ORIGINAL ARTICLE

Neural Activation Patterns of Methamphetamine-Dependent Subjects During Decision Making Predict Relapse

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Context: Relapse is a common clinical problem in individuals with substance dependence. Previous studies have implicated a multifactorial process underlying relapse; however, the contribution of specific neural substrates has not yet been examined.

Objective: To determine whether results from functional magnetic resonance imaging (fMRI) shortly after drug cessation could predict relapse in stimulant-dependent individuals.

Participants and Design: Treatment-seeking methamphetamine-dependent males (N=46) underwent fMRI 3 to 4 weeks after cessation of drug use. Of the 40 subjects who were followed up a median of 370 days, 18 relapsed and 22 did not.

Main Outcome Measure: Blood oxygen level–dependent fMRI activation during a simple 2-choice prediction task.

Results: The fMRI activation patterns in right insular, posterior cingulate, and temporal cortex obtained early in recovery correctly predicted 20 of 22 subjects who did not relapse and 17 of 18 subjects who did. A Cox regression analysis revealed that the combination of right middle frontal gyrus, middle temporal gyrus, and posterior cingulate activation best predicted the time to relapse.

Conclusion: To our knowledge, this is the first investigation to show that fMRI can be used to predict relapse in substance-dependent individuals.

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IN 2002, ABOUT 22 MILLION AMERIcans, or 9.4% of the US population 12 years or older, were estimated to have substance abuse or dependence.[1] Among these, the prevalence with methamphetamine-related problems has more than doubled between 1991 and 1998.[1] Worldwide, more than 40 million people have used methamphetamine and other synthetic stimulants, making amphetamines and cocaine the most widely misused illicit substances after cannabis.[2] Many of these men and women develop repetitive problems with these drugs and fulfill criteria for dependence.[3]

A central characteristic of substance dependence is the relapsing nature of the disorder.[4] The return to drug use is a complex process that occurs within a year in more than 50% of people with stimulant dependence who seek treatment.[5] A multitude of factors contribute to relapse, such as the environmental context, presence of substance cues, personal coping repertoire, and an escalation of craving after experience with the drug.[6] The processes of relapse are thought to include cognitive-behavioral,[7] person-situation interactional,[8] cognitive-appraisal,[9] and outcome-expectation factors.[10,11] In comparison, neural system factors have been less well studied.

The ability to make appropriate decisions (to select the best action from a set of alternatives with uncertain outcomes) is critical for daily functioning in healthy human beings. Dysfunctional decision making may characterize substance-dependent individuals[12] and may contribute to relapse. Methamphetamine-dependent subjects tend to select actions associated with short-term gains, even when they lead to long-term losses, more often than actions with small short-term but larger long-term gains.[13] Relative to healthy volunteers, these individuals are more likely to select risky responses[14] and less likely to consider long-term sequelae of choices.[15] In addition, stimulant-dependent individuals do not appropriately take into account the probability and magnitude of reward of the available options.[16] Finally, these subjects generate perseverative response patterns when making a prediction and select actions that are more stimulus bound and less related to changes in the frequency of prediction errors.[17,18] These behavioral dysfunctions may reflect an alteration of brain circuits that are critical for decision making. Functional neuroimaging studies have revealed dysfunctions of the inferior prefrontal and dorsolateral prefrontal cortex in stimulant-dependent subjects.[19-21] It has been argued that some of these abnormalities may remit over time.[20]

The main aim of this study was to determine whether functional magnetic resonance imaging (fMRI) during a decision-making task can be used to predict relapse in treatment-seeking methamphetamine-dependent individuals. Specifically, we hypothesized that relapsing methamphetamine-dependent subjects relative to nonrelapsing individuals show less activation in inferior and dorsolateral prefrontal cortex, parietal cortex, and insula. Support for this hypothesis would provide an approach for assessing susceptibility to relapse during early treatment.

METHODS

SUBJECTS

The University of California San Diego (La Jolla), Human Research Protections Program approved this study, and each subject gave informed consent prior to participating. The 46 treatment-seeking male subjects all met criteria for current (ie, at least prior 6 months) dependence on methamphetamine according to *DSM-IV* as gathered from face-to-face interviews using the Structured Clinical Interview for *DSM-IV*.[3,22] These individuals were not dependent on any other drug or alcohol but could fulfill criteria for abuse. Twelve subjects had comorbid marijuana abuse and 14 had alcohol abuse. All men had voluntarily entered and completed a 28-day inpatient alcohol and drug treatment program at the San Diego Veterans Affairs Medical Center, which is based on a cognitive-behavioral model and includes a 12-step component with intense daily group sessions, education, and regularly scheduled Alcoholics Anonymous meetings. All individuals are randomly tested for drugs and presence of alcohol; any positive screen resulted in immediate discharge from the program. At the time of scanning, participants were abstinent from methamphetamine for 27.6 days (SD=9.5; range, 14-51 days) and had used methamphetamine for 16.0 years (SD=9.1; range, 3-34 years).

PSYCHIATRIC ASSESSMENTS

A comprehensive assessment was obtained to determine whether performance on the decision-making task or fMRI activation patterns at baseline were related to patients' psychiatric symptom profiles. Interview-based symptomatic assessment was based on the Hamilton Depression Rating Scale,[23] Brief Psychiatric Rating Scale,[24] and the Young Mania Rating Scale.[25]

fMRI TASK

The 2-choice prediction task has been described in detail elsewhere.[26] Briefly, subjects were instructed to "predict" where a stimulus would appear on a computer screen. Unbeknownst to the participants, the outcome for each trial was predetermined in such a way that individuals "correctly predict" 50% of all trials. To isolate the brain activation due to the decision-making process, a comparison task was used during which subjects were asked to push a button to acknowledge a target on the screen. The key difference between these 2 tasks was that during the prediction task, the subject did not know the correct response in advance and had to decide in the presence of uncertainty using the previous responses, stimuli, and outcomes. In comparison, during the response task, the subject knew the correct answer before selecting a response, decided in the presence of certainty, and did not need to use the sequences of previous responses or outcomes.

fMRI PROTOCOL AND IMAGE ANALYSIS PATHWAY

Magnetic resonance images were obtained using a 1.5-T, whole-body system (Siemens, Erlangen, Germany). Anatomical T1-weighted images of the whole brain (magnetization prepared rapid acquisition gradient echo, repetition time=11.4 milliseconds, echo time=4.4 milliseconds, flip angle=10°, field of view=256 × 256, 1-mm^3 voxels) were obtained sagittally to identify the anterior and posterior commissures for coregistration of the echo planar images and transformation of the images into Talairach space.[27] Thirty-two sections of T2-weighted images were obtained in the transverse plane using gradient-recalled echo planar imaging (echo time=40 milliseconds, flip angle=90°, 64 × 64-pixel field of view=220 × 220 mm, 3-mm contiguous section thickness) every 3000 milliseconds for 112 (n=19) or 128 (n=27) repetitions yielding a voxel size of 3.43 $mm^2 \times 3$ mm.

All structural and functional image processing used the Analysis of Functional Neuroimages software package.[28] Echo planar images were coregistered using a 3-dimensional coregistration algorithm[29] that resulted in the smallest amount of image translation and rotation relative to all other images. All data were resampled to 4.0-mm^3 voxels, and a Gaussian filter with full width at half maximum of 6 mm was applied to account for individual variations in anatomical landmarks. Data for each subject were normalized to standard coordinates.[27] The voxelwise percentage signal change data (ie, signal difference between echo planar image intensity during the prediction task and the response task) were entered into a mixed model analysis of variance, which nested group (relapsers vs nonrelapsers) and subjects as a random factor. A threshold-adjustment method based on Monte-Carlo simulations guarded against identifying false-positive areas of activation,[30] and labels for brain activation foci were confirmed using the Talairach Daemon software.[31]

FOLLOW-UP

Participants were contacted 1 year after the imaging session. Several approaches that have been successful in large-scale longitudinal studies[32] were used. For example, individuals were contacted by telephone or mail 12 months after the initial evaluation, using addresses of friends or family members or the Department of Motor Vehicle records to locate them. Despite these efforts, 6 individuals could not be reached for follow up. Four subjects who were unable to complete in-person or telephone interviews returned questionnaires by mail. Sobriety was assessed using a questionnaire based on the Semi-Structured Assessment for the Genetics of Alcoholism,[33] focusing on the use of methamphetamines during the interval between the neuroimaging evaluation and date of the follow-up. Relapse was defined as any use of methamphetamine during any time after discharge from the inpatient unit, with the date of relapse defined as the day of first use. No other substance use was considered. The median duration of the follow-up interval for the 40 individuals for whom follow-up data were available was 370 days (SD = 203.3; range, 360-967 days).

STATISTICAL ANALYSIS

Several analyses were carried out to determine the degree to which brain activation 1 month after cessation of drug use predicted relapse. The receiver operating characteristic curves were determined for each functional region of interest. Two exploratory analyses were carried out to determine whether activation patterns at baseline predicted relapse at follow-up. A stepwise linear discriminant function analysis (F_{enter}: $P<.05$) was computed with relapse as the dependent measure and the activation patterns in the areas that differed across relapsers and nonrelapsers as independent measures. A cross-validation procedure using a leave-1-out classification method (predictions were generated by resampling with 1 subject removed) was used to determine sensitivity and specificity of the activation patterns to predict relapse. Finally, a stepwise Cox regression analysis (F_{enter}: $P<.05$) with time to relapse as the dependent measure and activation in the regions that differentiated relapsers from nonrelapsers as independent measures was used to determine whether the activation patterns at baseline were able to predict the time to relapse. For the Cox regression analyses, time zero was taken as the sobriety date before entering the alcohol and drug treatment program and relapse was defined by the date of first use.

RESULTS

BEHAVIORAL CHARACTERISTICS OF RELAPSERS VS NONRELAPSERS

During the follow-up period, 18 of 40 subjects relapsed a median of 279 days after initial testing (SD = 214; range, 36-820 days) (**Figure 1**). None of the sociodemographic characteristics, baseline symptom indicators, use characteristics, or behavioral measures on the 2-choice prediction task significantly differentiated those who relapsed during the follow-up period vs those who did not (**Table 1**). Specifically, both nonrelapsers and relapsers generated nonrandom sequences of responses as evidenced by significantly more win-stay (nonrelapsers, $t_{17}=2.63$; $P=.01$; relapsers, $t_{17}=4.65$; $P<.01$) as well as lose-shift (nonrelapsers, $t_{17}=2.42$; $P=.03$; relapsers, $t_{17}=3.85$; $P<.01$) consistent responses than would be expected by chance. There were no significant differences between the groups except relapsers had higher scores on the Young Mania Rating Scale (ie, exhibited more symptoms consistent with hypomania or mania at time of fMRI testing); however the Young Mania Rating Scale scores were not correlated with any brain activation during the 2-choice prediction task.

FUNCTIONAL NEUROIMAGING CHARACTERISTICS

Similar to previous studies,[34] bilateral prefrontal cortex, striatum, posterior parietal cortex, and anterior insula were more active during the 2-choice prediction task relative to the 2-choice response task.[35] Within these regions, 9 areas differentiated relapsing and nonrelapsing subjects (**Figure 2**) (**Table 2**), including prefrontal, parietal, and insular cortex. Nonrelapsing individuals showed more activation in these areas relative to relapsing individuals (Figure 2). The difference in activation patterns was not due to differences in motion between relapsers and nonrelapsers during imaging ($t_{roll38}=0.48$; $P=.63$; $t_{pitch24}=0.67$; $P=.50$; $t_{yaw24}=0.90$; $P=.37$) and were not correlated with motion parameters obtained during magnetic resonance imaging.

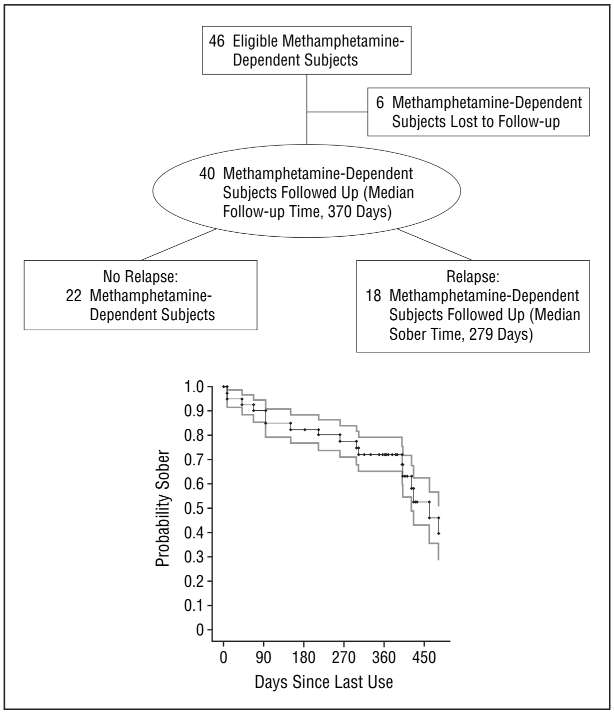

Figure 1. Flowchart of all eligible participants and associated sobriety survival function.

RELATIONSHIP BETWEEN RELAPSE AND fMRI FINDINGS

For each area with a specificity of at least 83.3% (correctly predicting 15 of 18 individuals who relapsed), sensitivity ranged from 54.5% (12 of 22 correctly predicted to not relapse) to 90.9% (20 of 22 correctly predicted to not relapse) (Figure 2). The stepwise discriminant function (**Table 3**), with the areas of differences between relapsers and nonrelapsers as the independent measure and relapse status as the dependent measure, revealed that right insula, right posterior cingulate, and right middle temporal gyrus response best differentiated between relapsing and nonrelapsing methamphetamine-dependent subjects (Wilks $\lambda=0.37$; $\chi^2=36.5$; $P<.01$). As presented in **Table 4**, cross-validation analysis was able to correctly predict 19 of 22 individuals who did not relapse (but predicted 3 individuals to relapse who did not) and predicted 17 of 18 who relapsed (94.4% sensitivity; 86.4% specificity). The stepwise Cox regression analysis (**Table 5**) showed that time to relapse was best predicted by right middle frontal gyrus, right middle temporal gyrus, and right posterior cingulate cortex activation. In combination, low activation in these areas at baseline

Table 1. Characteristics of Methamphetamine-Dependent Participants*

Characteristic	Nonrelapsers (n = 22)	Relapsers (n = 18)	Test Value	*P* Value
Sociodemographics				
Age, y	40.3 ± 8.8	41.9 ± 9.0	*t* = 0.56	.57
Race/ethnicity, No. of participants				
White	15	12	$\chi^2 = 3.16$	.67
African American	1	3		
Latino	1	1		
Other	5	2		
Marital status, No. of participants				
Married	1	2	$\chi^2 = 5.57$	.13
Divorced	12	10		
Separated	5	0		
Never married	4	6		
Education, y	12.9 ± 1.2	13.5 ± 1.0	*t* = 1.74	.09
No. of children	1.5 ± 2.0	0.8 ± 0.9	*t* = 1.41	.16
Use characteristics				
Use duration, y	14.9 ± 10.0	17.3 ± 8.0	*t* = 0.81	.41
Sober days before imaging	27.4 ± 8.3	27.8 ± 11.0	*t* = 0.14	.88
Current alcohol/marijuana abuse, No. of participants	5	7	*t* = 1.2	.31
Follow-up characteristics				
Follow-up duration, d	437 ± 165	440 ± 304	*t* = 0.04	.96
Marijuana use during follow-up, No. of participants	1	2	*t* = 0.80	.66
Cocaine use during follow-up, No. of participants	1	0	*t* = 1.03	.59
Symptom ratings				
HDRS 21-item[23]	7.1 ± 7.8	10.2 ± 7.6	*t* = 1.23	.22
BPRS[24]	27.3 ± 7.9	30.4 ± 6.8	*t* = 1.25	.21
YMRS[25]	1.7 ± 2.7	5.4 ± 6.9	*t* = 2.20	.03
Behavioral measures				
Response latency, ms	808 ± 361	794 ± 794	*t* = 0.13	.89
Switching rate	0.50 ± 0.12	0.49 ± 0.10	*t* = 0.10	.91
Win-stay fraction	0.61 ± 0.19	0.67 ± 0.15	*t* = 1.01	.31
Lose-shift fraction	0.62 ± 0.22	0.67 ± 0.18	*t* = 0.73	.46

Abbreviations: BPRS, Brief Psychiatric Rating Scale; HDRS, Hamilton Depression Rating Scale; YMRS, Young Mania Rating Scale.
*Values expressed as mean ± SD unless otherwise indicated.

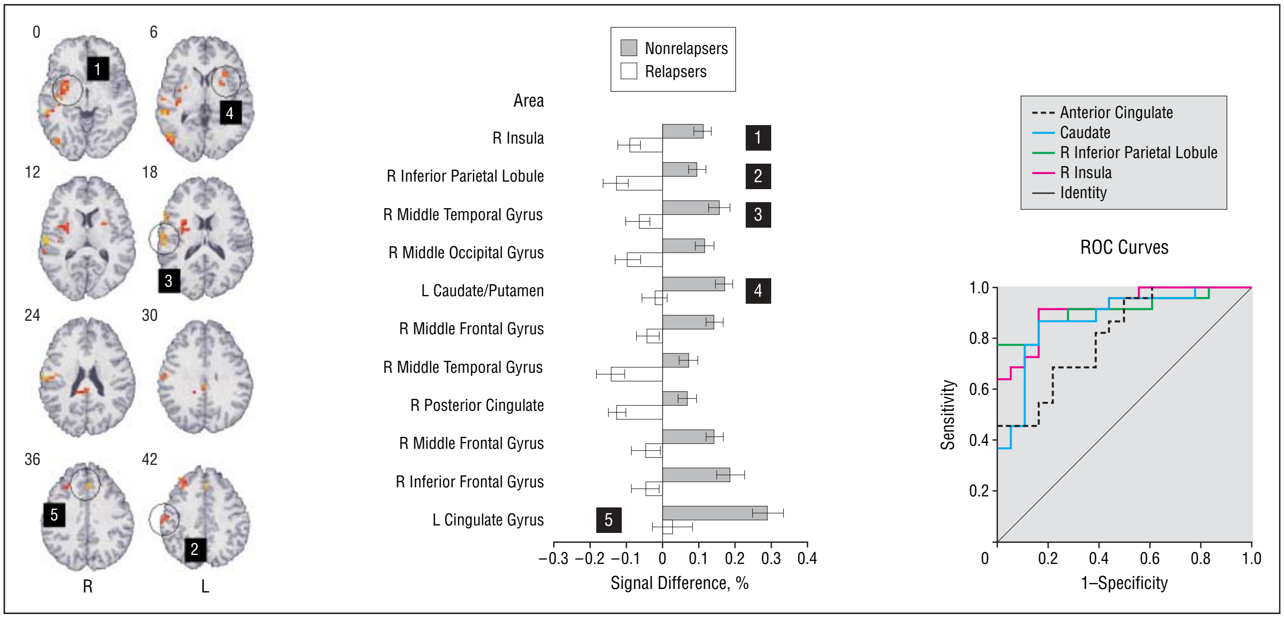

Figure 2. Areas of differences in activation between relapsing and nonrelapsing methamphetamine-dependent subjects. Numeric results are shown as percentage signal change of functional clusters. All graphical results are presented as volume-thresholded t maps of the planned comparisons across the different conditions. The numbers to the left of each image in the left-hand column are z coordinates from the Talairach atlas; the numbers in the black boxes correspond to the labels along the bar graphs. R indicates right; L, left; and ROC, receiver operating characteristic.

Table 2. Talairach Coordinates[27] and Descriptions of Areas That Differentiated Methamphetamine-Dependent Nonrelapsers From Relapsers*

Volume	Left/Right	Anterior/Posterior	Inferior/Superior	Description	Brodmann Area	t_{38} Value	Sensitivity, %	Specificity, %
4544	34	−7	1	R insula	13	5.39	90.9	83.3
3456	54	−18	20	R inferior parietal lobule	40	5.30	86.4	83.3
1280	54	−36	5	R middle temporal gyrus	22	4.88	90.9	83.3
1280	45	−72	4	R middle occipital gyrus	19	5.04	81.8	83.3
1088	−25	11	7	L caudate/putamen/insula	13	4.64	86.4	83.3
1024	16	−1	52	R middle frontal gyrus	6	4.67	86.4	83.3
832	53	−9	−18	R middle temporal gyrus	21	4.73	81.8	83.3
768	4	−34	25	R posterior cingulate	23	5.28	81.8	88.9
704	29	28	39	R middle frontal gyrus	8/9	4.27	68.2	83.3
512	54	12	18	R inferior frontal gyrus	45	4.19	59.1	83.3
512	−4	25	36	L cingulate gyrus	32	3.83	54.5	83.3

Abbreviations: L, left; R, right.
*Sensitivity and specificity are shown for each area, with more than 15 of 18 correctly predicted relapsers.

Table 3. Coefficients and Statistics for the Stepwise Discriminant Function Analysis

Step	Area	Coefficient	F Statistic	P Value
1	Right insula	0.52	29.02	<.001
2	Right posterior cingulate	0.46	25.34	<.001
3	Right middle temporal gyrus	0.59	20.68	<.001

Table 4. Discriminant Function Analysis Results and Cross-validation Predictions*

	Predicted Group Membership, No. (%)		Negative/Positive Predictive Value
	No Relapse	Relapse	
Original grouped cases			
Nonrelapsers	20 (90.9)	2 (9.1)	0.95
Relapsers	1 (5.6)	17 (94.4)	0.89
Cross-validation grouped cases			
Nonrelapsers	19 (86.4)	3 (13.6)	0.95
Relapsers	1 (5.6)	17 (94.4)	0.85

*Of original grouped cases, 92.5% were correctly classified; of cross-validated grouped cases, 90% were correctly classified.

was highly predictive of time to relapse (χ^2_3=23.9; $P<.01$). Additional Cox regression and discriminant function analyses using individuals who were followed up for up to mean±SD 365±30 days yielded similarly sensitive and specific results in a stepwise discriminant function analysis (data not shown).

COMMENT

To our knowledge, this investigation provides evidence for the first time that functional neuroimaging can be used to predict relapse in individuals with methamphetamine dependence. As hypothesized, methamphetamine-dependent subjects who relapse during the follow-up interval show less activation in dorsolateral prefrontal, parietal, and temporal cortex, as well as insula, a network of structures that is critical for decision making. More importantly, the degree of predictability (ie, the high sensitivity and specificity) supports the idea that functional neuroimaging may prove to be a useful clinical tool to assess relapse susceptibility.

The neural activation differences between relapsing and nonrelapsing methamphetamine-dependent subjects are part of a system involved with the processing of decision making. Specifically, the right inferior parietal lobule, which maintains bidirectional connections to right dorsolateral prefrontal and anterior insular cortex, has been implicated in a number of processes that are part of the assessment component of decision making. These include sustained, and possibly selective, attention,[36] switching from task-relevant local to global targets,[37] and voluntary attentional control,[38] as well as the distinction between task-irrelevant and task-relevant events.[39] Thus, this area may be critical for the extraction and selection of task-relevant information and has been implicated in inhibitory control with a number of different paradigms.[40] Moreover, several studies have implicated the right inferior parietal lobule in autonomic arousal processes,[41] risk-taking decision making,[42] and guessing.[43] The right inferior parietal lobule, which integrates attentional resources to select actions (predicting the location of the stimulus) and inhibits previous prediction strategies as they relate to success or failure, may be critical for the assessment process during decision making. Therefore, proper activation during decision making is important for allocating processing resources to actions that have to compete with habitual behavior.[44] Attenuated activation by subjects who are at high risk for relapse may represent defective assessment abilities and subsequent reliance on habitual behavior. In other words, these individuals do not mount sufficient executive and/or controlled processing when making a decision.

Similarly, insula activation occurs in a wide variety of task conditions, but there is an emerging consensus that insula activation is frequently associated with the assessment of emotionally aversive states. Specifically, func-

Table 5. Statistical Results for the Stepwise Cox Regression Analysis Indicating Which Areas Best Predict Time to Relapse

Area	Coefficient	Standard Error	Wald Statistic	*P* Value	Exp(B)	(95% Confidence Interval)
Right middle frontal gyrus	−4.36	1.82	5.68	.02	.013	0-0.46
Right middle temporal gyrus	−3.38	1.66	4.10	.04	.034	0.001-0.89
Right posterior cingulate	−5.96	2.22	7.18	.007	.003	0-0.20

Abbreviation: Exp(B), the hazards ratio.

tional neuroimaging studies have shown insula-related activation during the processing of fearful[45] or disgusted[46] faces and during the anticipation of electric shocks,[47] as well as during script-evoked sad mood induction.[48] Moreover, insula activity was modulated by perceptual awareness of threat,[49] penalty,[50] or error-related processes.[44] The insular cortex appears to be important for integrating cognitive and affective information.[51] Anatomical studies in rhesus monkeys have shown that the insula receives input from both dorsolateral prefrontal and posterior parietal cortex.[52] In particular, the rostral part of the posterior parietal lobe sends efferents to the insular cortex,[53] and the insula receives projections from the amygdala.[54] Insula activation during decision-making tasks may alert the individual of expected aversive outcomes. Thus, a reduced activation in this area would be consistent with a diminished ability to differentiate between choices that lead to good vs poor outcomes, which may be a key factor in relapse.

We used a block fMRI paradigm during a simple 2-choice prediction task to assess decision making.[18,35] Although this task yields robust activations in circuits that are important for decision making, such as anterior cingulate,[55,56] anterior insula,[57] posterior parietal cortex,[58] and dorsolateral prefrontal cortex,[35] it is difficult to identify a precise component of decision making. Thus, one cannot rule out that other processes (eg, attentional dysfunction, working memory problems, or impulsivity) contribute to the observed differences. However, the lack of behavioral differences between relapsers or nonrelapsers on response latency, frequency of responses, or use of different strategies render it less likely that general attentional factors account for the neuroimaging differences. Nevertheless, future investigations will need to use event-related designs to begin to better isolate which aspect of decision making is most important for predicting relapse and accounts for the activation differences.

Methamphetamine is known to have neurotoxic effects.[59] Specifically, increased apoptosis[60] and altered concentration of *N*-acetylaspartate, a marker of neuronal integrity, in the basal ganglia[61] and in the anterior cingulate[62] support the general hypothesis that methamphetamine structurally alters the brain.[63] Therefore, it would not be surprising if long-term use affects the neural substrates important for decision making. Although the current study cannot address whether the differences between relapsing and nonrelapsing individuals are due to structural brain differences, the current results provide compelling evidence that functional differences exist and may stimulate future investigations into the underlying structural differences.

The degree of outcome predictability based on the neuroimaging findings is striking. However, several cautionary notes are necessary. First, subjects in this study were treatment-seeking male veterans with methamphetamine dependence who were included in the study only if they did not fulfill criteria for another comorbid substance dependence. Thus, it is unclear how these findings generalize to other substances of abuse or to individuals who use multiple intoxicants. Second, although the follow-up period was initially set for 1 year, we included subjects who were eventually located and studied up to 967 days later. Although the Cox regression model takes different follow-up intervals into account when calculating the factors contributing to relapse, one may argue that a more rigorous study is necessary to substantiate the current finding. Third, a limited number of variables, focused on the presence of psychiatric symptoms at baseline, were included in the assessment. It has been pointed out that models of relapse prediction should be multifactorial and should include cognitive, psychophysiological, sociodemographic or social, and psychological assessment domains.[6] Therefore, future studies will need to include these factors and begin to relate differences in these domains to brain activation patterns. Finally, stepwise regression analyses are often sensitive to the sample characteristics. Therefore, it may be beneficial to consider the statistical characteristics of individual functional regions of interest when predicting relapse. In this study, sensitivity ranged from 54% to 91%; future investigations will need to identify why different neural substrates are more predictive (ie, have high specificity and high sensitivity).

The current investigation demonstrates that functional neuroimaging may be useful for long-term clinical predictions in stimulant dependence. Altered activation during decision making may play a critical role in processes that "set the stage" for relapse.[6] Understanding the nature of these dysfunctions may ultimately help to develop new treatment approaches that are targeted to attenuate or rehabilitate these dysfunctions and to increase patients' chances for long-term sobriety.

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Correction

Errors in Byline, Author Affiliations, and Acknowledgment. In the Original Article titled "Lifetime Prevalence and Age-of-Onset Distributions of *DSM-IV* Disorders in the National Comorbidity Survey Replication," published in the June issue of the ARCHIVES (2005;62:593-602), an author's name was inadvertently omitted from the byline and author affiliations footnote on page 592, and another author's affiliation was listed incorrectly. The byline should have appeared as follows: "Ronald C. Kessler, PhD; Patricia Berglund, MBA; Olga Demler, MA, MS; Robert Jin, MA; Kathleen R. Merikangas, PhD; Ellen E. Walters, MS." The author affiliations footnote should have appeared as follows: "**Author Affiliations:** Department of Health Care Policy, Harvard Medical School, Boston, Mass (Dr Kessler; Mss Demler and Walters; and Mr Jin); Institute for Social Research, University of Michigan, Ann Arbor (Ms Berglund); and Section on Developmental Genetic Epidemiology, National Institute of Mental Health, Rockville, Md (Dr Merikangas)." On page 601, the first sentence of the acknowledgment should have appeared as follows: "The authors appreciate the helpful comments of William Eaton, PhD, and Michael Von Korff, ScD." Online versions of this article on the *Archives of General Psychiatry* Web site were corrected on June 10, 2005.