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Risky Decision-making: Prefrontal Function and Mesocorticolimbic Resting-state Connectivity in Methamphetamine Users

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Abstract

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 subjects 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—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.

Setting—Clinical research center at an academic institution.

Participants—Twenty-five methamphetamine-dependent and 27 control subjects.

Main Outcomes and Measures—1) Parametric modulation of activation in the striatum and right dorsolateral prefrontal cortex, i.e., the degree to which activation changed as a linear function of risk and potential reward, both indexed by pump number; and 2) resting-state functional connectivity, measured in whole brain with seeds in the midbrain and right dorsolateral prefrontal cortex. 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 right

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dorsolateral prefrontal cortex in methamphetamine-dependent participants than controls. Methamphetamine-dependent subjects also exhibited greater resting-state functional connectivity of the midbrain with the putamen, amygdala, and hippocampus. This connectivity was negatively related to modulation of right dorsolateral prefrontal cortex activation by risk level during risky decision-making. In controls, parametric modulation of right dorsolateral prefrontal cortex activation by risk during decision-making was positively related to resting-state functional connectivity of the right dorsolateral prefrontal cortex 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.

Keywords

risk-taking; decision-making; prefrontal cortex; striatum; mesolimbic; fMRI; resting state

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]. Little is known, however, about the links between these observations and problems with decision-making.

The mesocorticolimbic system, originating in the midbrain ventral tegmental area (VTA) 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 methamphetamine users. We therefore used RSFC and task-based fMRI to clarify how circuit-level abnormalities may influence adaptive decision-making in methamphetamine users.

Functional magnetic resonance imaging (fMRI) 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 subjects in modulation of right dorsolateral prefrontal cortex (rDLPFC) and striatal activation by risk and potential reward (both indexed by pump number) during decision-making. As chronic methamphetamine users exhibit ventral striatal hyper-responsivity 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 controls. RSFC was assessed with seeds in the midbrain, because of its dopaminergic projections to limbic and cortical regions, and in 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 controls.

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 controls 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.

METHODS

Participants

Fifty-three volunteers, recruited via newspaper and Internet advertisements, provided written informed consent, as approved by the UCLA Institutional Review Board. Exclusion criteria, 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 two groups: Methamphetamine and Control. 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 non-treatment seeking subjects (13 men/women, 20 smokers, 35.68 ±1.64 years old), who provided a positive urine test for methamphetamine, and reported using 3.57 ± 1.04 g/week of methamphetamine and using methamphetamine, alcohol, and marijuana on 23.60 ± 1.29, 4.68 ± 1.64, and 1.68 ± 0.70 days of the month before enrollment, respectively (Table 1). Eleven participated on a residential basis, abstinent from methamphetamine for 4–7 days before scanning; 14 participated on a nonresidential basis, abstaining from methamphetamine for 5.78 ± 1.84 days before scanning. The Control group included twenty-seven subjects (11 women/16 men, 16 smokers, 33.88 ± 2.30 years old), partly overlapping with subjects from a previous study[7]. They reported alcohol and marijuana use on 4.36 ± 1.15 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 1). Urine testing at intake and on test days verified abstinence from cocaine, methamphetamine, benzodiazepines, opiates, and cannabinoids.

Balloon Analogue Risk Task

A event-related fMRI version of the BART[22] was administered in two 10-min runs (Fig. 1). Active trials, presenting red or blue balloons, and control trials, presenting white balloons, were randomly dispersed throughout the task. On active trials, subjects 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-s 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-s display of total earnings. Subjects 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 pre-determined; and that it was selected from a uniform probability distribution, ranging from 1–8 and 1–12 pumps for red and blue balloons, respectively. Subjects 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 1–12, according to a uniform distribution. As the task was self-paced, the numbers of trials and pumps within a trial varied between subjects. The inter-stimulus interval for balloon presentations was 1–3 s, and the inter-trial interval was 1–14 s with a mean of 4 s.

fMRI

Task-based scans were collected from 26 Methamphetamine and 27 Control subjects. One Methamphetamine subject was excluded due to excessive head motion (> 2 mm translational displacement, > 1.5 degrees rotation), leaving a final sample of 25. Eighteen Control and 15 Methamphetamine subjects underwent resting-state fMRI in the same session while viewing a black screen for 5 min. Imaging was performed on a 3-T Siemens Trio MRI system, with 302 functional task-based and 152 resting-state T2*-weighted, echoplanar images (EPI) acquired (slice thickness = 4 mm; 34 slices; TR = 2 s; TE = 30 ms; flip angle = 90°; matrix = 64 x 64; fov = 200 mm). High-resolution, T2-weighted, matched-bandwidth (MBW) and magnetization-prepared rapid-acquisition gradient echo (MPRAGE) scans were also acquired. The orientation for these scans was oblique axial to maximize brain coverage and to optimize signal from ventromedial PFC.

Data Analysis

A general linear mixed model (GLMM) was used to examine trial-by-trial, risk-taking behavior, accounting for individual subject variables. The model included trial number (across both runs), balloon color, and outcome of the immediately preceding trial, with pumps/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 (MNI coordinates: x = 30, y = 36, z = 20) from a cluster showing modulation of activation during balloon pumping on the BART[9,7]. 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 (MNI: 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 (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 FWHM Gaussian kernel). The EPI images were registered to the MBW image, then to the high-resolution MPRAGE image, and finally into standard Montreal Neurological Institute space, using 12-parameter affine transformation and FNIRT nonlinear registration[37].

Four types of events were included in the general linear model (GLM): pumps on active balloons, cash outs, balloon explosions and pumps on control balloons. Two regressors for each of the four 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 of 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 (i.e., 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 versus 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 eight task-related regressors were included to capture variance associated with the temporal lag of the hemodynamic response along with six 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 italic> 0.05, unless otherwise noted. All analyses included sex, age, smoker status (smoker, 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 bold> 0.05). 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 pre-processed to include additional nuisance regressors: average signal of cerebrospinal fluid, and two metrics of motion-related artifact, specifically frame-wise 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 pre-processed images were used as covariates in separate whole-brain, voxel-wise correlation analyses.

Parameter estimates (average of β-values) corresponding to modulation of activation by pump number in the rDLPFC ROI were regressed against whole-brain voxel-wise 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, blue) ($F(1, 1{,}828.28) = 16.684$, $p < 0.001$) on pumping, but no significant main effect of group ($F(1, 62.413) = 0.043$, $p = 0.836$) and no interactions. There were no significant group differences in the average number of pumps before cashing out ($t = 1.342$, $p = 0.180$: Control: 2.84 ± 1.518 (mean ± SD); Methamphetamine: 2.74 ± 1.544). A two-tailed t-test showed significant differences in overall performance ($t(49) = 2.357$, $p = 0.022$) with Controls (33.33 ± 3.83 USD) earning more than Methamphetamine subjects (30.15 ±6.65 USD).

Task-Based fMRI

During pumping, modulation of rDLPFC activation by pump number was greater in the Control group than the Methamphetamine group, but Methamphetamine subjects displayed greater modulation of ventral striatal activation than Controls ($p < 0.05$, cluster-corrected) (Fig. 2) in ROI analyses. In a whole-brain analysis, Controls exhibited greater modulation of activation than the Methamphetamine Group in a cluster that included and extended beyond the rDLPFC ROI (peak coordinates: $x = 42$, $y = 40$, $z = 30$; extent: 610 voxels; Z-statistic: 3.4, $p < 0.001$, whole-brain corrected). No other significant group differences in whole-brain or in 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 bilateral anterior insula and right caudate in the Control group. Controls showed no positive correlations, and there were no positive or negative correlations in the Methamphetamine group ($p < 0.05$, whole-brain cluster-corrected).

RSFC and Relationship to Task-Based Activation

Compared with Controls, Methamphetamine subjects exhibited greater RSFC (midbrain seed) with the putamen, amygdala, hippocampus, insula, orbital, superior, and inferior frontal cortices, temporal cortices and parietal operculum ($p < 0.05$, whole-brain cluster-corrected) (Fig. 3, eTable 1). There were no regions where Controls exhibited greater midbrain RSFC than Methamphetamine subjects, nor were there any group differences in RSFC of the rDLPFC.

A group interaction with the modulation of rDLPFC activation on RSFC between midbrain and putamen was found at $p < 0.0005$, 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 ($p < 0.05$, whole-brain cluster-corrected) (Fig. 4, eTable 2). Controls showed no correlations between modulation of rDLPFC activation and midbrain RSFC.

There was a significant group interaction with modulation of rDLPFC activation during risk-taking on RSFC between rDLPFC and nucleus accumbens, putamen, amygdala, hippocampus, thalamus, and orbital frontal cortex ($p < 0.05$, whole-brain, cluster-corrected) (Fig. 5A, eTable 3). In post-hoc analysis, modulation of rDLPFC activation during risk-taking in Controls was positively correlated with 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 ($p < 0.05$, whole-brain cluster-corrected) (Fig. 5B, eTable 3). Methamphetamine subjects exhibited a negative correlation between modulation of rDLPFC activation during risk-taking and rDLFPC RSFC with the anterior cingulate cortex ($p < 0.05$, whole-brain cluster-corrected).

CONCLUSION

Methamphetamine users earned less than controls on the BART, and showed less sensitivity to risk and reward in the rDLPFC, greater sensitivity in ventral striatum, and greater mesocorticolimbic RSFC. Controls exhibited greater association between 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 controls 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 controls, and reported greater impulsiveness on the Barratt Impulsiveness Scale (BIS-11)[13], as did Methamphetamine subjects in this study ($t = 4.491$, $p < 0.001$ for BIS-11 total score: Control: 53.46 ± 10.24 (mean ± SD); Methamphetamine: 70.13 ± 9.27). Group differences in this study support this view, as 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 controls, 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 subjects. 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 that 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]. Repeated stimulant exposure, however, 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 subjects reflect dysregulated corticostriatal connectivity.

Greater midbrain RSFC in methamphetamine users than controls may reflect stimulant-induced sensitization as posited by the Incentive Sensitization Theory[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.

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 RSFC provides no directional information, it is unknown to what extent RSFC between rDLPFC and striatum reflects top-down control or spontaneous coherence of activation.

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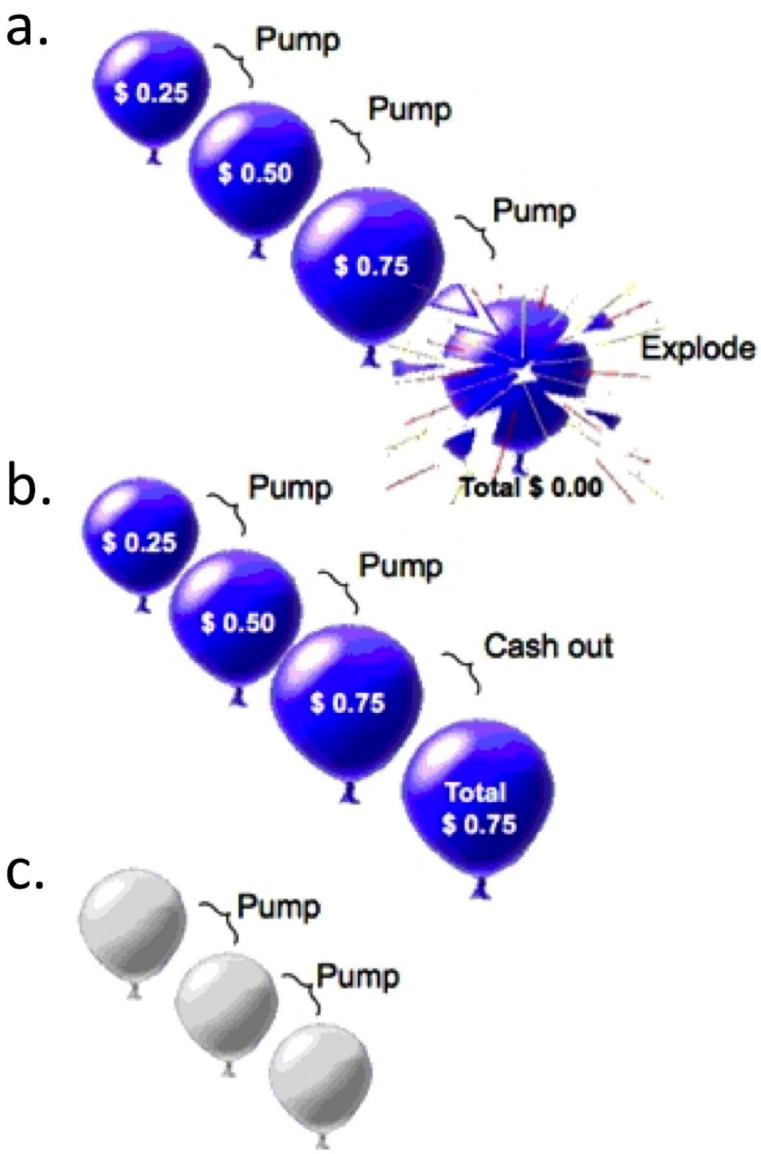

Figure 1. Schematic of Balloon Analogue Risk Task

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).

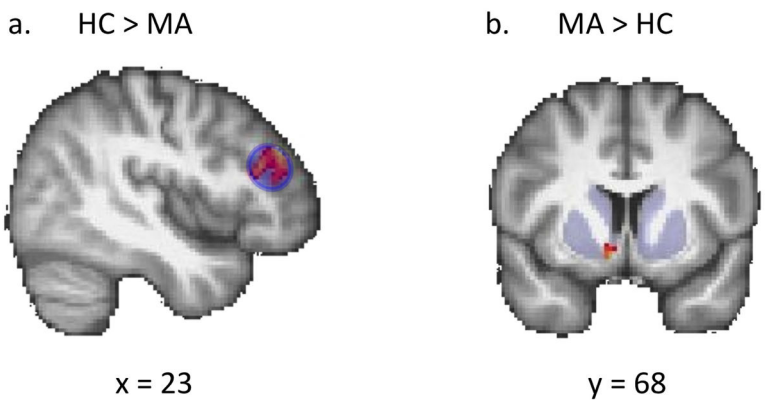

Figure 2. Modulation of ventral striatal and right DLPFC activation by pump number during risky decision-making (ROI analysis)

a. The Control Group exhibited greater modulation of activation by pump number in the right DLPFC during active balloon pumps compared to the Methamphetamine Group (see Methods for details of parametric modulation and ROI analyses). **b.** Compared to 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 ($p < 0.05$, cluster corrected). Results were controlled for age, sex, smoking status, and marijuana use.

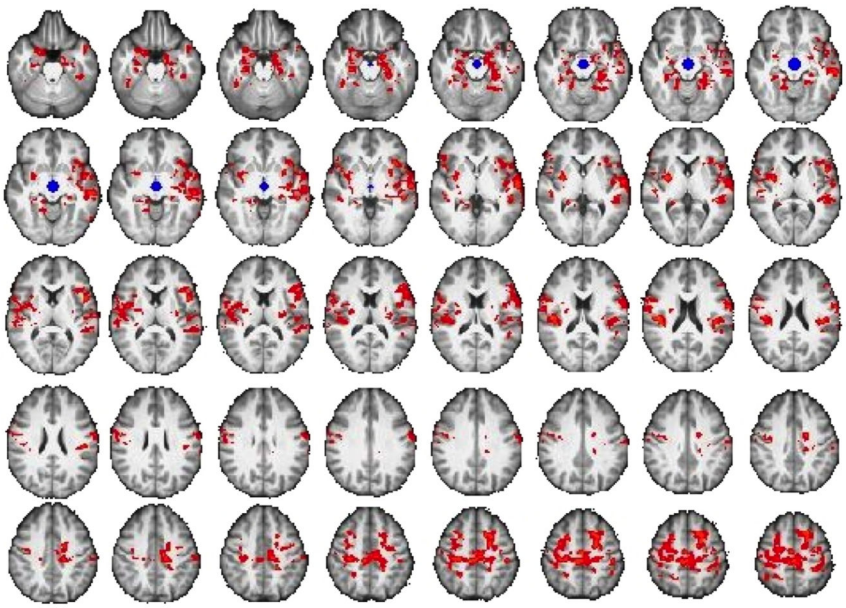

Figure 3. Comparison of mesocorticolimbic resting-state connectivity in Methamphetamine- and Control Group

Connectivity maps show greater connectivity between midbrain seed (shown in blue) and putamen, amygdala, hippocampus, insula, and prefrontal cortex in the Methamphetamine Group compared to the healthy control group ($p < 0.05$, whole-brain cluster corrected) (see eTable 2 for list of regions). Results controlled for age, sex, smoking status and marijuana use.

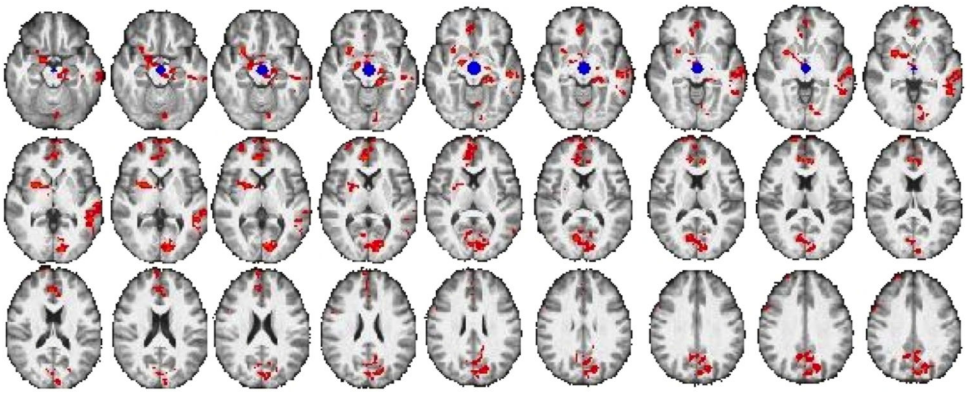

Figure 4. Relationship between resting-state connectivity of the midbrain and modulation of activation in DLPFC during risky decision-making in Methamphetamine Group

Connectivity maps show a negative correlation between modulation of activation in right DLPFC during balloon pumps and the connectivity between midbrain seed (shown in blue) and nucleus accumbens, putamen, amygdala, hippocampus, orbital frontal cortex, anterior cingulate, and superior frontal gyrus in the Methamphetamine Group ($p < 0.05$, whole-brain cluster corrected) (see eTable 3 for list of regions). Results controlled for age, sex, smoking status and marijuana use.

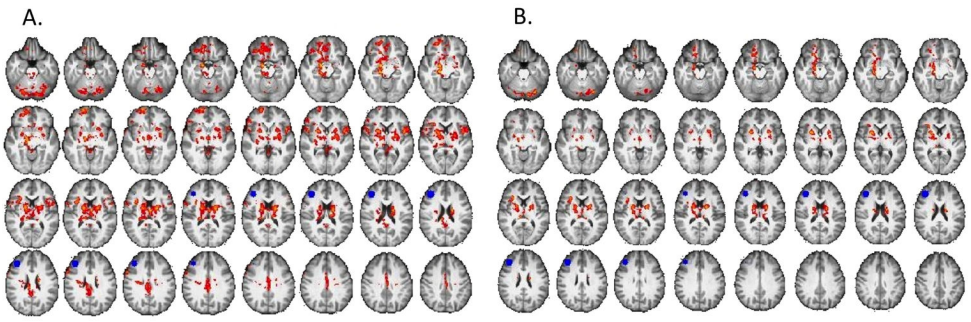

Figure 5. Relationship between resting-state connectivity of DLPFC and modulation of activation in DLPFC during risky decision-making

A. Brain regions where the relationship between resting-state connectivity with the DLPFC seed (shown in blue) and modulation of activation in right DLPFC by pump number varied by group. Connectivity maps show a group interaction between modulation of activation in right DLPFC during balloon pumps and RSFC of DLPFC with nucleus accumbens, putamen, amygdala, hippocampus, thalamus, orbital frontal cortex and cerebellum ($p < 0.05$, whole-brain cluster corrected) (see eTable 4 for list of regions). **B.** Post-hoc analysis within the Control Group showed a positive correlation between modulation of activation in right DLPFC during balloon pumps and RSFC of right DLFPC (show in blue) with caudate, putamen, nucleus accumbens, and orbital frontal cortex ($p < 0.05$, whole-brain cluster corrected) (see Table 4 for list of regions).

Table 1

Characteristics of Research Participants

	Healthy Control (n=27)[a]	MA-dependent (n=25)[b]
Age (years)[c]	33.88 ± 2.30	35.68 ± 1.64
Sex (# male)	16	12
Education (years)	13.62 ± 0.38	13.00 ± 0.38
Alcohol Use		
Days used in the last 30 d	4.36 ± 1.15	4.68 ± 1.64
Marijuana Use*		
Days used in the last 30 d	0.08 ± 0.08	1.68 ± 0.70
Tobacco Use (# smokers)	16	20
Days used in the last 30 d	17.57 ± 2.87	21.16 ± 2.54
Methamphetamine Use		
Days used in the last 30 d		23.60 ± 1.29
Grams per week		3.57 ± 1.04
Years of heavy use		8.59 ± 1.37

[a] n=18 and

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

[c] Data shown are means ± SEM

* Significant differences between the groups by Student's t-test (p = 0.033).