Risky Decision Making, Prefrontal Cortex, and Mesocorticolimbic Functional Connectivity in Methamphetamine Dependence

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IMPORTANCE Various neuropsychiatric disorders, especially addictions, feature impairments in risky decision making; clarifying the neural mechanisms underlying this problem can inform treatment.

OBJECTIVE To determine how methamphetamine-dependent and control participants differ in brain activation during a risky decision-making task, resting-state functional connectivity within mesolimbic and executive control circuits, and the relationships between these measures.

DESIGN, SETTING, AND PARTICIPANTS A case-control, functional magnetic resonance imaging study of methamphetamine-dependent and healthy comparison participants at rest and when performing the Balloon Analogue Risk Task, which involves the choice to pump a balloon or to cash out in the context of uncertain risk. Conducted at a clinical research center at an academic institution, this study involved 25 methamphetamine-dependent and 27 control participants.

MAIN OUTCOMES AND MEASURES Parametric modulation of activation in the striatum and right dorsolateral prefrontal cortex (rDLPFC; ie, the degree to which activation changed as a linear function of risk and potential reward), both indexed by pump number, and resting-state functional connectivity, measured in the whole brain with seeds in the midbrain and rDLPFC. Relationships between these outcomes were also tested.

RESULTS Parametric modulation of cortical and striatal activation by pump number during risk taking differed with group. It was stronger in the ventral striatum but weaker in the rDLPFC in methamphetamine-dependent participants than control individuals. Methamphetamine-dependent participants also exhibited greater resting-state functional connectivity of the midbrain with the putamen, amygdala, and hippocampus ($P < .05$, whole brain, cluster corrected). This connectivity was negatively related to modulation of rDLPFC activation by risk level during risky decision making. In control participants, parametric modulation of rDLPFC activation by risk during decision making was positively related to resting-state functional connectivity of the rDLPFC with the striatum.

CONCLUSIONS AND RELEVANCE Maladaptive decision making by methamphetamine users may reflect circuit-level dysfunction, underlying deficits in task-based activation. Heightened resting-state connectivity within the mesocorticolimbic system, coupled with reduced prefrontal cortical connectivity, may create a bias toward reward-driven behavior over cognitive control in methamphetamine users. Interventions to improve this balance may enhance treatments for stimulant dependence and other disorders that involve maladaptive decision making.

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Deficits in decision making have been linked with addiction and likely contribute to addiction vulnerability and to the maintenance and severity of dependence.1-5 Chronic methamphetamine use is associated with abnormalities in the neural circuits involved in risky decision making6-9 including structural and functional deficits in the prefrontal cortex (PFC) and striatum10-12 and in striatal dopaminergic markers.13-17 However, little is known about the links between these observations and problems with decision making.

The mesocorticolicmbic system, originating in the midbrain ventral tegmental area and projecting to the nucleus accumbens, amygdala, hippocampus, and medial PFC,18 substantially influences goal-directed behaviors, and pathological drug-seeking behavior may result from drug-induced changes in this circuitry.18,19 Studies using resting-state functional connectivity (RSFC) to assess temporal correlations of spontaneous regional activity when participants are at rest20 have identified abnormalities in connectivity between nodes of the mesocorticolimbic system in cocaine and opiate users.18 However, PFC and striatal dysfunction during risky decision making by substance-dependent individuals21 has not been linked directly to network activity nor has it yet been examined in the context of methamphetamine dependence. Therefore, we used RSFC and task-based functional magnetic resonance imaging (fMRI) to clarify how circuit-level abnormalities may influence adaptive decision making in methamphetamine users.

Functional magnetic resonance imaging was paired with the Balloon Analogue Risk Task (BART),22 which presents sequential choices—pumping a balloon to increase monetary gains while risking loss or cashing out to retain earnings. Using a parametric modulation analysis, we tested for differences between methamphetamine-dependent and control participants in modulation of the right dorsolateral prefrontal cortex (rDLPFC) and striatal activation by risk and potential reward (both indexed by pump number) during decision making. As methamphetamine users exhibit ventral striatal hyperresponsivity to reward23 but rDLPFC hypoactivity during decision making,24,25 we expected them to display greater modulation of striatal activation by pump number during risky decision making but less modulation in the rDLPFC and to earn less on the BART than participants are at rest26 have identified abnormalities in connectivity between nodes of the mesocorticolicmbic system in cocaine and opiate users.18 However, PFC and striatal dysfunction during risky decision making by substance-dependent individuals21 has not been linked directly to network activity nor has it yet been examined in the context of methamphetamine dependence. Therefore, we used RSFC and task-based functional magnetic resonance imaging (fMRI) to clarify how circuit-level abnormalities may influence adaptive decision making in methamphetamine users.

Modulation of rDLPFC activation would suggest that mesolimbic circuit dysfunction promotes maladaptive decision making in methamphetamine users. As faulty decision making is a target for addiction therapies, understanding its determinants might facilitate the development of more effective interventions.

**Methods**

**Participants**

Fifty-three volunteers, recruited via newspaper and Internet advertisements, provided written informed consent as approved by the University of California–Los Angeles institutional review board. Exclusion criteria, as determined by physical examination, medical history, and laboratory blood tests, were systemic, neurological, cardiovascular, or pulmonary disease or head trauma with loss of consciousness. They were assigned to 2 groups: methamphetamine users and control individuals. Current Axis I diagnoses—other than nicotine dependence for either group and methamphetamine dependence for the methamphetamine group—assessed with the Structured Clinical Inventory for DSM-IV-TR were exclusionary.

The methamphetamine group included 26 nontreatment-seeking participants (13 men and 13 women; 20 smokers; mean [SD] age, 35.68 [1.64] years) who provided a positive urine test result for methamphetamine and reported using a mean (SD) of 3.57 (1.04) g/week of methamphetamine and using methamphetamine, alcohol, and marijuana a mean (SD) of 23.60 (1.29), 4.68 (1.64), and 1.68 (0.70) days of the month before enrollment, respectively (Table). Eleven participated on a residential basis, abstinent from methamphetamine use for 4 to 7 days before scanning; 14 participated on a nonresidential basis, abstaining from methamphetamine use for a mean (SD) of 5.78 (1.84) days before scanning. The control group included 27 individuals (11 women and 16 men; 16 smokers; mean [SD] age, 33.88 [1.64] years) who provided a positive urine test result for nicotine dependence and reported using tobacco a mean (SD) of 17.57 (2.87) grams per week and alcohol a mean (SD) of 4.36 (1.15) drinks per day.

**Table. Characteristics of Research Participants**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Healthy Control (n=27)</th>
<th>Methamphetamine Dependent (n=25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>33.88 (2.30)</td>
<td>35.68 (1.64)</td>
</tr>
<tr>
<td>Male, No.</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Education, y</td>
<td>13.62 (0.38)</td>
<td>13.00 (0.38)</td>
</tr>
<tr>
<td>No. of d substance was used in the last 30 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>4.36 (1.15)</td>
<td>4.68 (1.64)</td>
</tr>
<tr>
<td>Marijuana</td>
<td>0.08 (0.08)</td>
<td>1.68 (0.70)</td>
</tr>
<tr>
<td>Tobacco</td>
<td>17.57 (2.87)</td>
<td>21.16 (2.54)</td>
</tr>
<tr>
<td>No. of smokers</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Methamphetamine use</td>
<td>23.60 (1.29)</td>
<td>23.60 (1.29)</td>
</tr>
<tr>
<td>Grams/wk</td>
<td>3.57 (1.04)</td>
<td>3.57 (1.04)</td>
</tr>
<tr>
<td>Duration of heavy use, y</td>
<td>8.59 (1.37)</td>
<td>8.59 (1.37)</td>
</tr>
</tbody>
</table>

* N = 18 for resting-state functional connectivity analysis.
* N = 15 for resting-state functional connectivity analysis.
* Significant differences between the groups by t test (*P* = .03).
Figure 1. Schematic of Balloon Analogue Risk Task

A, Pumping the balloon increased potential earnings but carried the risk of the balloon exploding, resulting in a loss of accumulated earnings during the trial. B, If participants cashed out before the balloon exploded, they retained the earnings accumulated. C, In control trials, white balloons were presented. These balloons did not increase in size with pumping, did not explode, and were not associated with reward potential (see Methods section).

A general linear mixed model was used to examine trial-by-trial, risk-taking behavior, accounting for individual participant variables. The model included trial number (across both runs), balloon color, and outcome of the immediately preceding trial, with pumps per trial as the dependent variable. Data were analyzed using the Statistical Package for the Social Sciences.

The rDLPFC region of interest (ROI) was sampled with a 10-mm sphere around the peak voxel (Montreal Neurological Institute coordinates: \(x = 30, y = 36, z = 20\)) from a cluster showing modulation of activation during balloon pumping on the BART.\(^7\)\(^9\) A bilateral striatal ROI was derived from the Harvard-Oxford Atlas (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/Atlases). A 9-mm spherical midbrain ROI was created using the coordinates \((x = 0, y = -15, z = 9)\) from a study examining the effect of methylphenidate on midbrain RSFC.\(^{35}\)

Image analysis was performed using FSL 5.0.2.1 (http://www.fmrib.ox.ac.uk/fsl). Images were realigned to compensate for motion,\(^{39}\) and high-pass temporal filtering was applied. Data were skull stripped and spatially smoothed (5-mm full-width-at-half-maximum gaussian kernel). The echopla-
nary images were registered to the matched-bandwidth image, then to the high-resolution magnetization-prepared rapid-acquisition gradient echo image, and finally into standard Montreal Neurological Institute space using 12-parameter affine transformation and FMRIB’s nonlinear image registration tool.37

Four types of events were included in the general linear model: pumps on active balloons, cash outs, balloon explosions, and pumps on control balloons. Two regressors for each of the 4 types of events were included to obtain estimates of parametric modulation38 of activation by pump number and of mean activation for each event type. As a trial progressed, the risk for balloon explosion increased with each pump, as did the amount earned with cashing out. Parametric regressors tested the linear relationship between pump number and activation (ie, modulation of activation by pump number) by assigning greater weight to events that carried greater risk and potential reward. For example, within a trial, the second pump, for which twice the reward was at stake, was given twice the weight as the first. For regressors that estimated mean activation for each event, the escalation of risk was not considered and each pump was assigned equal weight. To test for differences in overall activation during risky decision making and for the modulation of activation with risk and reward levels, the contrasts of interest were mean pump events vs mean control-balloon events and parametric pump events, respectively.

Regressors were created by convolving a set of delta functions, representing onset times of each event with a canonical (double-gamma) hemodynamic response function. The first temporal derivatives of the 8 task-related regressors were included to capture variance associated with the temporal lag of the hemodynamic response along with 6 motion parameters estimated during motion correction.

Fixed-effects analyses were conducted for each imaging run of data from each participant and again to combine contrast images across both runs. For within- and between-group mixed-effects analyses, all whole-brain fMRI statistics were corrected for multiple comparisons by using cluster correction with voxel height threshold of $Z > 2.3$ and cluster significance of $P < .05$, unless otherwise noted. All analyses included sex, age, smoker status (smoker or non-smoker), and marijuana use (days used in preceding month) as nuisance covariates. Analyses of group differences in the modulation of activation by pump number were restricted to the rDLPFC and striatal ROIs (voxel height threshold of $Z > 2.3$ and cluster corrected at $P < .05$). The interaction of group with the association of total earnings on the modulation of activation during risky decision making in the rDLPFC ROI and whole brain was also tested.

For resting-state analysis, images were further preprocessed to include additional nuisance regressors: average signal of cerebrospinal fluid and 2 metrics of motion-related artifact, specifically framewise displacement and a combination of the temporal derivative of the time series and root mean squared variance over all voxels.39 Global signal regression was not applied. The mean time series across all voxels within the rDLPFC and midbrain seeds from preprocessed images were used as covariates in separate whole-brain, voxelwise correlation analyses.

**Results**

**Task Performance**

There was a significant main effect of active balloon color (red and blue) ($F_{1, 1828.28} = 16.684; P < .001$) on pumping but no significant main effect of group ($F_{1, 62.433} = 0.043; P = .84$) and no interactions. There were no significant group differences in the average number of pumps before cashing out ($t = 1.342; P = .18$; mean [SD], control: 2.84 [1.518]; methamphetamine: 2.74 [1.544]). A 2-tailed $t$ test showed significant differences in overall performance ($t_{62.433} = 2.357; P = .02$), with control participants (USD $33.33 [3.83]) earning more than methamphetamine users (USD $30.15 [6.65]).

**Task-Based fMRI**

During pumping, modulation of rDLPFC activation by pump number was greater in the control group than the methamphetamine group; however, methamphetamine users displayed greater modulation of ventral striatal activation than control participants ($P < .05$, cluster corrected in ROI analyses (Figure 2). In a whole-brain analysis, control participants exhibited greater modulation of activation than the methamphetamine group in a cluster that included and extended be-
beyond the rDLPFC ROI (peak coordinates: $x = 42, y = 40, z = 30$; extent: 610 voxels; Z statistic: 3.4; $P < .001$, whole-brain corrected). No other significant group differences in whole-brain or mean activation were found.

A group interaction with monetary earnings on modulation of activation by risk was found in whole-brain, but not ROI, analysis. Post hoc analyses showed a negative correlation between the amount earned and modulation of activation in the bilateral anterior insula and right caudate in the control group. Control participants showed no positive or negative correlations in the methamphetamine group ($P < .05$, whole brain, cluster corrected).

RSFC and Relationship to Task-Based Activation

Compared with control participants, methamphetamine users exhibited greater RSFC (midbrain seed) with the putamen; amygdala; hippocampus; insula; orbital, superior, and inferior frontal cortices; temporal cortices; and parietal operculum ($P < .05$, whole brain, cluster corrected) (Figure 3, eTable 1 in Supplement). There were no regions where control participants exhibited greater midbrain RSFC than methamphetamine users nor were there any group differences in RSFC of the rDLPFC.

A group interaction with the modulation of rDLPFC activation on the RSFC between the midbrain and putamen was found at $P < .001$, uncorrected. Post hoc analyses showed a negative correlation in the methamphetamine group between modulation of rDLPFC activation during risk taking and midbrain RSFC with orbitofrontal cortex, putamen, ventral striatum, amygdala, insula, hippocampus, anterior cingulate cortex, orbital medial and superior frontal cortices, and temporal and occipital cortices ($P < .05$, whole brain, cluster corrected) (Figure 4, eTable 2 in Supplement). Control participants showed no correlations between modulation of rDLPFC activation and the midbrain RSFC.

There was a significant group interaction with modulation of rDLPFC activation during risk taking on the RSFC between the rDLPFC and nucleus accumbens, putamen, amygdala, hippocampus, thalamus, and orbital frontal cortex ($P < .05$, whole brain, cluster corrected) (Figure 5A, eTable 3 in Supplement). In post hoc analysis, modulation of rDLPFC activation during risk taking in control participants was positively correlated with the rDLPFC RSFC to ventral striatum; caudate; putamen; hippocampus; orbital, medial frontal, and subcallosal cortices; insula; thalamus; paracingulate cortex; and the superior and inferior frontal gyri ($P < .05$, whole brain, clus-
Methamphetamine users exhibited a negative correlation between modulation of rDLPFC activation during risk taking and rDLPFC RSFC with the anterior cingulate cortex ($P < .05$, whole brain, cluster corrected).

Discussion

Methamphetamine users earned less than control participants on the BART, and they showed less sensitivity to risk and reward in the rDLPFC, greater sensitivity in the ventral striatum, and greater mesocorticolimbic RSFC. Control participants exhibited greater association between the RSFC of the rDLPFC and sensitivity of the rDLPFC to risk during risky decision making, suggesting that a deficit in rDLPFC connectivity contributes to dysfunction in methamphetamine users. These findings suggest that circuit-level abnormalities affect brain function during risky decision making in stimulant users.

Methamphetamine users took fewer pumps than control participants, although this effect was not statistically significant. While risk taking may be problematic, moderate risk taking on the BART can be the adaptive.46 Risk-averse choices may reflect the preference for smaller, but more immediate, rewards over later, larger ones and there may be indicative of impulsive behavior. In line with this view, methamphetamine users previously exhibited greater temporal discounting of rewards44,45 than control participants and reported greater impulsiveness on the Barratt Impulsiveness Scale version 11,22 as did methamphetamine users in this study ($t = 4.491; P < .001$ for Barratt Impulsiveness Scale version 11 total mean [SD] score, control group: 53.46 [10.24]; methamphetamine group: 70.13 [9.27]). Group differences in this study support this view because rDLPFC activation has been related to selection of choices leading to large, future rewards despite small immediate losses, whereas ventral striatal activation has been related to obtaining short-term reward.43

As modulation of activation was stronger in the ventral striatum but weaker in the rDLPFC of methamphetamine users than control participants, decision making in methamphetamine users may reflect the influence of immediate reward on behavior. Notably, the amount of earnings was negatively associated with modulation of striatal activation in control participants. Moreover, deactivation of the medial PFC, the rodent analog of the DLPFC,44,45 promotes maladaptive risk taking in animals46; and in humans, modulation of rDLPFC activation by risk was associated positively with earnings but negatively with striatal D2/D3 dopamine receptor availability.7 The relationship between rDLPFC RSFC and modulation of rDLPFC activation in the control, but not methamphetamine, group suggests that PFC deficits contribute to top-down impairments in stimulant dependence.34 Computational models have indicated a modulatory effect of PFC on striatal activity47,48 and suggest PFC activity can override striatal representations of reinforcement value.47 Dynamic causal modeling analyses also have shown a modulatory role of the DLPFC on nucleus accumbens activation during reward cues.49 However, repeated stimulant exposure can alter corticostriatal synaptic activity, with reductions in extracellular glutamate60 and depression of activity in corticostriatal afferents.51 Taken together, these findings suggest that heightened ventral striatal but blunted rDLPFC sensitivity to risk and reward of methamphetamine users reflect dysregulated corticostriatal connectivity.

Greater midbrain RSFC in methamphetamine users than control participants may reflect stimulant-induced...
Figure 5. Relationship Between Resting-State Connectivity of the Dorsolateral Prefrontal Cortex (DLPFC) and Modulation of Activation in the DLPFC During Risky Decision Making

A, Brain regions where the relationship between resting-state connectivity with the DLPFC seed (shown in blue) and modulation of activation in the right DLPFC by pump number varied by group. Connectivity maps show a group interaction between modulation of activation in the right DLPFC during balloon pumps and resting-state functional connectivity of the DLPFC with the nucleus accumbens, putamen, amygdala, hippocampus, thalamus, orbital frontal cortex, and cerebellum (P < .05, whole brain, cluster corrected) (eTable 3 in Supplement provides a list of regions). B, Post hoc analysis within the control group showed a positive correlation between modulation of activation in the right DLPFC during balloon pumps and resting-state functional connectivity of the right DLPFC (shown in blue) with the caudate, putamen, nucleus accumbens, and orbital frontal cortex (P < .05, whole brain, cluster corrected) (eTable 3 in Supplement for list of regions).
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minereleasecanbelonglasting.55Heightened midbrain RSFC in humans, amphetamine-induced sensitization of dopamine release can be long lasting.55 Heightened midbrain RSFC in methamphetamine users may reflect such sensitization even in the absence of reward-related stimuli. Sensitization has been studied primarily in terms of facilitating drug self-administration, conditioned place preference, and the motivation for drugs.56-58 The present findings suggest more extensive effects on psychological processes and support a link between neural dysfunction during decision making and circuit-level abnormalities in methamphetamine dependence. However, this study had some limitations. The temporal resolution of fMRI with the BART did not completely isolate decision-making processes, such as evaluation, selection, and anticipation, and tasks that provide finer resolution are needed.59 This study had a priori hypotheses regarding the rDLPFC and striatum and tested functionally connected networks, bolstering the view that the cognitive processes under study were in fact examined. Still, caution is warranted to avoid making conclusions from reverse inference.60 In this regard, anticipation of either reward or aversive stimuli can elicit striatal activation.61,62 Therefore, the cognitive process underlying the modulation of ventral striatal activation is uncertain. Finally, as the RSFC provides no directional information, it is unknown to what extent the RSFC between rDLPFC and striatum reflects top-down control or spontaneous coherence of activation.

Conclusions

Heightened resting-state connectivity within the mesocorticolimbic system, along with reduced prefrontal cortical connectivity, may create a bias toward reward-driven behavior over cognitive control in methamphetamine users. Interventions to improve this balance may enhance treatments for stimulant dependence and other disorders that involve maladaptive decision making.

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Study concept and design: Kohno, London.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Kohno, London.

Critical revision of the manuscript for important intellectual content: All authors.

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Study supervision: London.

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REFERENCES


