Original Investigation

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 making[6-9] including structural and functional deficits in the prefrontal cortex (PFC) and striatum[10-12] and in striatal dopaminergic markers.[13-17] However, little is known about the links between these observations and problems with decision making.

The mesocorticolimbic 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 rest[20] 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 individuals[21] 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 reward[23] 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 control participants. Resting-state functional connectivity was assessed with seeds in the midbrain, because of its dopaminergic projections to limbic and cortical regions, and in the rDLPFC, which exhibits risk sensitivity while participants perform the BART.[7,9,26,27] Because stimulants produce adaptations in the mesolimbic dopamine system, which are thought to underlie psychomotor sensitization in animals,[28-30] it was expected that midbrain RSFC would be greater in methamphetamine users than in control participants.

Finally, because adaptations in mesolimbic and prefrontal cortical regions are thought to underlie addiction-related cognitive deficits,[31-34] the relationship between task-based activation and connectivity within mesocorticolimbic (midbrain seed) and corticostriatal circuits (rDLPFC seed) was tested. It was expected that modulation of rDLPFC activation would be positively related to rDLPFC RSFC in control participants and negatively related to midbrain RSFC in methamphetamine users. Negative association of midbrain RSFC with 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.

Table. Characteristics of Research Participants

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

[a] N = 18 for resting-state functional connectivity analysis.

[b] N = 15 for resting-state functional connectivity analysis.

[c] Significant differences between the groups by *t* test (*P* = .03).

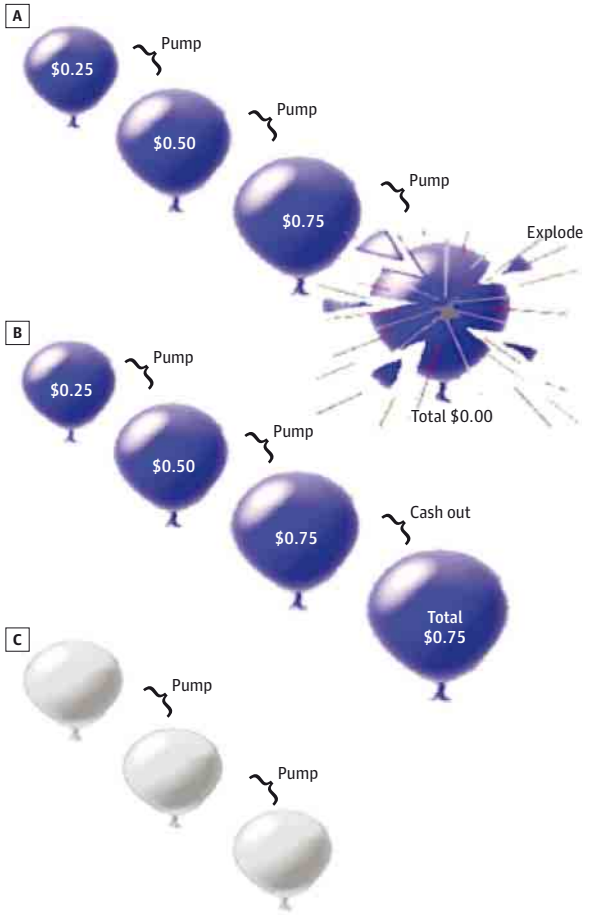
Methods

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]

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).

age, 33.88 [2.30] years), partly overlapping with participants from a previous study.[7] They reported alcohol and marijuana use on a mean (SD) of 4.36 (1.15) days and 0.08 (0.08) days in the month before enrollment, respectively, but no other drug use. The groups differed in frequency of marijuana but not alcohol use (Table). Urine testing at intake and on test days verified abstinence from cocaine, methamphetamine, benzodiazepines, opiates, and cannabinoids.

BART

A event-related fMRI version of the BART[22] was administered in two 10-minute runs (**Figure 1**). Active trials, presenting red or blue balloons, and control trials, presenting white balloons, were randomly dispersed throughout the task. On active trials, participants chose between pumping a balloon to increase earnings ($0.25/pump) or to cash out, retaining accumulated earnings. Pumping either increased the balloon size or was followed by a 2-second display of an exploded balloon and the message, "Total = $0.00." Each trial included all pumps before an explosion or cashing out, followed by a 2-second display of total earnings. Participants were informed that the colored balloons were associated with monetary reward, with winnings distributed after scanning. They were unaware that the number of pumps before an explosion was predetermined and that it was selected from a uniform probability distribution, ranging from 1 to 8 and 1 to 12 pumps for red and blue balloons, respectively. Participants were told that the white balloons did not explode and had no monetary value and that they should pump each one until the trial ended. The number of white balloons in a trial varied randomly between 1 to 12, according to a uniform distribution. As the task was self-paced, the numbers of trials and pumps within a trial varied between participants. The interstimulus interval for balloon presentations was 1 to 3 seconds, and the intertrial interval was 1 to 14 seconds, with a mean of 4 seconds.

fMRI

Task-based scans were collected from 26 methamphetamine users and 27 control participants. One methamphetamine user was excluded owing to excessive head motion (>2-mm translational displacement, >1.5° rotation), leaving a final sample of 25. Eighteen control and 15 methamphetamine participants underwent resting-state fMRI in the same session while viewing a black screen for 5 minutes. Imaging was performed on a 3-T Siemens Trio MRI system, with 302 functional task-based and 152 resting-state T2*-weighted, echoplanar images acquired (slice thickness = 4 mm; 34 slices; repetition time = 2 seconds; echo time = 30 milliseconds; flip angle = 90°; matrix = 64 × 64; field of view = 200 mm). High-resolution, T2-weighted, matched-bandwidth and magnetization-prepared rapid-acquisition gradient echo scans were also acquired. The orientation for these scans was oblique axial to maximize brain coverage and optimize signal from ventromedial PFC.

Data Analysis

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,[36] 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-

nar 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]

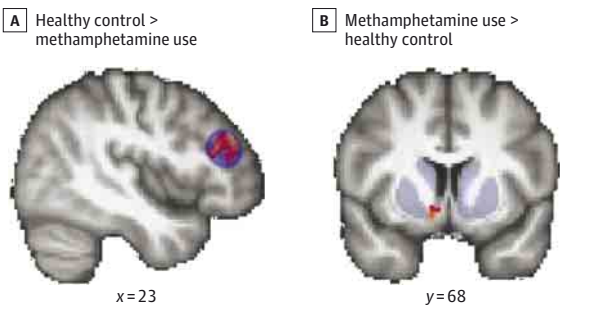
Four types of events were included in the general linear model: pumps on active balloons, cash outs, balloon explosions, and pumps on control balloons. Two regressors for each of the 4 types of events were included to obtain estimates of parametric modulation[38] of activation by pump number and of mean 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 nonsmoker), 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.

Figure 2. Modulation of Ventral Striatal and Right Dorsolateral Prefrontal Cortex Activation by Pump Number During Risky Decision Making (Region of Interest Analysis)



A, The control group exhibited greater modulation of activation by pump number in the right dorsolateral prefrontal cortex during active balloon pumps compared with the methamphetamine group (see Methods section for details of parametric modulation and region of interest analyses). B, Compared with the control group, the methamphetamine group displayed greater modulation of ventral striatal activation by pump number during active balloon pumps. Statistical maps representing *Z* statistic values are shown, masked by regions of interest in which statistical comparisons were confined ($P < .05$, cluster corrected). The results were controlled for age, sex, smoking status, and marijuana use.

Parameter estimates (average of β values) corresponding to modulation of activation by pump number in the rDLPFC ROI were regressed against whole-brain voxelwise maps of RSFC with rDLPFC and midbrain seeds between and within groups. First, the interaction of participant group with the associations between RSFC and modulation of activation was tested. Subsequently, the relationship between RSFC and modulation of activation during decision making was examined within each group.

Results

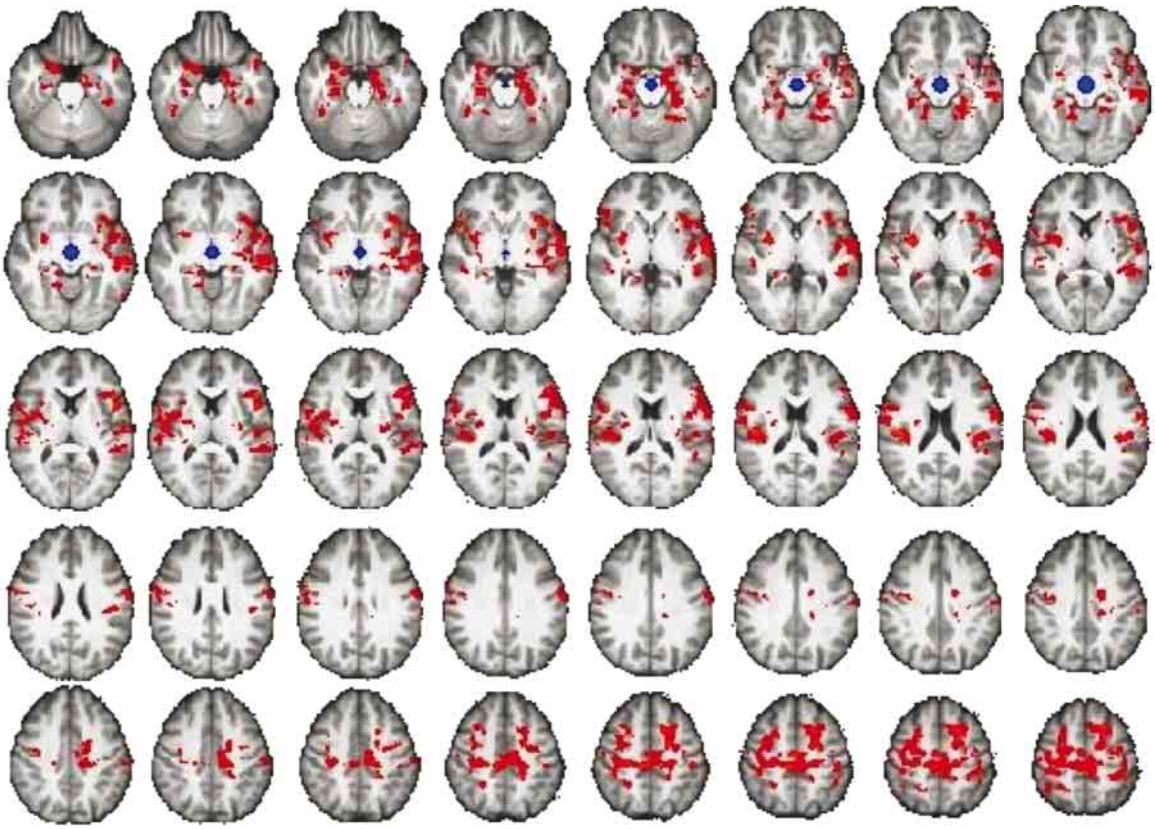
Task Performance

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 ($F_{1, 62.413} = 0.043$; $P = .84$) 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 ($t_{49} = 2.357$; $P = .02$), 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-

Figure 3. Comparison of Mesocorticolimbic Resting-State Connectivity in Methamphetamine and Control Groups



Connectivity maps show greater connectivity between the midbrain seed (shown in blue) and the putamen, amygdala, hippocampus, insula, and prefrontal cortex in the methamphetamine group compared with the healthy control group ($P < .05$, whole brain, cluster corrected) (eTable 1 in Supplement provides a list of regions). The results controlled for age, sex, smoking status, and marijuana use.

yond 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 correlations, and there were no positive or negative correlations in the methamphetamine group ($P < .05$, whole brain, cluster corrected).

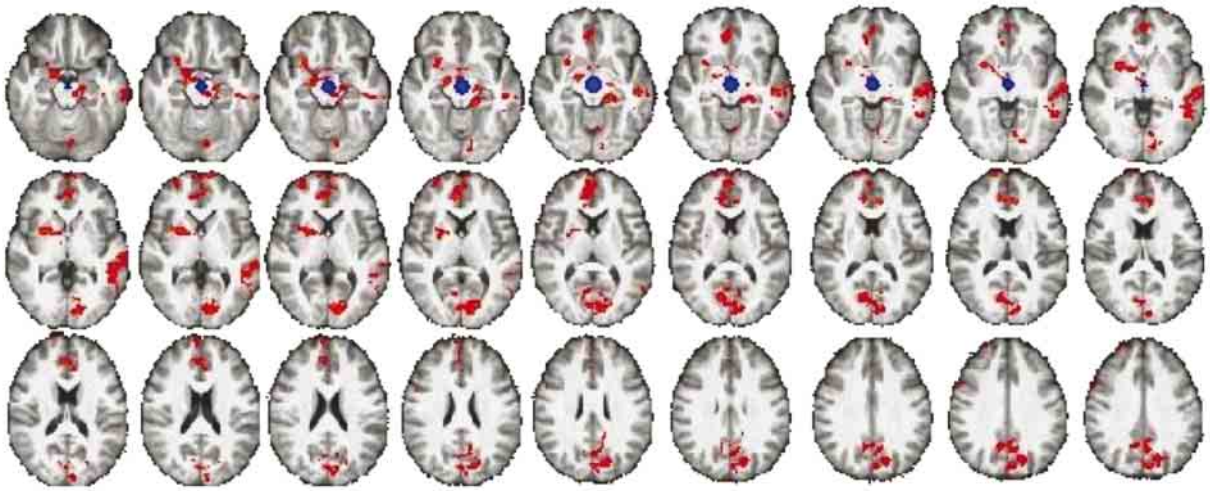
RSFC and Relationship to Task-Based Activation

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 5**A, 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-

Figure 4. Relationship Between Resting-State Connectivity of the Midbrain and Modulation of Activation in the Dorsolateral Prefrontal Cortex During Risky Decision Making in the Methamphetamine Group



Connectivity maps show a negative correlation between modulation of activation in the right dorsolateral prefrontal cortex during balloon pumps and the connectivity between the midbrain seed (shown in blue) and the nucleus accumbens, putamen, amygdala, hippocampus, orbital frontal cortex, anterior cingulate, and superior frontal gyrus in the methamphetamine group ($P < .05$, whole brain, cluster corrected) (eTable 2 in Supplement provides a list of regions). The results controlled for age, sex, smoking status, and marijuana use.

ter corrected) (Figure 5B, eTable 3 in Supplement). Methamphetamine users exhibited a negative correlation between modulation of rDLPFC activation during risk taking and rDLFPC RSFC with the anterior cingulate cortex ($P < .05$, whole brain, cluster corrected).

Discussion

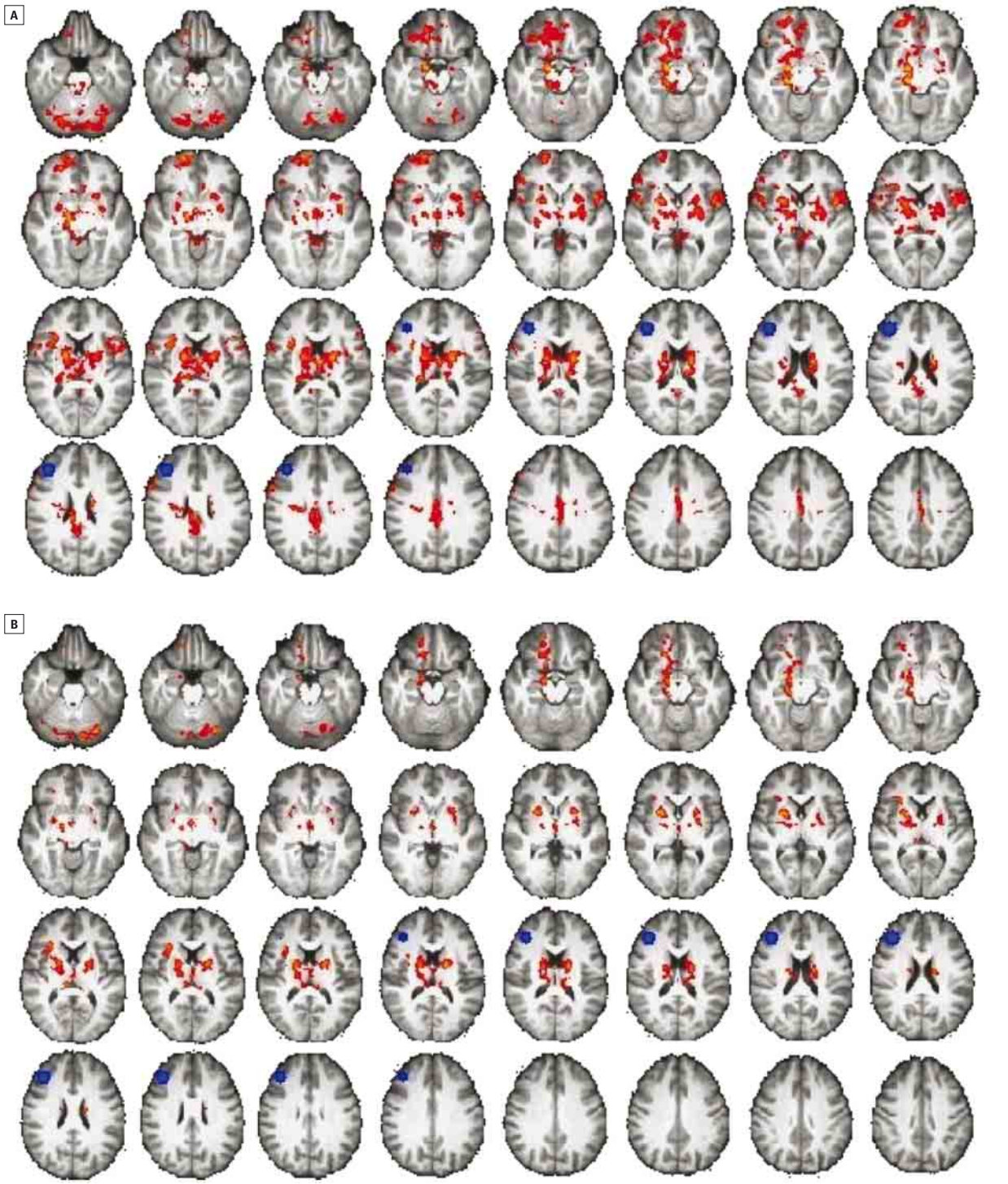
Methamphetamine users earned less than control participants on the BART, and they showed less sensitivity to risk and reward in the rDLPFC, greater sensitivity in the ventral striatum, and greater mesocorticolimbic RSFC. Control participants exhibited greater association between the RSFC of the rDLPFC 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.[40] Risk-aversive choices may reflect the preference for smaller, but more immediate, rewards over larger, later ones[40] and therefore may be indicative of impulsive behavior. In line with this view, methamphetamine users previously exhibited greater temporal discounting of rewards[41,42] than control participants and reported greater impulsiveness on the Barratt Impulsiveness Scale version 11,[13] 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 animals[46]; 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 activity[47,48] 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 glutamate[50] and depression of activity in corticostriatal affents.[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 DLFPC (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).

sensitization as posited by the Incentive Sensitization Theory of Addiction.[52,53] Amphetamine-induced sensitization in rats increases neuronal firing within mesolimbic structures,[54] and 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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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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