
Decision Making by Methamphetamine-Dependent Subjects Is Associated with Error-Rate-Independent Decrease in Prefrontal and Parietal Activation

Martin P. Paulus, Nikki Hozack, Lawrence Frank, Gregory G. Brown, and Marc A. Schuckit

Background: *One important aspect in decision making is how success or failure influences the selection of a response. In a previous investigation, methamphetamine-dependent subjects (MD) selected win–stay/lose–shift consistent responses than normal comparison subjects (NC), which may imply that MD are more influenced by success. This study examined whether the degree of success and the degree of predictability differentially affected MD’s decision making.*

Methods: *Using functional magnetic resonance imaging, 14 MD were compared with 14 NC while performing the two-choice prediction task at three success rates and the two-choice response task.*

Results: *The increase in win–stay/lose–shift consistent responses by MD relative to NC was independent of success rate. Irrespective of success, MD showed less task-related activation in orbitofrontal cortex (Brodmann’s area [BA] 10), dorsolateral prefrontal cortex (BA 9), anterior cingulate (BA 32), and parietal cortex (BA 7). Whereas NC showed success-related patterns of neural activation in the orbitofrontal, dorsolateral prefrontal, and parietal cortex, MD showed activation that was highest when the outcome was most unpredictable.*

Conclusions: *Our results are consistent with the hypothesis of a more rigid stimulus–response relationship during MD’s decision making, which may be due to a shift from processing “success” toward processing the degree of stimulus “predictability.”* Biol Psychiatry 2003;53:65–74 © 2003 Society of Biological Psychiatry

Key Words: Decision making, stimulant dependence, fMRI

Introduction

Decision making is a complex process and occurs whenever a person selects an action with an uncertain outcome (Tversky and Kahneman 1981). There are many components to the process of decision making, and most studies attempt to address a few of these components at a time. For example, in experimental studies of outcome-related aspects of decision making, subjects typically choose the response that is associated with the highest anticipated reinforcement (i.e., select an action that is most likely associated a “correct” outcome; Calfee and Atkinson 1966; Goulet and Barclay 1967; Ludvigson 1966). This behavior is consistent with the notion that anticipated “success” or “failure” critically influences response selection during decision making (Egelman et al 1998).

Various aspects of decision making can be dysfunctional in a number of neuropsychiatric disorders (American Psychiatric Association 1994; Mogg et al 1991; Rahman et al 1999, 2001) including substance-related syndromes (Bechara et al 2001; Grant et al 2000; Rogers et al 1999). The precise nature of the decision-making dysfunctions in subjects with substance use disorders, however, is still unclear. Several investigators have proposed that stimulant-dependent subjects are less efficient in decision making because they do not appropriately take into account the prior positive or negative outcomes. Although some have argued that stimulant-dependent subjects have an exaggerated response to success (Bechara et al 2001), others have suggested that they are less sensitive to aversive consequences (Lane and Cherek 2000). Therefore, it is important to clarify how outcome affects response selection in stimulant-dependent subjects.

Functional magnetic resonance imaging (fMRI) can be used to elucidate the role of different neural systems and their dysfunction in how outcome affects response selection during decision making. Previous neuroimaging studies using a simple two-choice decision-making paradigm have shown task-related activation in both ventromedial (Elliott et al 1999) and dorsolateral prefrontal cortex

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(Paulus et al 2001), as well as anterior cingulate activation (Elliott and Dolan 1998), an area that has been implicated in the monitoring of response conflict (Carter et al 1999). Specifically, premotor (BA 6), parahippocampal (BA 36), dorsolateral (BA 9, 46), inferior prefrontal cortex (BA 44), parietal (BA 40), and cingulate cortex (BA 25, 32) exhibit outcome-related changes in activation during decision making (Paulus et al 2002a).

Another area of brain functioning has been shown to relate to diverse aspects of decision making, although this has not been related to outcome success or failure directly. Specifically, the orbitofrontal cortex, including the ventromedial and ventrolateral prefrontal cortex, has been associated with the assessment of short-term versus long-term gains or losses (Bechara 2001). Moreover, dopaminergic modulation of the orbitofrontal cortex (Schultz et al 2000) has been implicated in the process of cumulative tallying of success and failures. An altered dopaminergic modulation of the orbitofrontal cortex in stimulant-dependent subjects is supported by findings that methamphetamine-dependent subjects show decreased D2 receptor availability (Volkow et al 2001a), dopamine transporter concentration levels (Volkow et al 2001c), and increased metabolic activation in nondopaminergic target areas (Volkow et al 2001b). Thus, one important hypothesis regarding decision-making dysfunctions in stimulant-dependent subjects is the notion that the orbitofrontal cortex may compute inadequately the cumulative outcomes of success or failure (London et al 2000; Rolls 2000; Volkow and Fowler 2000).

In a previous study using a simple two-choice prediction task, stimulant-dependent subjects showed significantly less decision-making related activation in both dorsolateral prefrontal cortex (BA 9) and orbitofrontal cortex (BA 11) and selected responses more frequently that were consistent with a win–stay/lose–shift strategy (Paulus et al 2002b). These results support the hypothesis of an altered relationship between outcome and response selection during decision making, which may involve both dorsolateral prefrontal and orbitofrontal cortex.

This investigation examined two possible processes that can account for the altered relationship between outcome and response selection during decision making in stimulant-dependent subjects. First, methamphetamine-dependent subjects may be more or less sensitive to different degrees of success or failure; this would imply that various measures of decision-making behavior and associated neural substrates should vary more or less strongly as a function of the degree of success. Second, stimulus presentation rather than outcome success or failure determines response selection during decision making by methamphetamine-dependent subjects. In this case, uniform “success” or “failure” may not differentiate methamphet-

amine-dependent from normal comparison subjects. Instead, behavioral characteristics, such as switching rate or win–stay/lose–shift consistent responses, and neural substrate activation of methamphetamine-dependent subjects should differ most from normal comparison subjects when the stimulus presentation is most uncertain, that is, when the outcome success is at chance level. The first alternative would be consistent with the notion that stimulant-dependent subjects are either more sensitive to success (Bechara et al 2001) or less sensitive to aversive consequences (Lane and Cherek 2000). In contrast, the second alternative would be consistent with the hypothesis that response selection during decision making by stimulant-dependent subjects is not driven as much by success or failure as by the degree to which the stimulus comes to control the selection of the response (Robbins and Everitt 1999).

Methods and Materials

Subjects

The University of California at San Diego Institutional Review Board approved this study (#000730), and each subject gave informed consent before participating in the study. We compared 14 male subjects meeting criteria for current stimulant dependence according to the Structured Clinical Interview for DSM-IV diagnoses (SCID-P; Spitzer et al 1992), aged 41.4 years \pm 2 (range 29–54) with 13.6 \pm 0.25 years of education (range 12–15), were compared with 14 normal comparison subjects (4 women and 10 men) aged 38.7 years \pm 1.7 (range 28–47) with 14.8 \pm .4 years of education (range 12–18). The groups did not differ in age ($t(26) = -1.07$, *ns*), but methamphetamine-dependent subjects were less educated than normal comparison subjects ($t(26) = 2.58$, $p < .05$).

Stimulant-dependent subjects had voluntarily entered the 28-day inpatient Alcohol and Drug Treatment Program (ADTP) at the San Diego Veterans Affairs Medical Center. The stimulant-dependent subjects' diagnosis was due to methamphetamine use. Of the fourteen subjects, 3 also fulfilled criteria for current cannabis abuse but not dependence. No other substance use disorder was present. At the time of testing, these subjects had been abstinent from methamphetamine for an average of 25.0 days \pm 2.7 (range 6–46 days) and had used methamphetamine an average of 16.8 \pm 2.6 years (range 4–33 years). Normal comparison subjects were recruited via advertisement in local newspapers. Only those subjects without a life-time history of Axis I DSM-IV disorders based on a structured clinical interview for DSM-IV diagnosis (First et al 1999) were asked to participate in the study.

Exclusion criteria for both normal comparison and stimulant-dependent subjects were as follows: lifetime history of dependence on alcohol, opiates, hallucinogens or PCP-like stimulants; treatment with psychotropic medication; serious medical conditions; current major depressive, bipolar, schizophrenic, posttraumatic stress, panic, or obsessive–compulsive disorder; lifetime history of antisocial personality disorder; and acute signs of withdrawal as indicated by the presence of at least two DSM-IV

withdrawal signs. In addition, urine toxicology was obtained before testing and revealed no evidence of cannabis, stimulants, sedative hypnotics, cocaine, or PCP.

Task

The two-choice prediction task has been described in detail elsewhere (Paulus 1997). Briefly, a house flanked by a person to the left and right is shown on a computer screen. The subject is instructed to “predict” whether a car will be shown on the left or right side of the computer screen and to press a left or right button. After the subject has made a response, the car is presented for 300 msec on the far left or right side, and a new trial begins immediately after. Unbeknownst to the subject, a computer program takes the response of the subject into account and determines *a priori* whether a response will be “correct” or “incorrect.”

During the fMRI session, activation by the two-choice prediction task is compared with activation obtained during a two-choice response task, which is needed to obtain activation differences in the echoplanar image that are due to decision making and not to stimulus presentation or response requirements. In the two-choice response task, the car is presented on the left or right side before the subject is asked to respond. The key difference between these two tasks is that during the two-choice prediction task, the subject does not know the correct response in advance and has to decide in the presence of uncertainty using the previous responses, stimuli, and outcomes. In comparison, during the two-choice response task the subject knows the correct answer before selecting a response, decides in the presence of certainty, and does not need to use the sequences of previous responses or outcomes.

A block-design was used in this fMRI study. The two-choice prediction task was divided into three trial blocks, each lasting 90 sec. During the first trial block, the computer program ensured that 50% of all responses were “correct” (50% error rate); likewise, during the second trial block, 20% of all responses “correctly predicted” the location of the car (80% error rate), and during the third trial block, 80% of all responses were “correct” predictions (20% error rate). To examine task-related activation for the two-choice prediction task, the two-choice response task was presented between the 50% and 20% as well as between the 20% and 80% trial blocks for 30 sec. All fMRI activations were measured as relative echoplanar signal differences between the two-choice prediction and the two-choice response task.

Behavioral Measures

For both the two-choice prediction task and the two-choice response task, three variables were recorded: 1) the choice selected by the subject (left or right), 2) the computer selected response (left or right), and 3) the number of trials per block. Based on these variables, the strategies of decision making in the presence of uncertainty were assessed by two sets of measures: 1) general response biases, that is, the number of left or right responses or stay (a left response followed by left response), versus switch (left followed by right response) responses; and 2) the degree to which the current response is determined by the

previous response, the previous stimulus, or a combination of both is quantified by mutual information measures (Herzel and Grosse 1995). These mutual information measures quantify the degree to which prior response, stimulus, and outcome are related to the current response above chance level.

fMRI Protocol and Image Analysis Pathway

Magnetic resonance images were obtained using a 1.5-Tesla whole-body system (Siemens, Erlangen). Anatomic T1-weighted images of the whole brain (MPRAGE, TR = 11.4 msec, TE = 4.4 msec, flip angle = 10°, field of vision [FOV] = 256 × 256, 1 mm³ voxels) were obtained sagittally to identify the anterior–posterior commissure, to coregister the echoplanar image, and to transform the images into Talairach space (Talairach and Tournoux 1988). Thirty-two slices of T2*-weighted images were obtained in the transverse plane using gradient-recalled echo planar imaging (TE = 40 msec, flip angle = 90°, 64 × 64 pixel, FOV = 220 × 220 mm, 3 mm contiguous slice thickness) every 3000 msec for 112 repetitions, yielding a voxel size of 3.43 mm × 3.43 mm × 3 mm to minimize signal dropout related to magnetic susceptibility variations in the orbitofrontal cortex.

All structural and functional image processing was done using the Analysis of Functional Neuroimages (AFNI) software package (Cox 1996). Echoplanar images were coregistered using a three-dimensional coregistration algorithm to the echoplanar image that resulted in the smallest amount of image translation and rotation relative to all other images. The main dependent measure was the signal difference between echoplanar image intensity during the two-choice prediction task and the intensity during the two-choice response task averaged across three delay times. Multiple regression analysis was used to quantify the fMRI time series data (Courtney et al 1997). Three regressors were used to measure echoplanar signal change during the 50%, 80%, and 20% error rate conditions, respectively, and the AFNI program 3dDeconvolve was used to calculate the estimated voxelwise impulse response function using a time shift of 1–3 TR (i.e., 3–9 sec). The relative signal change was computed by dividing the regressor coefficients for each time shift by the zeroth order regressor coefficient, which measures the average signal intensity during the two-choice response task. A Gaussian filter with full width half maximum (FWHM) 3.4 mm was applied to voxelwise percent signal change data to account for individual variations of the anatomic landmarks. Data of each subject were normalized to Talairach coordinates. The voxelwise percent signal change data were entered into a mixed model analysis of variance (ANOVA), which was nested for group (methamphetamine-dependent subjects, normal comparison subjects) with task condition (20%, 50%, 80% error rate) as a fixed factor and subjects as a random factor. A threshold adjustment method based on Monte Carlo simulations was used to guard against identifying false positive areas of activation (Forman et al 1995). Based on these simulations, it was determined that a voxelwise *a priori* probability of 0.05 would result in a corrected clusterwise activation probability of 0.05 if a minimum volume of 350 μ L and a connectivity radius of 3.43 mm was considered. This statistical threshold was applied to all subsequent analyses and corresponds to an uncorrected voxelwise probability of $p <$

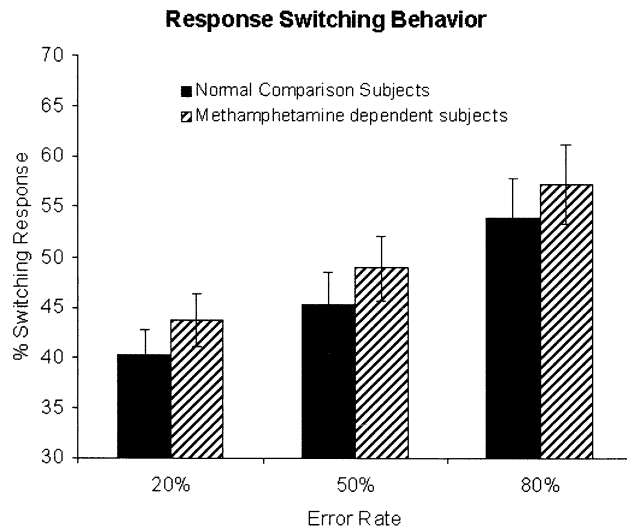


Figure 1. Mean response switching rate and SEM as a function of error rate during the two-choice prediction task by methamphetamine-dependent and normal comparison subjects.

8.83×10^{-6} . Numerical results are shown as percent signal change of functional clusters as defined by the above mentioned cluster conditions. All graphic results are presented as volume-thresholded *t* maps of the planned comparisons across the different conditions. Labels for brain activation foci were obtained in Talairach coordinates using the Talairach Demon software (Lancaster et al 2000).

Statistical Analysis

All behavioral analyses were carried out using a mixed model ANOVA (fixed factor: task conditions, random factor: subjects) using SPSS 10.0 (Norusis 1990) with the Greenhouse-Geisser (GG) corrections to adjust the degrees of freedom for the correlations of within-subjects designs (violations of sphericity). Education was entered as a covariate into an ANOVA analyses. The planned comparisons were evaluated using the least significant difference (LSD) post hoc analysis.

Results

Behavioral Measures

The first set of analyses examined the effect of “success” or “failure” on simple behavioral characteristics during the two-choice prediction task. These analyses revealed no differences between methamphetamine-dependent and normal comparison subjects. The switching rate (i.e., selecting alternative responses during subsequent trials) was directly proportional to the error rate for both methamphetamine-dependent and normal comparison subjects (Figure 1). Accordingly, response switching was significantly affected by the error rate [$F_{GG}(2,52) = 11.58, p <$

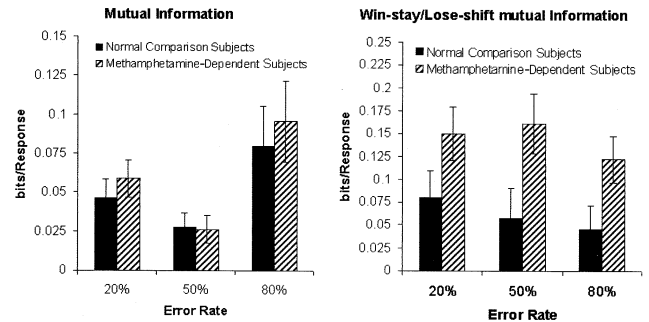


Figure 2. Mean and SEM for mutual information and win-stay/lose-shift mutual information as a function of error rate for methamphetamine-dependent and normal comparison subjects.

.01] but did not differ between groups [$F_{GG}(1,26) = 2.52, ns$] or differentially according to error rate [$F_{GG}(2,52) = 0.78, ns$]. The number of responses during the two-choice prediction and two-choice response task was examined to rule out the possibility that activation differences were related to differences in simple motor responses. Methamphetamine-dependent subjects made 89.9 ± 6.65 responses and controls made 83.8 ± 6.65 during a 90-sec two-choice prediction task block [$F(1,26) = 2.33, ns$]. In comparison, methamphetamine-dependent subjects generated 31.2 ± 1.35 responses and control subjects responded 30.6 ± 1.35 during a 30-sec two-choice response task block [$F(1,26) = 0.16, ns$]. The error rate [$F_{GG}(2,52) = 2.40, ns$] did not significantly affect the number of responses during the two-choice prediction task.

The second set of analyses examined whether outcome predictability (“predictably correct” or “predictably incorrect” vs. being “correct” at chance level) affected the predictability of the behavioral sequences. This analysis revealed no differences across groups. Specifically, there was a U-shaped relationship in both groups between error rate and response rigidity as measured by the mutual information, which quantifies the degree to which the previous response predicts the current response (Figure 2). Thus, mutual information differed significantly across error rates [$F_{GG}(2,52) = 6.09, p < .05$] but not across groups [$F(1,26) = 0.465, ns$]. Responses were more predictable when the error rate was either low (20%, LSD $< .05$) or high (80%, LSD $< .01$) relative to a chance level error rate.

The third set of analyses determined whether the degree of “success” or “failure” affected outcome-related response strategies. This analysis revealed an error rate independent increase in win-stay/lose-shift consistent responses in methamphetamine-dependent subjects (Figure 2). The win-stay/lose-shift mutual information, which measures the degree to which success or failure of the last response predicts the next response, was significantly

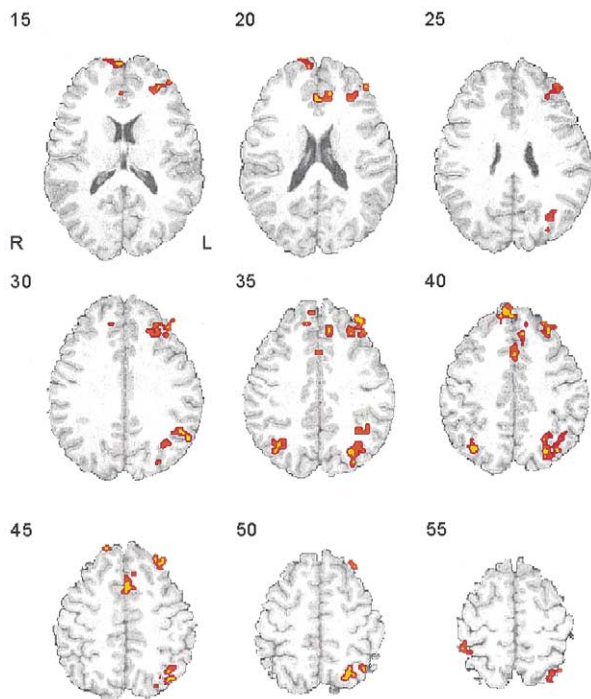


Figure 3. Main effect of group: axial sections in radiologic convention (right corresponds to the left side of the brain) of cluster-thresholded t-maps of the difference in activation between normal comparison subjects and methamphetamine-dependent subjects. Numbers indicate z coordinate of the axial section in Talairach space.

higher for methamphetamine-dependent relative to normal comparison subjects [$F(1,26) = 6.01, p < .05$]. This effect was independent of error rate [$F_{GG}(2,52) = 1.23, ns$] and was not more or less pronounced in methamphetamine-dependent subjects at high or low error rates [$F_{GG}(2,52) = 0.35, ns$].

fMRI Results

Methamphetamine-dependent subjects showed less task-related activation in bilateral inferior prefrontal cortex (BA 10, medial frontal gyrus) and dorsolateral prefrontal cortex (BA 8,9; Figure 3, Table 1) independent of error rate. In addition to these prefrontal differences, methamphetamine-dependent subjects showed less task-related activation in bilateral parietal cortex (BA 7/19), left postcentral gyrus (BA 5), and left superior temporal gyrus (BA 39).

Different error rates had significant effects on task-related activation in both methamphetamine-dependent and normal comparison subjects in the right insula (BA 13), right inferior (BA 44, 45), right middle frontal (BA 9) gyrus, and in left middle frontal gyrus (BA 6, 9; Figure 4, Table 1). With exception of task-related activation in the

left middle frontal gyrus, methamphetamine-dependent and normal comparison subjects showed more task-related activation at low error rates and the least activation when the stimulus was most unpredictable (i.e., at 50% error rates; Figure 5, top).

Methamphetamine-dependent relative to normal comparison subjects showed an altered response to different error rates in several areas (Table 1, Figure 6). Specifically, methamphetamine-dependent subjects showed more task-related activation when the outcome was most unpredictable (50% error rate), and significantly less activation during both high and low error rates (Figure 5, bottom right). In contrast, normal comparison subjects showed more task-related activation when the error rate was low (Figure 5, bottom left). These group differences were observed in left insula (BA 13), inferior frontal gyrus (BA 46), middle frontal gyrus (BA 10), precuneus (BA 7), and inferior parietal lobule (BA 40) and yielded a significant group by error rate-related interaction [$F_{GG}(1,26) = 17.14, p < .01$] with a significant contrast effect across groups of success versus uncertainty [$F(1,26) = 24.26, p < .001$]. Thus, whereas most areas that are critical for decision making in normal comparison subjects were more active at low error rates (i.e., when subjects were “successfully” predicting the outcome of the stimulus), these areas were most active in methamphetamine-dependent subjects when the outcome of the stimulus was most unpredictable.

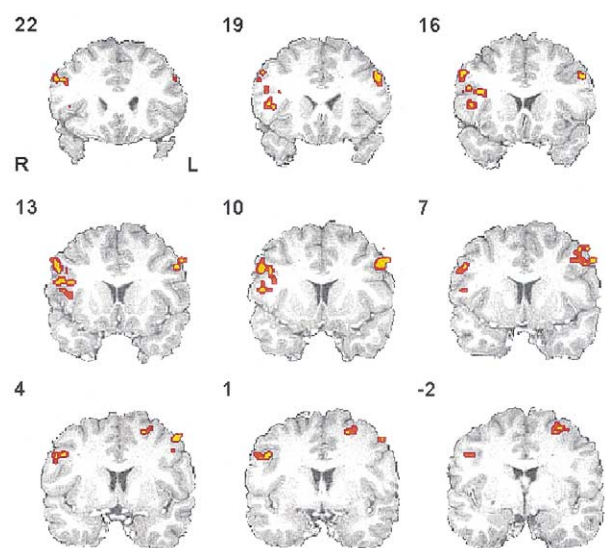


Figure 4. Main effect of error rate: coronal sections of cluster-thresholded t-maps of the error-rate-related activation common to both normal comparison subjects and methamphetamine-dependent subjects. Numbers indicate y coordinate of the axial section in Talairach space.

Table 1. Volume and Center of Mass for Mixed Analysis of Variance Clusters of Task-Related Activation

Volume (μ L)	X	Y	Z	L/R	Comment	BA
Group effect						
1890	-29	32	35	L	Middle frontal gyrus	9
567	-37	39	28	L	Middle frontal gyrus	9
837	8	44	39	R	Medial frontal gyrus	8
432	-8	29	39	L	Medial frontal gyrus	8
351	8	62	17	R	Medial frontal gyrus	10
459	-33	42	17	L	Middle frontal gyrus	10
729	-1	13	42	L/R	Cingulate gyrus	32
459	-3	34	19	L	Anterior cingulate	32
2835	-31	-64	41	L	Precuneus	19/7
729	33	-63	37	R	Precuneus	19/7
459	38	-41	58	R	Postcentral gyrus	5
756	-44	-53	33	L	Superior Temporal gyrus	39
Error-rate effect						
351	41	17	7	R	Insula	13
702	-27	-2	52	L	Middle frontal gyrus	6
702	42	13	16	R	Inferior frontal gyrus	44/45
1080	-46	10	35	L	Middle frontal gyrus	9
1512	47	11	30	R	Middle frontal gyrus	9
Group by error-rate effect						
540	-30	9	19	L	Insula	13
1215	-35	33	17	L	Inferior frontal gyrus	46
351	-36	52	8	L	Middle frontal gyrus	10
1269	19	-52	41	R	Precuneus	7
486	-20	-42	45	L	Precuneus	7
486	37	-56	42	R	Inferior parietal lobule	40
594	-32	-29	37	L	Inferior parietal lobule	40

Labels are based on Talairach Demon software (Lancaster et al 2000). BA, Brodmann's area; L, left; R, right.

Clinical Measures and fMRI Results

Two correlational analyses were carried out to determine whether the neural activation differences between methamphetamine-dependent subjects and normal comparison subjects could be due to prolonged, but not clinically overt, withdrawal or due to long-term use of stimulants. Days of sobriety and years of use were entered into two linear regression analyses to predict the degree of task-related activation in areas with different task-related activity between methamphetamine-dependent and normal comparison subjects. Duration of methamphetamine use predicted activation differences between methamphetamine-dependent and normal comparison subjects in 3 of the 13 areas. Specifically, longer duration of use was related to less task-related activation in methamphetamine subjects in the left middle frontal gyrus (BA 9, $r = -.52$, $p < .05$), anterior cingulate (BA 32, $r = -.49$, $p < .05$), and left precuneus (BA 7, $r = -.69$, $p < .01$; Figure 7, top). The duration of sobriety predicted the pattern of activation differences in only one area, that is, longer duration of sobriety was associated with more activation in the left medial frontal gyrus (BA 8, $r = .55$, $p < .05$; Figure 7, bottom).

Discussion

This investigation yielded three main results. First, the behavioral results do not support the hypothesis that methamphetamine-dependent subjects are more or less sensitive to "success" or "failure" than normal comparison subjects during this task. Both groups showed an increase in response switching as a function of error rate. Moreover, the increase in win-stay/lose-shift consistent responses by methamphetamine-dependent subjects relative to normal comparison subjects was independent of error rate. Second, the behavioral results do not support the notion of an altered effect of outcome predictability on the predictability of response sequences by methamphetamine-dependent subjects. Instead, the degree of response predictability as measured by the mutual information was proportional to the degree of outcome predictability in both groups. Third, the neuroimaging results support the hypothesis of an attenuated processing of "success" or "failure" by neural substrates that are important for decision making. Specifically, whereas normal comparison subjects showed strong "success" related activation in the right insula (BA 13), right inferior (BA 44, 45), right middle frontal (BA 9) gyrus, and in left middle frontal

gyrus (BA 6, 9), the degree of activation was attenuated in methamphetamine-dependent subjects. In addition, whereas normal comparison subjects showed success-related patterns of neural activation in left insula (BA 13), inferior frontal gyrus (BA 46), middle frontal gyrus (BA 10), precuneus (BA 7), and inferior parietal lobule (BA 40), methamphetamine-dependent subjects showed activation in these areas that was inversely related to the degree of outcome predictability. In combination, the results are consistent with the hypothesis that response selection by methamphetamine-dependent subjects is characterized by a more rigid stimulus-response relationship, that is, increased win-stay/lose-shift mutual information is the result of an increased response to the previous stimulus and not a result of increased or attenuated processing of “success” or “failure.” This finding is consistent with the view of stimulant dependence is a state dominated by habit-based learning (i.e., when stimuli exert a strong influence on response selection irrespective of associated outcomes; Robbins and Everitt 1999).

Our findings provide new insights into previous reports of an increase in win-stay/lose-shift consistent responses by methamphetamine-dependent subjects (Paulus et al 2002b). The win-stay/lose-shift strategy consists of two steps. First, the subject needs to remember where the stimulus was presented during the previous trial and, second, the subject needs to determine whether the prediction was correct or incorrect. If the current choice was simply based on the presentation of the previous stimulus, irrespective of correct or incorrect prediction, one would expect increase win-stay/lose-shift consistent responses across all error rate conditions. The current behavioral results are consistent with this view. Therefore, the behavioral response characteristics of methamphetamine-dependent subjects relative to normal comparison subjects are more stimulus-driven and not more outcome-driven. In contrast, if “success” or “failure” had a stronger influence on the subsequent choice in methamphetamine-dependent subjects relative to normal comparison subjects, one would expect to find relatively more win-stay-consistent responses during low error rates and relatively more lose-shift consistent responses at high error rates; however, the results from win-stay/lose-shift mutual information analysis showed that the difference between methamphetamine-dependent and normal comparison subjects was independent of the error rate.

This behavioral interpretation has important implications for the underlying neural substrate activations. The echoplanar signal activation during the two-choice prediction task is thought to reflect activation of neural substrates engaged in computational processes that are important in decision making, such as computing the reinforcement history (Calfee and Atkinson 1966), adjust-

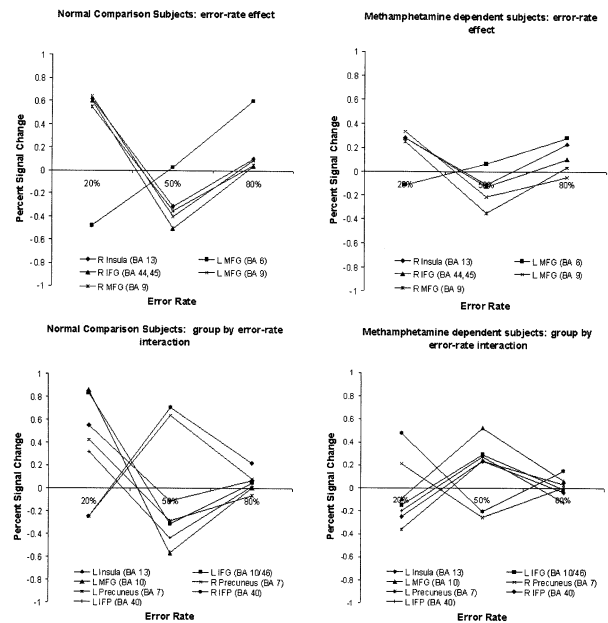


Figure 5. Cluster-averaged percent signal change of areas with error-rate effect (top) and group-by-error-rate interaction (bottom) for normal comparison subjects (left) and methamphetamine-dependent subjects (right). BA, Brodmann's area; MFG, middle frontal gyrus; IFG, inferior frontal gyrus; IFP, inferior parietal lobule.

ing prediction errors associated with different choices (Egelman et al 1998), or processing hunches that point toward advantageous versus disadvantageous responses (Bechara et al 1997). A stimulus-driven response selection would require more processing resources when the sequence of stimuli is maximally unpredictable (i.e., when the error rate is 50%). Accordingly, whereas normal comparison subjects showed increased activation in left medial frontal gyrus (BA 10), insula (BA 13), precuneus (BA 7), and inferior parietal lobule (BA 40) during low error rates, methamphetamine-dependent subjects showed an increased activation of these structures when the outcome was most unpredictable. Finally, the attenuated task-related activation as a function of error rate in methamphetamine-dependent subjects (Figure 5 top right vs. top left) is consistent with the notion that “success” or “failure” is less important to methamphetamine-dependent subjects. Although both groups showed increased activation during low error rates in the right inferior frontal gyrus (BA 44, 45), insula (BA 13), and middle frontal gyrus (BA 9) relative to the other error rate conditions, the magnitude of the activation pattern in methamphetamine-dependent subjects was attenuated as revealed by a group-by-error rate contrast. In combination, these neuroimaging findings support the hypothesis that methamphetamine-dependent subjects are less engaged in processing success

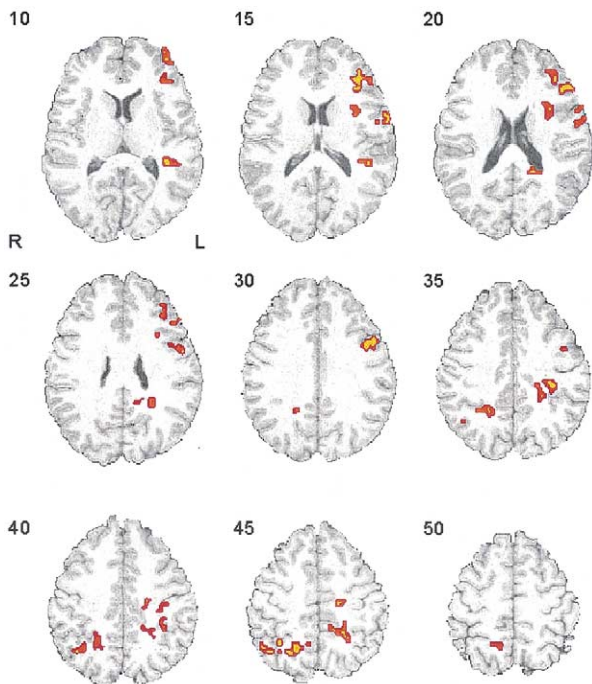


Figure 6. Interaction between group and error rate: axial sections of cluster-thresholded t-maps of the error-rate-related differential activation between normal comparison subjects and methamphetamine-dependent subjects. Numbers indicate z coordinate of the axial section in Talairach space.

or failure during decision making. Instead, these subjects are more stimulus driven and show an increase in neural activation in response to stimulus uncertainty.

The precise cognitive and affective dysfunction underlying the susceptibility to drug dependence or the consequence associated with long-term use is still unclear. Several key processes have been implicated in the neurobiology of drug dependence. Some have stressed that drug-dependent subjects have an impaired processing of stimulus-reward/punishment association (Bechara et al 2001; Grant et al 2000) and of reinforcement learning (Ornstein et al 2000). In particular, experimental studies have shown that drug-dependent subjects are hypersensitive to reward and less sensitive to aversive stimuli (Lane et al 1998). Others have suggested that drug-dependent subjects show impaired inhibition of immediate reward in the presence of long-term adverse outcomes (Bechara et al 2001). These stimulus-reward association processes have been linked to activation patterns in the inferior prefrontal and orbitofrontal cortex (Rolls 2000). Specifically, success and failure related activation during decision making has been reported in the orbitofrontal cortex (BA 47) and the anterior insula (Elliott et al 2000). Similarly, the presence of feedback (i.e., whether the subjects is informed about correct versus incorrect predictions) has been associated

with activation in the inferior frontal gyrus (BA 47), medial orbitofrontal gyrus (BA 11), and superior temporal gyrus (BA 39; Elliott et al 1997). Others have distinguished reward and punishment related activation in the lateral versus medial orbitofrontal cortex, respectively (O'Doherty et al 2001). Finally, recent investigation indicates that the modulation of the skin conductance response, a major indicator of autonomic arousal, is associated with activation fluctuations in the medial frontal gyrus (BA 10), the orbitofrontal cortex (BA 11), and the inferior parietal lobule (BA 40; Critchley et al 2000). Therefore, altered activation patterns in the inferior frontal

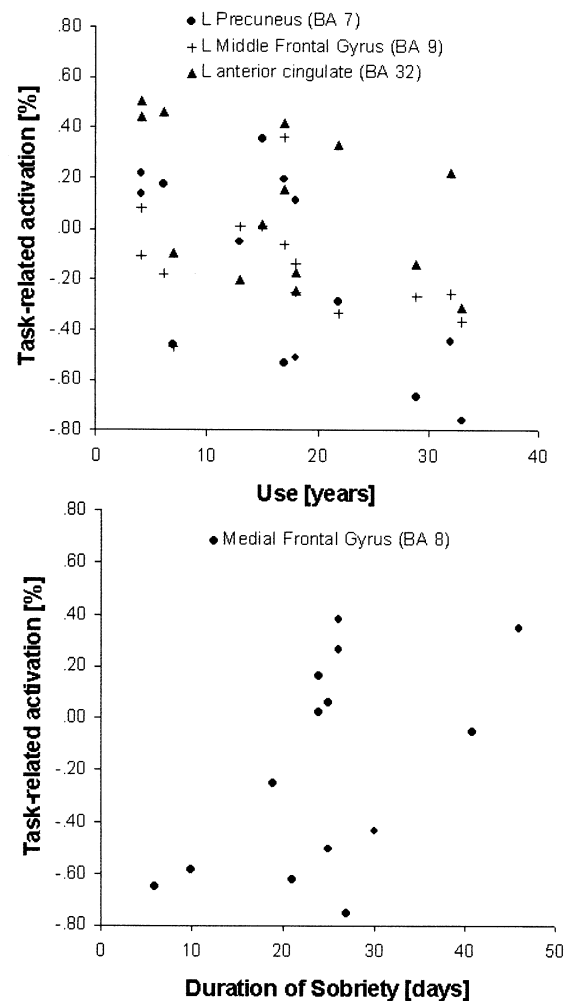


Figure 7. Scatter plots of years of use (top) and days of sobriety (bottom) versus cluster-averaged percent signal change for areas that showed a main effect of group. Longer duration of use was associated with less activation in left anterior cingulate, precuneus, and middle frontal gyrus. Longer duration of sobriety was associated with increased activation in bilateral medial frontal gyrus. Talairach coordinates are shown in Table 1. BA, Brodmann's area.

gyrus (BA 44), insula (BA 13), medial frontal gyrus (BA 10), and inferior parietal lobule (BA 40) in methamphetamine-dependent subjects may comprise the neural basis for an altered response selection process during decision making. Thus, instead of relying on success or failure, the response selection process in these subjects is driven by stimulus–response associations.

This study has several limitations. First, methamphetamine-dependent subjects were slightly less educated than the normal comparison subjects. Although education-covariates analyses did not yield different results, one cannot rule out that education level may have affected these results. Second, the number of responses was not controlled *a priori*. The two-choice prediction task and the two-choice response task are subject-initiated responses to examine the effect of self-generated actions as opposed to stimulus or cue contingent responses. Response rates during the two-choice prediction relative to the two-choice response task and during the different error-rate segments did not differ across subjects or across groups. Thus, it is unlikely that response rate contributes to the reported differences. Third, the methamphetamine-dependent subjects were recruited during an early remission state. Although psychiatric assessments and self-ratings did not indicate the presence of withdrawal symptoms, one cannot rule out that some of these effects are due to a protracted withdrawal state. Future studies will need to follow up these subjects to determine the long-term stability of these findings.

In conclusion, the response selection process during decision making by methamphetamine-dependent subjects is not consistent with an outcome-related selection strategy. Instead, the neural activation pattern differences between normal comparison subjects and methamphetamine-dependent subjects across different error rates during the two-choice prediction task are consistent with an altered top-down modulation from outcome-related to stimulus-related response selection during decision making.

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