI (2000): Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci* 4:215–222.

Cabeza R, Nyberg L (2000): Imaging cognition II: An empirical review of 275 PET and fMRI studies. *J Cogn Neurosci* 12:1–47.

Caldwell J, Dring LG, Williams RT (1972): Metabolism of [^{14}C]methamphetamine in man, the guinea pig, and the rat. *Biochem J* 129:11–22.

Carter CS, Braver TS, Barch DM, Botvinick MM, Noll D, Cohen JD (1998): Anterior cingulate cortex, error detection, and the online monitoring of performance. *Science* 280:747–749.

Cohen RM, Semple WE, Gross M, King AC, Nordahl TE (1992): Metabolic brain pattern of sustained auditory discrimination. *Exp Brain Res* 92:165–172.

Cohen RM, Semple WE, Gross M, Nordahl TE, DeLisi LE, Holcomb HH, et al (1987): Dysfunction in a prefrontal substrate of sustained attention in schizophrenia. *Life Sci* 40:2031–2039.

Corbetta M, Miezin FM, Shulman GL, Petersen SE (1993): A PET study of visuospatial attention. *J Neurosci* 13:1202–1226.

Denckla MB (1985): Revised neurological examination for subtle signs. *Psychopharmacol Bull* 21:773–800.

Devinsky O, Morrell MJ, Vogt BA (1995): Contributions of anterior cingulate cortex to behaviour. *Brain* 118:279–306.

First MB, Gibbon M, Spitzer RL, Williams JBW, Benjamin LS (1997): *Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II): User's Guide.* Washington, DC: American Psychiatric Press.

First MB, Spitzer RL, Gibbon M, Williams J (1996): *Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition (SCID-IP, Version 2.0)*. New York: Biometrics Research Department, New York State Psychiatric Institute.

Friston KJ, Ashburner J, Poline JB, Frith CD, Heather JD, Frackowiak RSJ (1995a): Spatial registration and normalization of images. *Hum Brain Mapp* 2:165–189.

Friston KJ, Holmes AP, Worsley KJ, Poline JP, Frith CD, Frackowiak RSJ (1995b): Statistical parametric maps in functional imaging: A general linear approach. *Hum Brain Mapp* 2:189–210.

George MS, Ketter TA, Parekh PI, Rosinsky N, Ring H, Casey BJ, et al (1994): Regional brain activity when selecting a response despite interference: An H2150 PET study of the Stroop and emotional Stroop. *Hum Brain Mapp* 1:194–209.

Green DM, Swets JA (1966): *Signal Detection Theory and Psychophysics*. New York: Wiley.

Hatsukami D, Fletcher L, Morgan S, Keenan R, Amble P (1989): The effects of varying cigarette deprivation duration on cognitive and performance tasks. *J Subst Abuse* 1:407–416.

Heinze HJ, Mangun GR, Burchert W, Hinrichs H, Scholz M, Munte TF, et al (1994): Combined spatial and temporal imaging of brain activity during visual selective attention in humans. *Nature* 372:543–546.

Ito S, Stuphorn V, Brown JW, Schall JD (2003): Performance monitoring by the anterior cingulate cortex during saccade countermanding. *Science* 302:120–122.

Kalechstein AD, Newton TF, Green M (2003): Methamphetamine dependence is associated with neurocognitive impairment in the initial phases of abstinence. *Neurophysiol Clin* 15:215–220.

La Berge D, Buchsbaum MS (1990): Positron emission tomographic measurements of pulvinar activity during an attention task. *J Neurosci* 10: 613–619.

London ED, Simon SL, Berman SM, Mandelkern MA, Lichtman AM, Bramen J, et al (2004): Mood disturbances and regional cerebral metabolic abnormalities in recently abstinent methamphetamine abusers. *Arch Gen Psychiatry* 61:73–84.

Maguire EA, Gadian DG, Johnsrude IS, Good CD, Ashburner J, Frackowiak RSJ, et al (2000): Navigation-related structural change in the hippocampi of taxi drivers. *Proc Natl Acad Sci U S A* 97:4398–4403.

Mazziotta J, Toga A, Evans A, Fox P, Lancaster J, Zilles K, et al (2001): A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). *Philos Trans R Soc Lond B Biol Sci* 356:1293–1322.

McCann UD, Wong DF, Yokoi F, Villemagne V, Dannals RF, Ricaurte GA (1998): Reduced striatal dopamine transporter density in abstinent methamphetamine and methcathinone users: Evidence from positron emission tomography studies with [^{11}C]WIN-35,428. *J Neurosci* 18:8417–8422.

McLellan AT, Kushner H, Metzger D, Peters R, Smith I, Grissom G, et al (1992): The fifth edition of the Addiction Severity Index. *J Subst Abuse Treat* 9:199–213.

Narr KL, Van Erp TGM, Cannon TD, Woods RP, Thompson PM, Jang S, et al (2002): A twin study of genetic contributions to hippocampal morphology in schizophrenia. *Neurobiol Dis* 11:83–95.

Nordahl TE, Salo R, Leamon M (2003): Neuropsychological effects of chronic methamphetamine use on neurotransmitters and cognition: A review. *J Neuropsychiatry Clin Neurosci* 15:317–325.

Nuechterlein KH (1991): Vigilance in schizophrenia and related disorders. In: Steinhauer SR, Gruzelier JH, Zubin J, editors. *Neuropsychology, Psychophysiology and Information Processing,* 5th ed. Amsterdam: Elsevier 397–433.

Pardo JV, Fox PT, Raichle ME (1991): Localization of a human system for sustained attention by positron emission tomography. *Nature* 349:61–64.

Pardo JV, Pardo PJ, Janer KW, Raichle ME (1990): The anterior cingulate cortex mediates processing selection in the Stroop attentional conflict paradigm. *Proc Natl Acad Sci U S A* 87:256–259.

Paulus MP, Hozack N, Frank L, Brown GG, Schuckit MA (2003): Decision making by methamphetamine-dependent subjects is associated with error-rate-independent decrease in prefrontal and parietal activation. *Biol Psychiatry* 53:65–74.

Paulus MP, Hozack NE, Zauscher BE, Frank L, Brown GG, Braff DL, et al (2002): Behavioral and functional neuroimaging evidence for prefrontal dysfunction in methamphetamine-dependent subjects. *Neuropsychopharmacology* 26:53–63.

Phelps ME, Huang SC, Hoffman EJ, Selin C, Sokoloff L, Kuhl DE (1979): Tomographic measurement of local cerebral glucose metabolic rate in humans with (F-18)2-fluoro-2-deoxy-D-glucose: Validation of method. *Ann Neurol* 6:371–388.

Reivich M, Kuhl D, Wolf A, Greenberg J, Phelps M, Ido T, et al (1979): The [^{18}F]fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man. *Circ Res* 44:127–137.

Rémy F, Frankenstein UN, Mincic A, Tomanek B, Stroman PW (2003): Pain modulates cerebral activity during cognitive performance. *Neuroimage* 19:655–664.

Riccio CA, Reynolds CR, Lowe P, Moore JJ (2002): The continuous performance test: A window on the neural substrates for attention? *Arch Clin Neuropsychol* 17:235–272.

Salo R, Nordahl TE, Possin K, Leamon M, Gibson DR, Galloway GP, et al (2002): Preliminary evidence of reduced cognitive inhibition in methamphetamine-dependent individuals. *Psychiatry Res* 111:65–74.

Seidman LJ, Breiter HC, Goodman JM, Goldstein JM, Woodruff PWR, O'Craven K, et al (1998): A functional magnetic resonance imaging study of auditory vigilance with low and high information processing demands. *Neuropsychology* 12:505–518.

Sekine Y, Iyo M, Ouchi Y, Matsunaga T, Tsukada H, Okada H, et al (2001): Methamphetamine-related psychiatric symptoms and reduced brain dopamine transporters studied with PET. *Am J Psychiatry* 158:1206–1214.

Sekine Y, Minabe Y, Ouchi Y, Takei N, Iyo M, Nakamura K, et al (2003): Association of dopamine transporter loss in the orbitofrontal and dorsolateral prefrontal cortices with methamphetamine-related psychiatric symptoms. *Am J Psychiatry* 160:1699–1701.

Sim T, Simon SL, Domier C, Richardson K, Rawson R, Ling W (2002): Cognitive deficits among methamphetamine users with attention deficit hyperactivity disorder symptomology. *J Addict Dis* 21:75–89.

Simon SL, Domier C, Sim T, Richardson K, Rawson R, Ling W (2002): Cognitive performance of current methamphetamine and cocaine abusers. *J Addict Dis* 21:61–74.

Spielberger CD (1983): *Manual for the State-Trait Anxiety Inventory (Form Y)*. Palo Alto, CA: Consulting Psychologists Press.

Strakowski SM, Adler CM, Holland SK, Mills N, DelBello MP (2004): A preliminary fMRI study of sustained attention in euthymic, unmedicated bipolar disorder. *Neuropsychopharm* 29:1734–1740.

Sturm W, Longoni F, Fimm B, Dietrich T, Weis S, Kemna S, et al (2004): Network for auditory intrinsic alertness: A PET study. *Neuropsychologia* 42:563–568.

Thompson PM, Hayashi K, Simon SL, Geaga JA, Hong MS, Sui Y, et al (2004a): Structural abnormalities in the brains of human subjects who use methamphetamine. *J Neurosci* 24:6028–6036.

Thompson PM, Hayashi KM, de Zubicaray G, Janke AL, Rose SE, Semple J, et al (2003): Dynamics of gray matter loss in Alzheimer's disease. *J Neurosci* 23:994–1005.

Thompson PM, Hayashi KM, de Zubicaray GI, Janke AL, Rose SE, Semple J, et al (2004b): Mapping hippocampal and ventricular change in Alzheimer's disease. *Neuroimage* 22:1–13.

Volkow ND, Chang L, Wang GJ, Fowler JS, Franceschi D, Sedler MJ, et al (2001a): Higher cortical and lower subcortical metabolism in detoxified methamphetamine abusers. *Am J Psychiatry* 158:383–389.

Volkow ND, Chang L, Wang G-J, Fowler JS, Franceschi D, Sedler MJ, et al (2001b): Loss of dopamine transporters in methamphetamine abusers recovers with protracted abstinence. *J Neurosci* 21:9414–9418.

Volkow ND, Chang L, Wang G-J, Fowler JS, Leonido-Yee M, Franceschi D, et al (2001c): Association of dopamine transporter reduction with psychomotor impairment in methamphetamine abusers. *Am J Psychiatry* 158:377–382.

Wang G-J, Volkow ND, Chang L, Miller E, Sedler M, Hitzemann R, et al (2004): Partial recovery of brain metabolism in methamphetamine abusers after protracted abstinence. *Am J Psychiatry* 161:242–248.

Woods RP, Cherry SR, Mazziotta JC (1992): Rapid automated algorithm for aligning and reslicing PET images. *J Comput Assist Tomogr* 16:620–633.