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Blunted Frontostriatal Blood Oxygen Level–Dependent Signals Predict Stimulant and Marijuana Use

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ABSTRACT

BACKGROUND: Occasional recreational stimulant (amphetamine and cocaine) use is an important public health problem among young adults because 16% of those who experiment develop stimulant use disorder. This study aimed to determine whether behavioral and/or neural processing measures can forecast the transition from occasional to problematic stimulant use.

METHODS: Occasional stimulant users completed a Risky Gains Task during functional magnetic resonance imaging and were followed up 3 years later. Categorical analyses tested whether blood oxygen level–dependent (BOLD) responses differentiated occasional stimulant users who became problem stimulant users (n = 35) from those who desisted from stimulant use (n = 75) at follow-up. Dimensional analyses (regardless of problem stimulant user or desisted stimulant use status; n = 144) tested whether BOLD responses predicted baseline and follow-up stimulant and marijuana use.

RESULTS: Categorical results indicated that relative to those who desisted from stimulant use, problem stimulant users 1) made riskier decisions after winning feedback; 2) exhibited lower frontal, insular, and striatal BOLD responses to win/loss feedback after making risky decisions; and 3) displayed lower thalamic but greater temporo-occipital BOLD responses to risky losses than to risky wins. In comparison, dimensional results indicated that lower BOLD signals to risky choices than to safe choices in frontal, striatal, and additional regions predicted greater marijuana use at follow-up.

CONCLUSIONS: Taken together, blunted frontostriatal signals during risky choices may quantify vulnerability to future marijuana consumption, whereas blunted frontostriatal signals to risky outcomes mark risk for future stimulant use disorder. These behavioral and neural processing measures may prove to be useful for identifying ultra–high risk individuals prior to onset of problem drug use.

Keywords: Amphetamine, Cocaine, Decision making, fMRI, Reward, Stimulant

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Recreational stimulant use is a growing concern among young adults, with 4.4% and 5% to 35% of college students endorsing cocaine (1) and recreational amphetamine (methylphenidate, dextroamphetamine) (2) use, respectively, and 16% of cocaine experimenters developing dependence within 10 years (3). To develop cost-effective prevention and intervention strategies, it is crucial to identify ultra–high risk recreational users. However, little is known about biobehavioral markers forecasting trajectory of occasional stimulant use to stimulant use disorder (SUD). Previous stimulant use research is predominantly cross-sectional, comparing individuals with chronic stimulant use with healthy individuals; although findings from these studies highlight brain disruptions related to drug use, they cannot disentangle whether disruptions preceded or were a result of chronic use.

Young adulthood is a period of increased independence, often providing more opportunities for risky behavior such as drug experimentation. Risky behavior can be defined as actions that may be subjectively desirable but are potentially harmful (4) and is typically quantified in young adults by their degree of substance use, unprotected sex, health habits, and crime engagement (5). Risk taking often occurs in clusters of maladaptive behaviors, suggesting underlying impairments in decision making (6–8).

Decision making involves several brain processes, including learning, inhibition, and outcome assessment, specifically appraising positive (i.e., safety or reward) or negative (i.e., risk or punishment) valence of choices (9,10). Functional magnetic resonance imaging (fMRI) research indicates that individuals with SUD show impaired decision making associated with altered brain activation in executive control and reward processing regions (11–15). Decision making is thought to involve a cooperative relationship between an impulsive system activated by immediate rewards and an

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inhibitory control system. Through learning, the control network allows individuals to resist immediate attraction to rewards in favor of longer-term advantageous outcomes (16). In SUD, biobehavioral indices of risk taking suggest an underlying imbalance between the control and impulsive systems.

The control system integral to decision making comprises prefrontal cortex (PFC), theorized as responsible for learning the relationship between stimuli and outcome, working memory, and inhibiting behavior (17). SUD samples exhibit frontal lobe impairments associated with compromised decision making and increased risk behavior (17). For example, cocaine abusers exhibit dorsolateral PFC (DLPFC) hypoactivation during response inhibition (18) and prediction of uncertain outcomes (19); in cocaine dependence, orbitofrontal cortex and DLPFC attenuation are linked to reduced ability to differentiate between variable monetary gains (20). Similarly, methamphetamine users inaccurately process success or failure of available options, a pattern associated with orbitofrontal cortex/DLPFC hypoactivation (21).

Working in conjunction with frontal regions is striatum, an area associated with reward processing (22), selecting and initiating actions (23), and learning (24). During the Iowa Gambling Task (25), healthy individuals show stronger striatal activation to wins than to losses (26,27), but amphetamine-dependent individuals demonstrate hypersensitive striatal responses to rewards (28). Cocaine and methamphetamine users also exhibit striatal hyperactivation but frontal hypoactivation during risky decision-making tasks such as the Iowa Gambling Task and the Balloon Analogue Risk Task (29) that is linked to riskier behavioral performance (13,28,30). This suggests that such neural patterns during decision making promote favoring of risky incentives (28).

Evidence from fMRI studies has led researchers to theorize that frontal lobe and striatum form a functional circuit with insular cortex and anterior cingulate cortex (ACC); these regions coordinate to integrate emotional and autonomic information about rewards into goal-oriented behavior (31,32). ACC is proposed to be involved in emotion and behavior management based on its neural connections to both the emotion processing limbic system and the cognitive control center, PFC (33). Insula is proposed to play a role in interoceptive processing, wherein individuals integrate physiological cues to differentiate between risky and safe decisions and transform these cues into conscious feelings and behaviors (32). ACC and insula hypoactivation is evident in chronic stimulant users in response inhibition and error monitoring during decision making (34–36). Evidence for aberrant activity in key components of the PFC-limbic network has led researchers to suggest that weakened ability to accurately process information about options and control behaviors leads to favoring choices that offer immediate, rather than delayed, rewards (37).

Cross-sectional studies of occasional stimulant users (OSUs) report decision-making impairments that parallel findings in stimulant-dependent individuals, including 1) weakened inhibitory control and reduced cognitive flexibility (38,39); 2) neuropsychological impairments in executive functions (e.g., attention, set shifting) (40,41); and 3) frontal, striatal, and insular attenuation during a Risky Gains Task (RGT) paired with reduced ability to differentiate between safe and risky decisions (42).

Several research groups have recognized limitations of cross-sectional addiction research and have shifted toward a longitudinal approach to understand the transition to problematic substance use (43–45). Structural MRI studies show that decreased brain volume in frontocentral regions at age 14 years predicts binge drinking at age 16 (46) and that frontostriatal regions are linked to heightened stimulant use in OSUs 1 to 2 years later (45). However, fMRI has been less applied to predict the development of SUD.

The current longitudinal study used follow-up clinical and drug use data from OSUs (n = 144) 3 years after an fMRI scan (42) to determine whether baseline behavioral and blood oxygen level–dependent (BOLD) responses during the RGT 1) differentiated young adults who became problem stimulant users (PSUs; n = 35) from those who desisted from stimulant use (desisted stimulant users [DSUs]; n = 75) during the 3-year interim (categorical approach) and 2) predicted cumulative baseline and follow-up stimulant and marijuana use across OSUs, regardless of clinical status (dimensional approach; n = 144), to address concerns regarding significant rates of marijuana and stimulant co-use (47). Analyses compared BOLD activity related to specific task requirements: decision contrasts compared BOLD activity during risk-taking choice trials versus safe choice trials; outcome contrasts compared BOLD activity on trials where each subject took a risk and subsequently earned a win or a loss.

Categorical hypotheses were tested based on prior biobehavioral findings in stimulant- dependent individuals: 1) PSUs would exhibit riskier task performance than DSUs; 2) PSUs would show greater striatal BOLD signals than DSUs to outcomes, particularly in response to risky wins; and 3) PSUs would exhibit lower PFC, insular, and cingulate BOLD signals during decision making. Because dimensional analyses were exploratory, no a priori hypotheses were tested.

METHODS AND MATERIALS

Participants

The University of California, San Diego, Human Subjects Review Board approved the study protocol. Participants were recruited through newspapers, internet ads, and fliers mailed to college students. Figure 1 demonstrates participant recruitment and categorical/dimensional data analysis protocol. A total of 1025 individuals were phone screened, and 184 OSUs meeting study criteria provided written informed consent to participate. OSU inclusionary criteria were as follows: 1) within the last 6 months, two or more separate occasions of cocaine or prescription amphetamine use (e.g., methylphenidate, dextroamphetamine) without a prescribed purpose; 2) no lifetime stimulant dependence; 3) no lifetime stimulant use for medical reasons; and 4) no drug treatment interest. Participants completed three sessions: 1) a baseline diagnostic interview to determine lifetime psychiatric diagnoses and current drug use patterns (n = 184), 2) a neuroimaging session completing the RGT (n = 161), and 3) a follow-up interview session 3 years later to determine changes in drug use and clinical diagnoses (n = 144). The current study includes data from OSUs who completed all three sessions (n = 144). No OSU reported using methamphetamines at baseline;

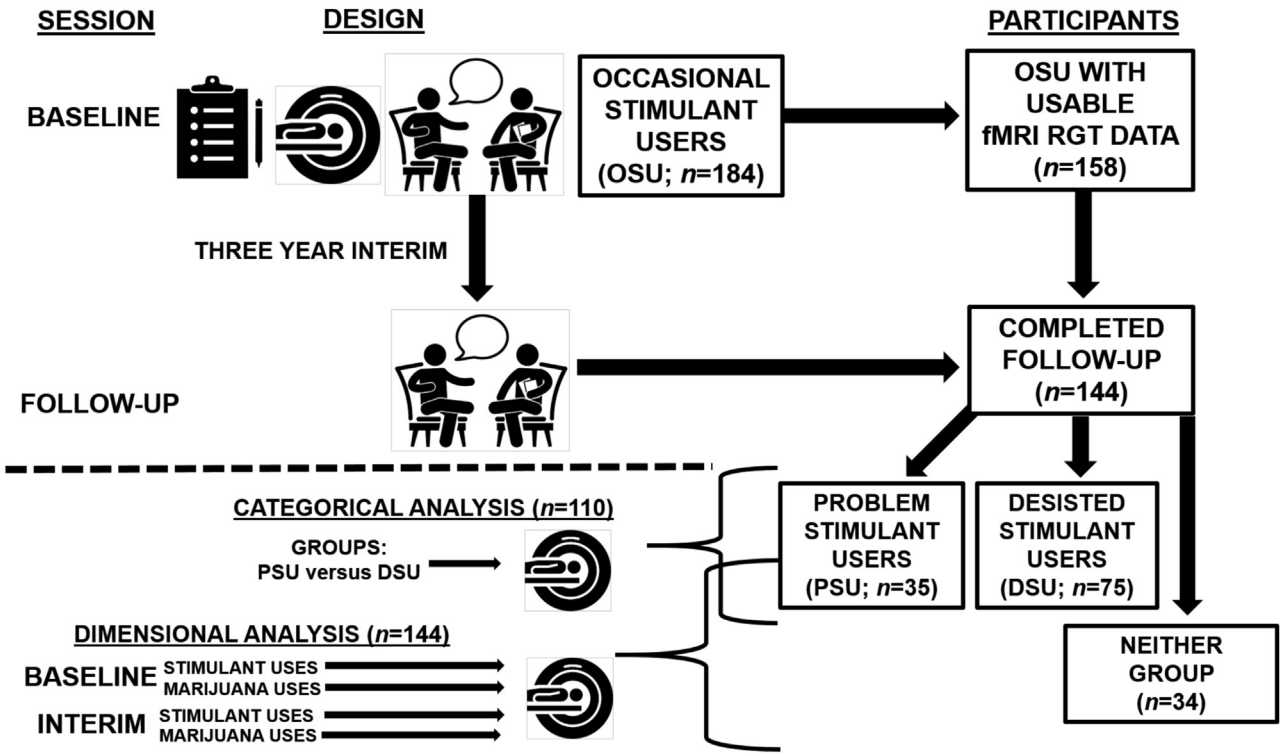

Figure 1. Overview of study design and data analyses. At baseline, occasional stimulant users (OSUs) completed questionnaires, a clinical interview, and a functional magnetic resonance imaging (fMRI) scan recorded during the Risky Gains Task (RGT). OSUs then completed a follow-up clinical interview 3 years later that included assessment of interim drug use. Only OSUs with both usable fMRI data at baseline and complete follow-up drug use data were included in longitudinal analyses. Categorical analysis of baseline self-report and fMRI data included a subset of OSUs who met criteria for problem stimulant user (PSU) or desisted stimulant user (DSU) groups on the basis of interim drug use patterns and follow-up interview diagnostic criteria. Dimensional analysis included all OSUs and compared relationships between interim stimulant and marijuana use and baseline self-report and fMRI data, controlling for baseline stimulant and marijuana use.

all baseline stimulant use was of cocaine and prescription stimulants.

Baseline Session

Participants were screened for lifetime DSM-IV Axis I diagnoses (including attention-deficit/hyperactivity disorder and substance abuse/dependence) and Axis II antisocial personality disorder by the Semi-Structured Assessment for the Genetics of Alcoholism II (48) and were administered the Wechsler Test of Adult Reading, a verbal intelligence measure (IQ) (49). Exclusion criteria are outlined in Stewart *et al.* (50) and are included in the Supplement. Subjects completed a baseline urine toxicology screen and were excluded if they tested positive for stimulants (thereby avoiding confounding effects from recent use). Testing positive for cannabis was not exclusionary because its presence in urine may last up to 6 weeks.

Risky Gains Task

The RGT (illustrated in Figure 2) has been previously described by our experimental group (42,51–54). On each trial, participants were shown the numbers 20, 40, and 80 in increasing order, which represented the number of cents to be added to their total. Participants were informed that 20 was always the "safe option" but that they had the option to wait 1 second to receive 40 cents or to wait an additional second to receive 80 cents. They were also informed of the potential that 40 or 80 would appear in red font, denoting actual losses of money (−40 or −80) from the total score, with 40 and 80 being explicitly called "risky options."

Unknown to subjects, −40 and −80 outcome frequencies were predefined so that the final gain was identical regardless of whether they selected 20, 40, or 80 cents. That is, there was no actual advantage to selecting risky options compared with safe options. Participants were told that a positive value needed to be collected via an index finger button press within a subsequent 1-second window. A press outside of that timeframe would result in a loss. The 1-second length was chosen to allow slow-responding individuals to collect an option. Auditory and visual feedback ("yay"/"You win" for wins and "yuck"/"You lose" for losses) followed each choice. Cumulative total (in dollars) was displayed after trial completion to allow performance monitoring. The task consisted of 96 trials lasting 3.5 seconds each. Three trial types were presented in a preset randomized order: 54 rewarded (+20, +40, +80) trials, 24 punished −40 trials, and 18 punished −80 trials. In addition to potential losses due to slow responses or nonresponses on rewarded trials, the RGT design led to each participant

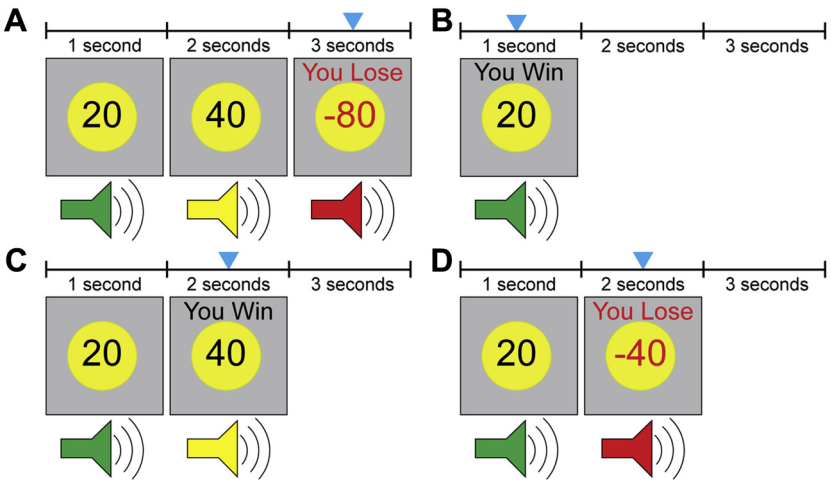

Figure 2. Depiction of trial types presented during the Risky Gains Task: **(A)** lose 80; **(B)** win 20; **(C)** win 40; **(D)** lose 40. The blue arrowhead indicates which value the participant chose [Reproduced with permission from Connolly *et al.* (75).]

receiving a different amount of −40 and −80 trials. If a participant pressed to collect 20 on a trial meant to be a −40 trial, or tried to collect 20 or 40 on a dedicated −80 trial, the participant received the collected amount, thereby reducing the number of punished trials.

Image Acquisition

The scanning session lasted approximately 60 minutes and included an anatomical scan as well as four functional tasks: Stop Signal (55), Paper Scissors Rock (56), two-choice prediction (57), and RGT. Prior to scanner entry, a brief RGT training session was conducted. The RGT was administered as a randomized fast–event related design, time locked to the onset of 256 whole brain acquisitions (T2*-weighted echo-planar images on a Signa EXCITE 3T scanner [GE Healthcare; Milwaukee, WI]: repetition time = 2000 ms, echo time = 32 ms, field of view = 230 × 230 mm^2, 64 × 64 matrix, 30 2.6-mm axial slices, 1.4-mm gap, flip angle = 90°, duration = 8 minutes 32 seconds). Six resting-state trials were intermixed throughout the 96 trials and were not used in analysis. A high-resolution T1-weighted image (repetition time = 8 ms, echo time = 3 ms, field of view = 250 × 250 mm^2, 192 × 256 matrix interpolated to a 256 × 256 matrix, flip angle = 12°, 172 sagittally acquired slices, .97 × .97 × 1 mm^3 voxels) was also obtained as a reference.

Three-Year Follow-Up Interview

OSUs participated in another standardized interview 3 years after their baseline sessions (Figure 1), by phone or in-person, to assess drug use severity during the interim period. Analyses were conducted using both categorical and dimensional definitions of interim stimulant use as recommended by Rabin and Moeller (58). For categorical analyses, participants were grouped into one of two categories: PSUs or DSUs. PSUs (n = 35) were a priori defined based on the current DSM-5 criteria for SUD (59): 1) continued stimulant use since baseline and 2) endorsement of two or more DSM-IV symptoms of stimulant abuse or dependence occurring together for 6 or more consecutive interim months. Among PSUs, 51% met criteria for cocaine abuse, 23% met criteria for cocaine dependence, 46% met criteria for amphetamine abuse, and 17% met criteria for amphetamine dependence. DSUs (n = 75) were defined based on the emphasis of the choice to desist as a critical part of addiction recovery models (60) and in the prevention of transition to SUD (61): 1) no 6-month periods of three or more stimulant uses and 2) no endorsement of interim SUD symptoms. OSUs who did not meet criteria for either PSU or DSU (n = 34) were excluded from categorical analyses because of the highly variable nature of those who did not fit either category (e.g., met only one abuse/dependence criterion, used too many times during interim but no accompanying symptoms). Dimensional analyses were conducted using all OSUs (n=144), where RGT BOLD signals were correlated with baseline and interim stimulant and marijuana uses (quantified as total sessions).

Data Analysis

Baseline Characteristics and Behavior. Group differences in age, IQ, education, drug use, and RGT behavior were compared in SPSS (version 24; IBM Corp., Armonk, NY) by independent-samples t tests, whereas differences in gender, race/ethnicity, and handedness were analyzed using chi-square tests (Table 1). To evaluate whether follow-up status differed as a function of baseline preferred stimulant type (cocaine vs. prescription amphetamines) or in relation to the history of/presence of comorbid alcohol and marijuana abuse or dependence, chi-square analyses were performed.

Risky Gains Task. The RGT was analyzed in two stages. First, decision contrasts evaluated differences between groups when individuals made a "risky" (±40 or ±80) versus "safe" (+20) decision. All risky responses were combined to create a relatively even split between risky and safe decisions. Second, outcome contrasts evaluated differences in response after wins (+40 and +80) versus losses (−40 and −80) on risky trials; participants without five of each trial type (safe [20] vs. risky [40 or 80]) were excluded from analysis.

Table 1. Group Demographics

	PSUs (n = 35)		DSUs (n = 75)		Statistics		
	(%)		(%)		df	χ^2	p
Gender, Female	45.71		38.67		1	0.49	.48
Marijuana-Positive Urine[a]	40.0		37.3		2	0.52	.77
Right Handedness	97.14		96.00		1	0.09	.77
Race/Ethnicity, Caucasian	74.30		77.30		1	0.12	.73
Met Criteria for History at Baseline							
Alcohol abuse	45.71		52.00		1	0.38	.54
Alcohol dependence	9.33		5.71		1	0.42	.52
Marijuana abuse	52		62.85		1	1.14	.29
Marijuana dependence	24		28.57		1	0.26	.61
Met Criteria for Interim Abuse or Dependence							
Alcohol abuse	54.29		38.67		2	3.67	.30
Alcohol dependence	11.43		8.00		2	2.70	.44
Marijuana abuse	51.43		37.33		2	3.03	.22
Marijuana dependence	8.57		6.67		2	2.38	.31
	Mean	SD	Mean	SD	df	t	p
Age, Years	20.74	1.70	20.95	1.43	108	0.65	.52
Education, Years	14.60	1.48	14.63	1.35	108	0.09	.93
Verbal IQ	109.71	6.07	108.87	7.74	103	0.56	.58
Impulsivity (BIS-11)	67.00	9.75	64.53	9.06	108	1.15	.25
Sensation Seeking (SSS-V)	25.00	4.81	24.59	4.45	108	0.38	.97
Depression (BDI)	1.53	1.54	3.03	3.81	104	2.21	.03
Behavioral Performance							
Won money followed by risk	0.58	1.91	0.50	0.18	108	2.05	.04
Lost money followed by risk	0.32	0.16	0.29	0.20	108	0.72	.48
Baseline Drug Use[b]							
Amphetamine	28.63	38.74	21.04	64.40	108	0.65	.52
Cocaine	26.03	41.73	17.72	38.82	108	1.02	.31
Marijuana	814.09	1118.75	842.08	1271.89	108	0.11	.91
Interim 3-Year Drug Use[c]							
Prescription stimulant	62.63	88.79	5.58	23.13	106	5.18	$< .001$
Cocaine	283.03	622.56	8.49	35.58	106	3.80	$< .001$
Marijuana	588.62	946.77	838.28	1974.42	106	0.70	.49
Methamphetamine	38.35	215.985					
All stimulants	384.01	627.911	14.09	41.64	106	5.07	$< .001$
Recency of Drug Use, Time of Scan[d]							
Prescription stimulant	74.56	88.93	193.43	294.44	70	−2.71	.01
Cocaine	78.29	100.33	125.46	223.12	72	−0.99	.33
Marijuana	57.17	149.62	30.46	73.56	35	0.93	.36

BDI, Beck Depression Inventory; BIS-11, Barratt Impulsiveness Scale–Version 11; DSUs, desisted stimulant users; PSUs, problem stimulant users; SSS-V, Sensation-Seeking Scale–Form V.

[a]Determined by urine screen at the outset of the neuroimaging session.

[b]Lifetime uses of the drug at the time of baseline clinical interview were quantified by the number of discrete sessions consumed.

[c]Number of discrete sessions of drug use from the time of the baseline clinical interview to the time of the 3-year follow-up interview.

[d]Recency of drug use at the time of the neuroimaging session was quantified by days since last use.

Neuroimaging. fMRI data were analyzed using Analysis of Functional Neuroimages software (62). Single-subject data preprocessing procedures are outlined in Reske *et al.* (42). Multiple regressor analysis and individual linear contrasts were computed in 3dDeconvolve, including six motion regressors as well as baseline and linear drift. Deconvolution was performed to examine the decision contrast (risky = ±40 and ±80; safe = +20) and outcome contrast (risky wins = +40 and +80; risky losses = −40 and −80). Voxels were resampled into $4 \times 4 \times 4$-mm^3 space, and whole-brain voxelwise normalized percentage signal change, the main dependent measure, was determined by dividing the beta coefficient for each of the predictors of interest (BOLD signals for risky vs. safe decisions and risky wins vs. risky losses) by the beta coefficient for the

baseline regressor and multiplying by 100. A Gaussian spatial filter (4 mm full width at half maximum) blurred percentage signal change values, which were then normalized to Analysis of Functional Neuroimages Talairach coordinates (40 × 48 × 38-voxel coverage). Individual subject values for risky decisions, safe decisions, risky win outcomes, and risky loss outcomes for each voxel included in a whole-brain mask were extracted for statistical analyses. Individual voxels meeting a $p < .01$ significance criterion as a result of statistical tests outlined below were evaluated further to determine whether they comprised a significant brain cluster after correction for multiple comparisons.

In categorical analyses, for each voxel, a linear mixed effects model was performed in R (63) to identify significant regions of percentage signal change between PSUs and DSUs for decision and outcome analyses separately. Group was the between-subjects variable, and subject was a random variable. Within-subject variables were decision type (risky vs. safe) and outcome type (risky wins vs. risky losses). Cohen's *d* was calculated to determine effect sizes.

In dimensional analyses, multiple regressions were computed for each brain voxel, with two separate dependent variables: 1) percentage signal change for risky minus safe decisions and 2) percentage signal change for risky wins minus losses. Predictors in each regression were the following: 1) baseline stimulant uses, 2) interim stimulant uses, 3) baseline marijuana uses, and 4) interim marijuana uses. All predictors were log transformed due to nonnormality and *Z*-scored prior to regression entry.

In extracting significant whole-brain clusters, neuroimaging analysis software has been criticized for underestimating spatial autocorrelation, leading to insufficient multiple comparison corrections. In response to these concerns, 1) the updated 3dFWHMx program was employed to more reliably estimate true autocorrelation and smoothness present following blurring (5 mm) and 2) an updated version of 3dClustSim was run to account for autocorrelation given our voxel/whole-brain mask size, 10,000 Monte Carlo simulations and two-sided thresholding with an overall voxel *p* statistical threshold of .01 and a corrected clusterwise alpha value of .01. Data smoothness was approximately 6 mm, and > 19 neighboring voxels (or > 1216 μL) comprised a significant brain cluster.

RESULTS

Demographic and Behavioral Characteristics

Although groups did not differ in baseline stimulant use (Table 1), PSUs used amphetamines more recently prior to the fMRI scan than DSUs. Groups did not differ on baseline or interim marijuana uses or on frequency of baseline/interim cannabis abuse or dependence diagnoses. DSUs endorsed higher depression scores than PSUs, although they were not clinically elevated. Preferred stimulant type at baseline was not related to follow-up group (Table 2).

Although groups did not differ in frequency of type of trial chosen (20, 40, or 80), rewarded/punished trials, or risky losses followed by a risky loss (Table 3), PSUs made a greater number of risky decisions after a win than DSUs, while DSUs made more safe decisions following a win.

Table 2. Chi-Square Results Evaluating Whether Preference of Stimulant Type at Baseline Differed Between DSUs and PSUs

	Preference			
Group	Cocaine	None	Prescription Amphetamines	Total
DSUs				
Count	27	14	34	75
% Within group	36	18.7	45.3	100
Expected count	25.9	13	36.1	75
PSUs				
Count	11	5	19	35
% Within group	31.4	14.3	54.3	100
Expected count	12.1	6	16.9	35
Total	38	19	53	110
	df	χ^2	*p*	
	2	0.81	.67	

DSUs, desisted stimulant users; PSUs, problem stimulant users.

Neuroimaging: Categorical Analyses

For purposes of illustration, interaction effects are graphed as difference scores (Table 4).

Decision Contrast. No group main effect emerged. The group by decision interaction indicated that PSUs exhibited greater cingulate and precuneus BOLD signals to risky decisions than to safe decisions when compared with DSUs (Figure 3).

Outcome Contrast. The group main effect demonstrated that across risky wins and losses, PSUs displayed weaker superior/middle frontal, cingulate, insula, striatum (putamen, lentiform nucleus), and posterior cingulate BOLD

Table 3. Behavioral Performance

	PSUs (*n* = 35)		DSUs (*n* = 75)		Statistics		
	Mean	SD	Mean	SD	*df*	*t*	*p*
Total 20 Trials	39.43	18.00	45.53	16.23	108	−1.77	.08
Total 40 Trials	35.71	11.23	34.03	10.33	108	0.78	.44
Total 80 Trials	20.77	13.32	16.27	10.81	108	1.89	.06
Total Risk Trials, 40 and 80 Combined	56.49	18.07	50.29	16.23	108	1.80	.08
Won Money Followed by Risky Choice	0.58	1.91	0.50	0.18	108	2.05	.04
Won Money Followed by Safe Choice	0.42	0.17	0.50	0.18	108	−2.15	.03
Lost Money Followed by Risky Choice	0.32	0.16	0.29	0.20	108	0.72	.48
Lost Money Followed by Safe Choice	0.45	0.28	0.52	0.28	108	−1.19	.24
Total Risky Win Trials	0.58	0.19	0.51	0.17	108	1.91	.06
Total Risky Loss Trials	18.46	7.34	16.07	6.32	108	1.75	.08
% of Loss After a Loss Trial	0.22	0.14	0.20	0.13	108	0.51	.61

DSUs, desisted stimulant users; PSUs, problem stimulant users.

Table 4. Categorical Neuroimaging Results: PSUs Versus DSUs

Voxels	*x*	*y*	*z*	L/R	Regions in Cluster	BA	Results
Group × Decision Interaction							
29	12	−56	29	R	Precuneus, cingulate gyrus	7/31	Safe: DSUs > PSUs; *d* = 0.65 Risky: NS
Outcome Group Main Effect							
43	−22	−32	60	L	Postcentral/precentral gyrus, superior/middle frontal gyrus, superior parietal lobule, paracentral lobule	3–7/40	DSUs > PSUs; *d* = 0.90
30	−30	−14	21	L	Insula, lentiform nucleus, putamen, claustrum	13	DSUs > PSUs; *d* = 1.06
20	9	−52	30	R	Precuneus, cingulate gyrus, posterior cingulate	7/31	DSUs > PSUs; *d* = 0.82
Group × Outcome Interaction							
34	6	−19	10	R	Thalamus, medial dorsal nucleus, pulvinar, ventral lateral nucleus		Lose risky: DSUs > PSUs; *d* = 0.58 Win risky: NS
24	−41	−68	5	L	Middle/inferior occipital gyrus, inferior/middle temporal gyrus	19/37	Lose risky: DSUs > PSUs; *d* = 0.40 Win risky: DSUs < PSUs; *d* = 0.24

Coordinates (*x*, *y*, *z*) reflect center of mass. Voxelwise threshold for effect > $F_{1,108} = 6.88$, $p < .01$, two tailed, for ≥ 19 contiguous voxels. Cohen's *d* represents effect size.

BA, Brodmann area; DSUs, desisted stimulant users; L, left hemisphere; NS, not significant; PSUs, problem stimulant users; R, right hemisphere.

signals than DSUs (Figure 4). The group by outcome interaction showed that PSUs exhibited greater thalamic, inferior/middle temporal, and occipital BOLD signals to win risky feedback than to lose risky feedback than DSUs (Figure 5).

Neuroimaging: Dimensional Analyses

Higher interim marijuana use was linked to lower superior/middle/inferior frontal, inferior parietal, superior/middle temporal, thalamus, and precuneus activation for risky decisions compared with safe decisions (Figure 6). No significant clusters emerged for baseline marijuana or baseline/interim stimulant uses (Table 5).

DISCUSSION

This study employed categorical and dimensional analysis strategies in OSUs to determine whether baseline biobehavioral RGT responses predicted future stimulant use.

Categorical Analyses: PSUs Versus DSUs

Three hypotheses were tested. First, consistent with the prediction that PSUs would exhibit riskier task performance than DSUs, PSUs more frequently made a risky decision following a win compared with DSUs, while DSUs more frequently made a safe decision following a risky win. This pattern supports previous findings that PSUs are more reactive to rewards (28). Second, although it was predicted that PSUs would show greater activation in reward processing striatal regions to risky wins than to risky losses when compared with DSUs, our results demonstrated the opposite effect, with PSUs exhibiting lower striatal BOLD signals across outcomes than DSUs. However, this finding is consistent with a longitudinal study of sensation-seeking adolescents in which striatal hypoactivation predicted future problematic drug use; the authors theorized that lower striatal activity may lead to a compensatory mechanism in which one seeks out increased risk to gain greater stimulation, thereby balancing reward center hypoactivation (44).

PSUs exhibited greater temporo-occipital BOLD signals to wins than to losses, findings consistent with a recent meta-analysis reporting that 86% of addiction-related neuroimaging studies demonstrate significant visual cortex activity to drug cues (64). Although the RGT did not test drug-related responses, our results demonstrate an analogous relationship to general reward cues, suggesting that PSUs may allocate greater visual attention to risky rewards than to risky losses. Middle temporal lobe is involved in memory of reward-based information critical for future-oriented decision making, suggesting that PSUs may be less able to consolidate information about outcomes differently (65). Together, PSUs are characterized by visual attention and memory activation during risky rewards but blunted responsivity to loss outcomes.

Our third prediction was supported in that PSUs exhibited lower PFC, insula, and cingulate BOLD signals than DSUs

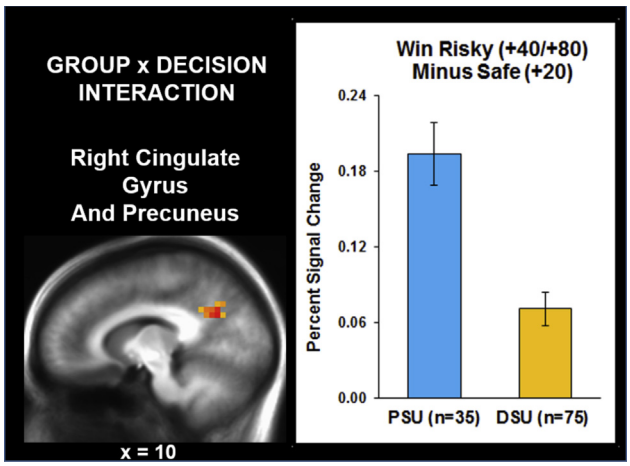

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Figure 3. Group × decision interaction. Problem stimulant users (PSUs) displayed greater blood oxygen level–dependent signals in precuneus and cingulate regions for risky decisions than for safe decisions when compared with desisted stimulant users (DSUs).

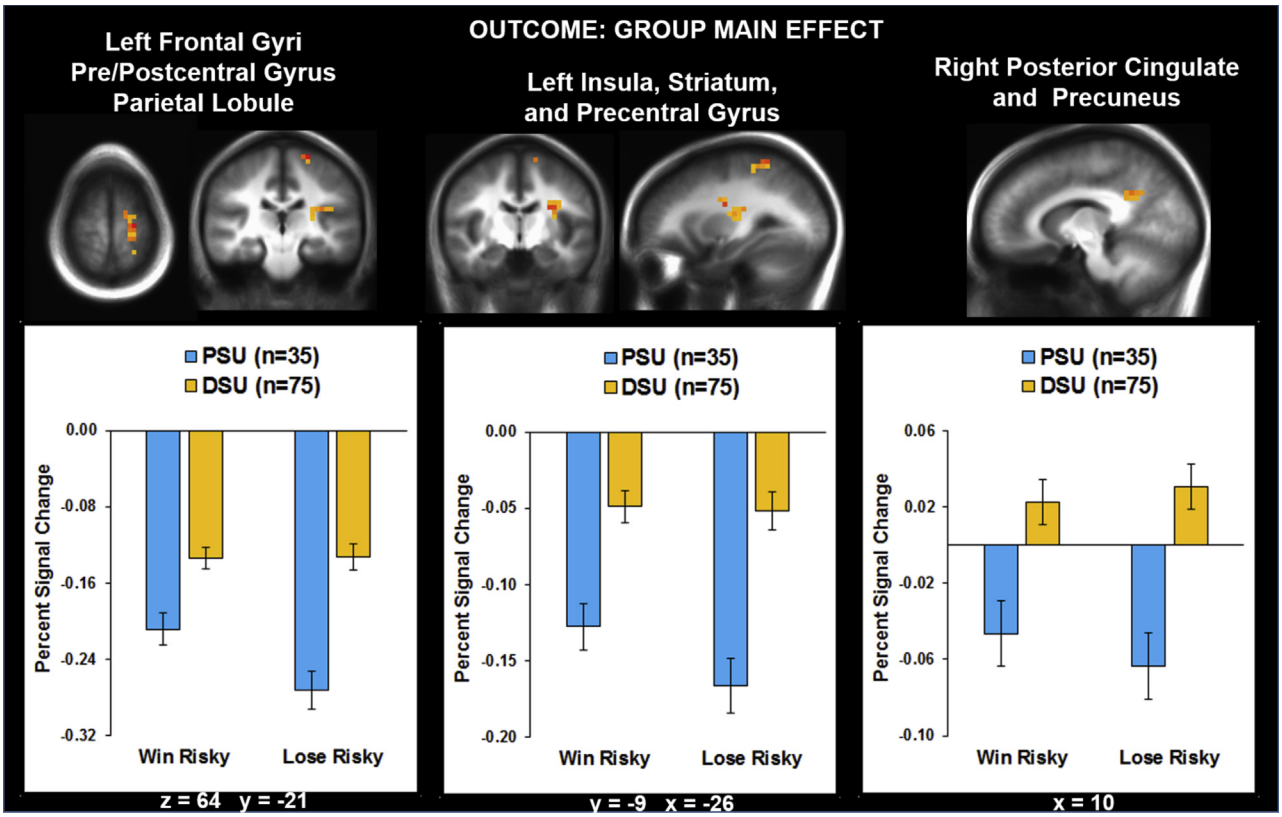

Figure 4. Outcome group main effect. Across risky wins and losses, problem stimulant users (PSUs) exhibited lower blood oxygen level–dependent signals than desisted stimulant users (DSUs) in left frontal, central, parietal, and limbic regions as well as right posterior cingulate and precuneus.

during risky feedback. These findings align with a recent study conducted by our research group demonstrating that during a task evaluating how individuals learn to make decisions, PSUs exhibited lower insula and ACC activation across all available outcomes (wins, losses, and ties) than DSUs (66). Such patterns are consistent with previous reports of PFC, insula, and ACC attenuations in chronic stimulant users that are linked with decreased ability to adapt behavior using prior experiences/reduced inhibitory control, interoceptive awareness, and conflict monitoring, respectively (34–36,52). Thus, young adults predisposed to SUD may have prior deficits in recruiting neural effort toward critical decision-making processes.

Nonhypothesized group differences also emerged in thalamic, precuneus, and posterior cingulate regions that warrant discussion. PSUs showed relatively greater precuneus and posterior cingulate BOLD signals when making risky decisions than when making safe decisions when compared with DSUs. Such differences are consistent with previous findings in SUD samples that heightened activation of these areas during exteroceptive awareness (evaluative processing of external stimuli) may underlie the maintenance and exacerbation of substance use (67). Greater thalamic response to risky reward versus loss feedback in PSUs is consistent with research demonstrating that thalamic BOLD signals are linked to relapse in cocaine-dependent individuals (68). Thalamus acts as a relay center for the brain by sending sensory information to insula for further interoceptive processing (32); hypoactivation to loss may reflect differences in relay and integration of information during decision making.

With respect to baseline characteristics, DSUs endorsed higher baseline levels of state depression than PSUs, which may have affected RGT performance given that individuals with depression tend to be risk averse (69). However, given that mean scores for DSUs are substantially below the Beck Depression Inventory threshold for clinical depression [in nonclinical populations, scores above 20 indicate depression (70); it is unlikely that DSUs performed in a manner consistent with samples with depression].

Dimensional Analyses: Interim Marijuana Use

Across OSUs, lower frontal, temporal, parietal, insular, and thalamic BOLD signals during risky decisions compared with safe decisions predicted greater future marijuana use (when accounting for baseline/future stimulant use and baseline marijuana use). These regions are considered important for executive functions such as inhibitory control, working memory, and attention as well as for being relay centers for integrating information critical for decision making (17,18,32,71). Therefore, blunted responses in these regions while making choices between risky and safe options

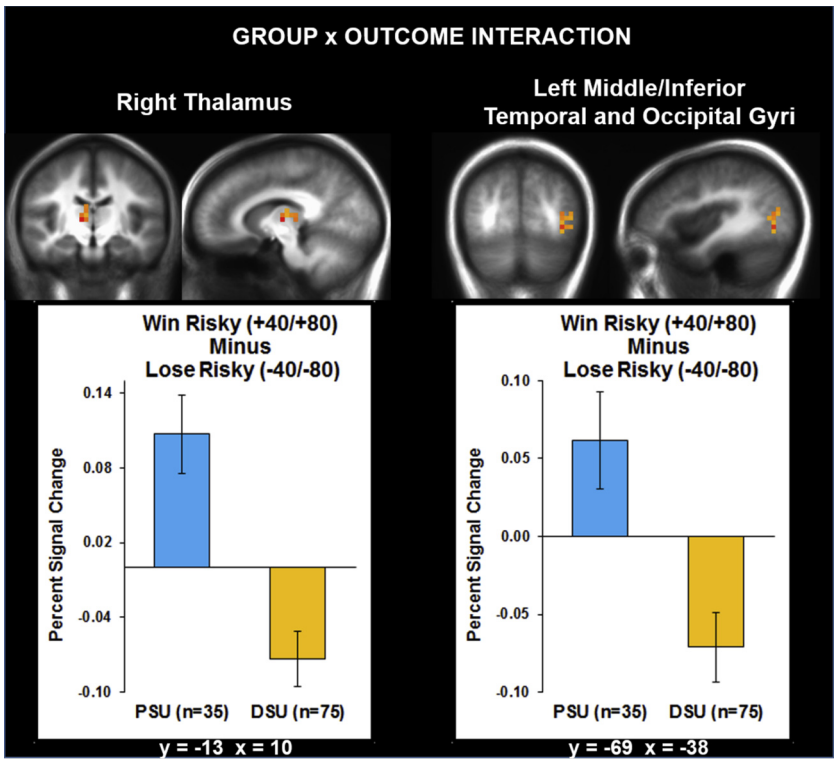

Figure 5. Group × outcome interaction. Problem stimulant users (PSUs) exhibited greater blood oxygen level–dependent signals to risky wins than to risky losses when compared with desisted stimulant users (DSUs) in right thalamus and left middle/inferior temporal and occipital gyri.

may predispose young adults to repeatedly choose marijuana consumption despite potential negative consequences (72). While cumulative marijuana uses (i.e., defined as a continuous variable) between study visits was related to baseline BOLD patterns, lack of relationship between cumulative interim stimulant use and baseline BOLD signal suggests that while a

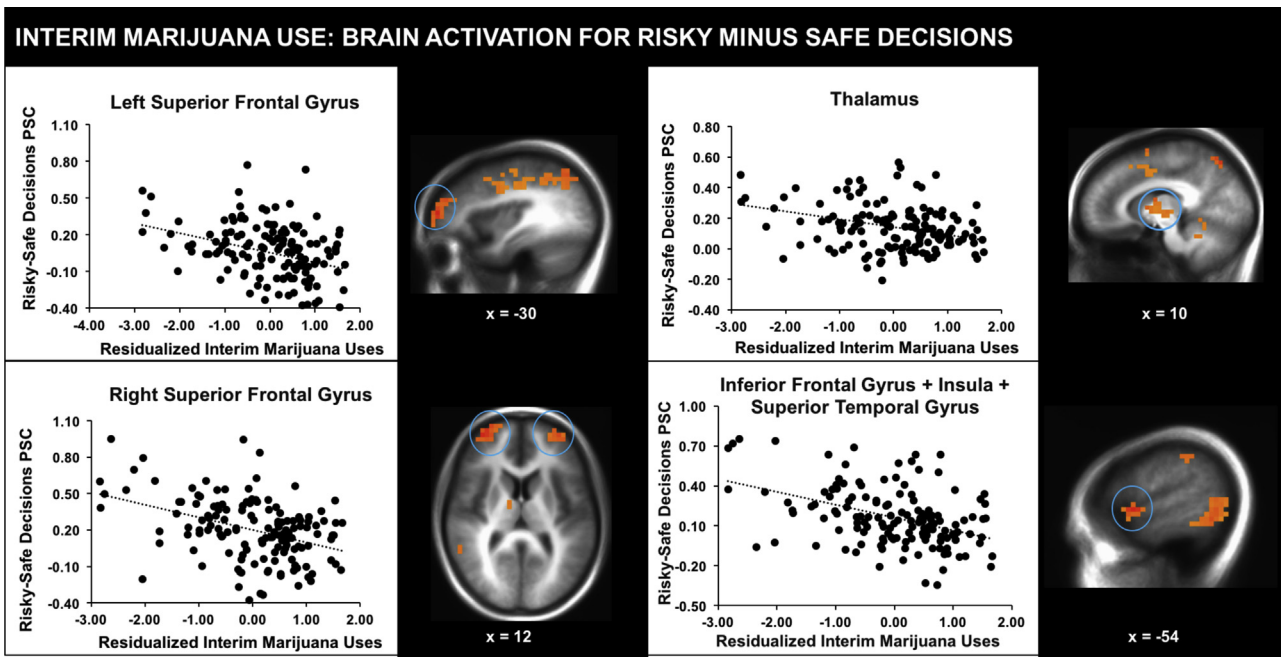

Figure 6. Interim marijuana use predicting blood oxygen level–dependent signals for risky minus safe decisions. Higher interim marijuana use was linked to lower superior/middle/inferior frontal gyri, inferior parietal lobule, superior/middle temporal gyri, thalamus, and precuneus activation for risky decisions compared with safe decisions at baseline.

Table 5. Dimensional Neuroimaging Results: Interim Marijuana Use Predicting BOLD Signal for Risky Minus Safe Decisions

Voxels	*x*	*y*	*z*	L/R	Regions in Cluster	BA	Standardized Beta
365	39	−19	43	R	Postcentral gyrus, inferior parietal lobule, middle/superior/inferior frontal gyrus, precentral gyrus, supramarginal gyrus, superior parietal lobule	2–4/6/9/40	−.56
108	−48	−55	−9	L	Middle/inferior temporal gyrus, fusiform gyrus, declive, culmen, middle occipital gyrus	19–20/37	−.51
105	−29	−53	40	L	Superior/inferior parietal lobule, precuneus	7/40	−.48
64	30	54	14	R	Superior/middle frontal gyrus	5/10	−.50
52	49	−49	−12	R	Fusiform gyrus, declive, middle/inferior temporal gyrus, culmen	20/37	−.46
45	−41	−6	39	L	Precentral gyrus, inferior/middle frontal gyrus	6	−.46
36	−51	7	−3	L	Superior temporal gyrus, insula, inferior frontal gyrus	13/22/38	−.54
34	5	10	46	R	Medial/superior frontal gyrus, cingulate gyrus	6/32	−.42
26	4	−68	52	R	Precuneus, superior parietal lobule	7	−.34
24	51	−44	18	R	Superior/middle temporal gyrus, inferior parietal lobule, supramarginal gyrus	13/21–22	−.40
24	−30	52	15	L	Superior/middle frontal gyrus	10	−.41
21	52	−19	−4	R	Superior/middle temporal gyrus	22	−.45
21	9	−9	7	R	Thalamus, caudate, caudate body, mammillary body, ventral anterior nucleus, lentiform nucleus		−.40
20	−11	−76	−22	L	Declive, lingual gyrus, uvula		−.40
20	6	−49	−12	R	Culmen, fastigium, cerebellar lingual		−.42
20	−26	−2	53	L	Middle frontal gyrus	6	−.39
19	−3	−65	−6	L	Culmen of vermis, lingual gyrus, culmen, declive		−.36

Coordinates (*x*, *y*, *z*) reflect center of mass. Voxelwise threshold for effect $> t_{139} = 2.61$, $p < .01$, two tailed, for ≥ 19 contiguous voxels.
BA, Brodmann area; BOLD, blood oxygen level–dependent; L, left hemisphere; R, right hemisphere.

dose–response effect may exist between brain activation and marijuana use, the relationship between brain activation and stimulant use may be better defined through a categorical perspective that includes accompanying clinical symptomology. Although PSUs and DSUs used marijuana at significantly high rates (range = 0–17,046 sessions), groups did not differ categorically in marijuana abuse/dependence frequency. In contrast, stimulant use in and of itself (range = 3–4862 sessions) might not be related to brain differences unless it is accompanied by clinical problems, suggesting that a categorical perspective is a more useful way to conceptualize differences.

Study Design: Strengths and Weaknesses

This study has several unique strengths, including its longitudinal design, use of a model previously applied to chronic stimulant users, and assessment of substance use from both categorical and dimensional perspectives (58). However, this study is limited by our sample's significant co-use of marijuana and the categorical criteria that prioritized differences as a function of SUD over marijuana use disorder given that PSUs and DSUs did not differ on baseline/interim marijuana use. In addition, although SUD has been associated with greater incidence of psychiatric illness (73,74), lack of clinical symptom measures collected at follow-up hinders our ability to determine whether mental health symptoms affected interim substance use. We are also limited by an inability to evaluate the RGT from a trial-by-trial perspective to determine whether BOLD response patterns translate into future behavior or are affected by the preceding trial; due to the limited number of separate 40 and 80 trials, it would not be possible to obtain sufficient statistical power to conduct such an analysis.

Conclusions and Future Directions

Preexisting BOLD signal patterns during risky decision making predict transition to SUD. Frontocingulate, insular, and striatal blunting to feedback after selection of a risky choice may predispose young adults to future decision-making impairments (continuing to use stimulants despite clinical problems). Moreover, blunted frontal, insular, and striatal BOLD signals during action selection predict greater frequency of future marijuana use. Future research is needed to determine whether these biomarkers can identify at-risk individuals who might benefit from targeted interventions.

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REFERENCES

1. Hedden SL, Kennet J, Lipari R, Medley G, Tice P (2015): Behavioral health trends in the United States: Results from the 2014 National Survey on Drug Use and Health (Department of Health and Human Services Publication No. SMA 15-4927, NSDUH Series H-50). Available at: http://www.samhsa.gov/data. Accessed March 28, 2017.
2. Wilens TE, Adler LA, Adams J, Sgambati S, Rotrosen J, Sawtelle R, *et al.* (2008): Misuse and diversion of stimulants prescribed for ADHD: A systematic review of the literature. J Am Acad Child Adolesc Psychiatry 47:21–31.
3. Wagner F, Anthony JC (2002): From first drug use to drug dependence developmental periods of risk for dependence upon marijuana, cocaine, and alcohol. Neuropsychopharmacology 26:479–488.
4. Geier C, Luna B (2009): The maturation of incentive processing and cognitive control. Pharmacol Biochem Behav 93:212–221.
5. Douglas KA, Collins JL, Warren C, Kann L, Gold R, Clayton S, *et al.* (1997): Results from the 1995 National College Health Risk Behavior Survey. J Am Coll Health 46:55–67.
6. Bannink R, Broeren S, Heydelberg J, van't Klooster E, Raat H (2015): Depressive symptoms and clustering of risk behaviours among adolescents and young adults attending vocational education: A cross-sectional study. BMC Public Health 15:396.
7. Busch V, Van Stel HF, Schrijvers AJ, de Leeuw JR (2013): Clustering of health-related behaviors, health outcomes and demographics in Dutch adolescents: A cross-sectional study. BMC Public Health 13:1118.
8. Huang DYC, Lanza HI, Murphy DA, Hser Y-I (2012): Parallel development of risk behaviors in adolescence: Potential pathways to co-occurrence. Int J Behav Dev 36:247–257.
9. Friston KJ, Shiner T, FitzGerald T, Galea JM, Adams R, Brown H, *et al.* (2012): Dopamine, affordance and active inference. PLoS Comput Biol 8:e1002327.
10. Koechlin E (2014): An evolutionary computational theory of prefrontal executive function in decision-making. Philos Trans R Soc Lond B Biol Sci 369:20130474.
11. Aron JL, Paulus MP (2007): Location, location: Using functional magnetic resonance imaging to pinpoint brain differences relevant to stimulant use. Addiction 102(suppl 1):33–43.
12. Bechara A, Damasio H (2002): Decision-making and addiction: I. Impaired activation of somatic states in substance dependent individuals when pondering decisions with negative future consequences. Neuropsychologia 40:1675–1689.
13. Bolla KI, Eldreth DA, London ED, Kiehl KA, Mouratidis M, Contoreggi C, *et al.* (2003): Orbitofrontal cortex dysfunction in abstinent cocaine abusers performing a decision-making task. NeuroImage 19:1085–1094.
14. Fowler JS, Volkow ND, Kassed CA, Chang L (2007): Imaging the addicted human brain. Sci Pract Perspect 3:4–16.
15. Lane SD, Steinberg JL, Ma L, Hasan KM, Kramer LA, Zuniga EA, *et al.* (2010): Diffusion tensor imaging and decision making in cocaine dependence. PLoS One 5:e11591.
16. Bechara A (2005): Decision making, impulse control and loss of willpower to resist drugs: A neurocognitive perspective. Nat Neurosci 8:1458–1463.
17. Goldstein RZ, Volkow ND (2011): Dysfunction of the prefrontal cortex in addiction: Neuroimaging findings and clinical implications. Nat Rev Neurosci 12:652–669.
18. Bolla K, Ernst M, Kiehl K, Mouratidis M, Eldreth D, Contoreggi C, *et al.* (2004): Prefrontal cortical dysfunction in abstinent cocaine abusers. J Neuropsychiatry Clin Neurosci 16:456–464.
19. Paulus M, Hozack NE, Zauscher BE, Frank L, Brown GG, Braff DL, *et al.* (2002): Behavioral and functional neuroimaging evidence for prefrontal dysfunction in methamphetamine-dependent subjects. Neuropsychopharmacology 26:53–63.
20. Goldstein RZ, Tomasi D, Rajaram S, Cottone LA, Zhang L, Maloney T, *et al.* (2007): Role of the anterior cingulate and medial orbitofrontal cortex in processing drug cues in cocaine addiction. Neuroscience 144:1153–1159.
21. Paulus MP, Hozack N, Frank L, Brown GG, Schuckit MA (2003): Decision making by methamphetamine-dependent subjects is associated with error-rate-independent decrease in prefrontal and parietal activation. Biol Psychiatry 53:65–74.
22. Volkow ND, Fowler JS, Wang GJ (2003): The addicted human brain: Insights from imaging studies. J Clin Invest 110:1444–1451.
23. Graybiel AM, Aosaki T, Flaherty AW, Kimura M (1994): The basal ganglia and adaptive motor control. Science 265:1826–1831.
24. White NM, McDonald RJ (2002): Multiple parallel memory systems in the brain of the rat. Neurobiol Learn Mem 77:125–184.
25. Bechara A, Damasio AR, Damasio H, Anderson SW (1994): Insensitivity to future consequences following damage to human prefrontal cortex. Cognition 50:7–15.
26. Fukui H, Murai T, Fukuyama H, Hayashi T, Hanakawa T (2005): Functional activity related to risk anticipation during performance of the Iowa Gambling Task. NeuroImage 24:253–259.
27. Lawrence NS, Jollant F, O'Daly O, Zelaya F, Phillips ML (2009): Distinct roles of prefrontal cortical subregions in the Iowa Gambling Task. Cereb Cortex 19:1134–1143.
28. Kohno M, Morales AM, Ghahremani DG, Hellemann G, London ED (2014): Risky decision making, prefrontal cortex, and mesocorticolimbic functional connectivity in methamphetamine dependence. JAMA Psychiatry 71:812–820.
29. Lejuez CW, Read JP, Kahler CW, Richards JB, Ramsey SE, Stuart GL, *et al.* (2002): Evaluation of a behavioral measure of risk taking: The Balloon Analogue Risk Task (BART). J Exp Psychol Appl 8:75–84.
30. Ersche KD, Fletcher PC, Lewis SJG, Clark L, Stocks-Gee G, London M, *et al.* (2005): Abnormal frontal activations related to decision-making in current and former amphetamine and opiate dependent individuals. Psychopharmacology (Berl) 180:612–623.
31. Xue G, Lu Z, Levin IP, Bechara A (2010): The impact of prior risk experiences on subsequent risky decision-making: The role of the insula. NeuroImage 50:709–716.
32. Naqvi NH, Bechara A (2009): The hidden island of addiction: The insula. Trends Neurosci 32:56–67.
33. Stevens FL, Hurley RA, Taber KH (2011): Anterior cingulate cortex: Unique role in cognition and emotion. J Neuropsychiatry Clin Neurosci 23:121–125.
34. Kaufman JN, Ross TJ, Stein EA, Garavan H (2003): Cingulate hypoactivity in cocaine users during a GO-NOGO task as revealed by event-related functional magnetic resonance imaging. J Neurosci 23:7839–7843.
35. Li CR, Huang C, Yan P, Bhagwagar Z, Milivojevic V, Sinha R (2008): Neural correlates of impulse control during stop signal inhibition in cocaine-dependent men. Neuropsychopharmacology 33:1798–1806.
36. Salo R, Ursu S, Buonocore MH, Leamon MH, Carter C (2009): Impaired prefrontal cortical function and disrupted adaptive cognitive control in methamphetamine abusers: A functional magnetic resonance imaging study. Biol Psychiatry 65:706–709.
37. Ray Li C, Sinha R (2008): Inhibitory control and emotional stress regulation: Neuroimaging evidence for frontal-limbic dysfunction in psycho-stimulant addiction. Neurosci Biobehav Rev 32:581–597.
38. Colzato LS, van den Wildenberg WPM, Hommel B (2007): Impaired inhibitory control in recreational cocaine users. PLoS One 2:e1143.
39. Colzato LS, Huizinga M, Hommel B (2009): Recreational cocaine polydrug use impairs cognitive flexibility but not working memory. Psychopharmacology (Berl) 207:225–234.
40. Soar K, Mason C, Potton A, Dawkins L (2012): Neuropsychological effects associated with recreational cocaine use. Psychopharmacology (Berl) 222:633–643.
41. Vonmoos M, Hulka LM, Preller KH, Jenni D, Baumgartner MR, Stohler R, *et al.* (2013): Cognitive dysfunctions in recreational and dependent cocaine users: Role of attention-deficit hyperactivity

disorder, craving and early age at onset. Br J Psychiatry 203:35–43.
42. Reske M, Stewart JL, Flagan TM, Paulus MP (2015): Attenuated neural processing of risk in young adults at risk for stimulant dependence. PLoS One 10:e127010.
43. Schneider S, Peters J, Bromberg U, Brassen S, Miedl SF, Banaschewski T, *et al.* (2012): Risk taking and the adolescent reward system: A potential common link to substance abuse. Am J Psychiatry 169:39–46.
44. Büchel C, Peters J, Banaschewski T, Bokde DL, Bromberg U, Conrod PJ, *et al.* (2017): Blunted ventral striatal responses to anticipated rewards foreshadow problematic drug use in novelty-seeking adolescents. Nat Commun 8:14140.
45. Becker B, Wagner D, Koester P, Tittgemeyer M, Mercer-Chalmers-Bender K, Hurlemann R, *et al.* (2015): Smaller amygdala and medial prefrontal cortex predict escalating stimulant use. Brain 138:2074–2086.
46. Whelan R, Watts R, Orr CA, Althoff RR, Artiges E, Banaschewski T, *et al.* (2014): Neuropsychosocial profiles of current and future adolescent alcohol misusers. Nature 512:185–189.
47. Lindsay JA, Stotts AL, Green CE, Herin DV, Schmitz JM (2009): Cocaine dependence and concurrent marijuana use: A comparison of clinical characteristics. Am J Drug Alcohol Abuse 35:193–198.
48. Bucholz KK, Cadoret R, Cloninger CR, Dinwiddie SH, Hesselbrock VM, Nurnberger JI Jr, *et al.* (1994): A new, semi-structured psychiatric interview for use in genetic linkage studies: A report on the reliability of the SSAGA. J Stud Alcohol 55:149–158.
49. Wechsler D (2001): Wechsler Test of Adult Reading: WTAR. San Antonio, TX: Psychological Corporation.
50. Stewart JL, Parnass JM, May AC, Davenport PW, Paulus MP (2013): Altered frontocingulate activation during aversive interoceptive processing in young adults transitioning to problem stimulant use. Front Syst Neurosci 7:89.
51. Behan B, Connolly CG, Datwani S, Doucet M, Ivanovic J, Morioka R, *et al.* (2014): Response inhibition and elevated parietal-cerebellar correlations in chronic adolescent cannabis users. Neuropharmacology 84:131–137.
52. Gowin JL, Stewart JL, May AC, Ball TM, Wittmann M, Tapert SF, *et al.* (2014): Altered cingulate and insular cortex activation during risk-taking in methamphetamine dependence: Losses lose impact. Addiction 109:237–247.
53. Gowin JL, Harlé KM, Stewart JL, Wittmann M, Tapert SF, Paulus MP (2014): Attenuated insular processing during risk predicts relapse in early abstinent methamphetamine-dependent individuals. Neuropsychopharmacology 39:1379–1387.
54. Leland DS, Paulus MP (2005): Increased risk-taking decision-making but not altered response to punishment in stimulant-using young adults. Drug Alcohol Depend 78:83–90.
55. Matthews SC, Simmons AN, Arce E, Paulus MP (2005): Dissociation of inhibition from error processing using a parametric inhibitory task during functional magnetic resonance imaging. NeuroReport 16:755–760.
56. Stewart JL, Flagan TM, May AC, Reske M, Simmons AN, Paulus MP (2013): Young adults at risk for stimulant dependence show reward dysfunction during reinforcement-based decision making. Biol Psychiatry 73:235–241.
57. Paulus MP, Geyer MA, Braff DL (1996): Use of methods from chaos theory to quantify a fundamental dysfunction in the behavioral organization of schizophrenic patients. Am J Psychiatry 153:714–717.
58. Rabin RA, Moeller SJ (2017): Commentary on Stewart et al. (2017): Stimulants and marijuana—The potential value in studying substance co-use. Addiction 112:1578–1579.
59. American Psychiatric Association (2013): Diagnostic and Statistical Manual of Mental Disorders: DSM-5. Washington, DC: American Psychiatric Press.
60. Frisher M, Beckett H (2006): Drug use desistance. Criminol Crim Justice 6:127–145.
61. Kirisci L, Tarter RE, Reynolds M, Vanyukov M (2006): Individual differences in childhood neurobehavior disinhibition predict decision to desist substance use during adolescence and substance use disorder in young adulthood: A prospective study. Addict Behav 31:686–696.
62. Cox RW. AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. Comput Biomed Res 29:162–173.
63. Pinheiro J, Bates D, DebRoy S, Sarkar D, Team RC (2013): Nlme: Linear and nonlinear mixed effects models. Available at: https://cran.r-project.org/package=nlme.
64. Hanlon CA, Dowdle LT, Naselaris T, Canterberry M, Cortese BM (2014): Visual cortex activation to drug cues: A meta-analysis of functional neuroimaging papers in addiction and substance abuse literature. Drug Alcohol Depend 143:206–212.
65. Palombo DJ, Keane MM, Verfaellie M (2015): The medial temporal lobes are critical for reward-based decision making under conditions that promote episodic future thinking. Hippocampus 25:345–353.
66. Stewart JL, May AC, Reske M, Tapert S, Paulus MP (2017): Neural responses to risk and reward predict transition to problem stimulant use. Drug Alcohol Depend 171:e196.
67. Dewitt SJ, Ketcherside A, McQueeny TM, Dunlop JP, Filbey FM (2015): The hyper-sentient addict: An exteroception model of addiction. Am J Drug Alcohol Abuse 41:374–381.
68. Luo X, Zhang S, Hu S, Bednarski SR, Erdman E, Farr OM, *et al.* (2013): Error processing and gender-shared and -specific neural predictors of relapse in cocaine dependence. Brain 136(pt 4):1231–1244.
69. Smoski MJ, Lynch TR, Rosenthal MZ, Cheavens JS, Chapman AL, Krishnan RR (2008): Decision-making and risk aversion among depressive adults. J Behav Ther Exp Psychiatry 39:567–576.
70. Kendall PC, Hollon SD, Beck AT, Hammen CL, Ingram RE (1987): Issues and recommendations regarding use of the Beck Depression Inventory. Cognit Ther Res 11:289–299.
71. Volkow ND, Fowler JS, Wang GJ (2004): The addicted human brain viewed in the light of imaging studies: Brain circuits and treatment strategies. Neuropharmacology 47(suppl 1):3–13.
72. Volkow ND, Wang G-J, Telang F, Fowler JS, Alexoff D, Logan J, *et al.* (2014): Decreased dopamine brain reactivity in marijuana abusers is associated with negative emotionality and addiction severity. Proc Natl Acad Sci U S A 111:E3149–E3156.
73. Kessler RC, Nelson CB, McGonagle KA, Edlund MJ, Frank RG, Leaf PJ (1996): The epidemiology of co-occurring addictive and mental disorders: Implications for prevention and service utilization. Am J Orthopsychiatry 66:17–31.
74. Maisto SA, Carey MP, Carey KB, Gordon CM, Gleason JR (2000): Use of the AUDIT and the DAST-10 to identify alcohol and drug use disorders among adults with a severe and persistent mental illness. Psychol Assess 12:186–192.
75. Connolly CG, Bischoff-Grethe A, Jordan SJ, Woods SP, Ellis RJ, Paulus MP, Translational Methamphetamine Aids Research Center (TMARC) Group (2014): Altered functional response to risky choice in HIV infection. PLoS One 9:e111583.