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Insular and Cingulate Attenuation during Decision Making is associated with Future Transition to Stimulant Use Disorder

Jennifer L. Stewart, Ph.D.^{1,2}, Mamona Butt¹, April C. May, M.A.³, Susan F. Tapert, Ph.D.³, and Martin P. Paulus, M.D.^{3,4}

¹Department of Psychology, Queens College, City University of New York, Flushing, NY 11367

²Department of Psychology, The Graduate Center, City University of New York, New York, NY 10016

³Department of Psychiatry, University of California San Diego, La Jolla, CA 92093

⁴Laureate Institute of Brain Research, Tulsa, OK 74136

Abstract

Aims—To understand processes placing individuals at risk for stimulant (amphetamine and cocaine) use disorder.

Design—Longitudinal study.

Setting—University of California, San Diego Department of Psychiatry, USA.

Participants—Occasional stimulant users (OSU; $n=184$) underwent a baseline clinical interview and a functional magnetic resonance imaging (fMRI) session. On the basis of a follow-up clinical interview completed three years later, OSU ($n=147$) were then categorized as problem stimulant users (PSU; $n=36$; those who developed stimulant use disorders in the interim) or desisted stimulant users (DSU; $n=74$; those who stopped using). OSU who did not meet criteria for PSU or DSU ($n=37$) were included in dimensional analyses.

Measurements—fMRI blood-oxygen-level dependent (BOLD) contrast percent signal change from baseline collected during a Paper-Scissors-Rock task was examined during three decision making conditions, those resulting in: (1) wins, (2) ties, and (3) losses. These data were used as dependent variables in categorical analyses comparing PSU and DSU as well as dimensional analyses including interim drug use as predictors, controlling for baseline drug use.

Findings—PSU exhibited lower anterior cingulate, middle insula, superior temporal, inferior parietal, precuneus and cerebellum activation than DSU across all three conditions (significant brain clusters required >19 neighboring voxels to exceed $F(1,108)=5.58$, $p<.01$ two-tailed; all Cohen's $d>.83$). Higher interim marijuana use was linked to lower precentral and superior temporal activation during choices resulting in wins (>19 neighboring voxels to exceed $t=2.61$, $p<.01$ two-tailed; R^2 change $>.11$).

Corresponding author: Jennifer L. Stewart, Ph.D., Queens College Department of Psychology, 6530 Kissena Boulevard, Flushing, NY 11367-1597; jennifer.stewart@qc.cuny.edu; Phone: (718) 997-3230.

Conflicts of Interest: The authors have none to report.

Conclusions—Individuals who transition from stimulant use to stimulant use disorder appear to show alterations in neural processing of stimulus valuation and outcome monitoring, patterns also evident in chronic stimulant use disorder. Attenuated anterior cingulate and insular processing may constitute a high-risk neural processing profile, which could be used to calculate risk scores for individuals experimenting with stimulants.

Keywords

reward; stimulants; anterior cingulate; insula

Introduction

Stimulant use disorders are a major concern in young adults, with cocaine and amphetamine dependence onset highest prior to age 25^{1–2}. Although several longitudinal studies demonstrate brain regions implicated in the trajectory of alcohol and marijuana use^{3–8}, the majority of studies examining occasional and chronic stimulant users are cross-sectional, limiting investigation of biobehavioral markers predicting transition to future stimulant addiction. In a recent cross-sectional functional magnetic resonance imaging (fMRI) study, our laboratory demonstrates that young adult occasional stimulant users (OSU) exhibit aberrant neural processing during decision making when compared to stimulant naïve comparison subjects⁹. The present longitudinal study tracks OSU three years later to determine whether neural patterns during decision making differentiate OSU transitioning to stimulant use disorder from those desisting stimulant use altogether.

Identifying dysfunctional decision making processes in addiction may help to explain the transformation of an occasional drug user to an addicted user as well as calculate the probability of drug relapse versus abstinence¹⁰. The decision making process involves assessing possible options, selecting an action, evaluating the outcome and consequences of the action (learning contingencies, or links between action and outcome), and determining whether to repeat that particular choice¹¹; brain mechanisms involved in this implementation include anterior cingulate cortex (ACC), prefrontal cortex, striatum, and insular cortex. ACC assigns predictive value and adjusts processing of salient stimuli based on a previous decision's outcome^{12–13}, whereas dorsolateral prefrontal cortex (DLPFC) is involved in representing and preserving goal-relevant task information¹⁴. DLPFC and ACC coordinate decision-making behaviors by strategizing based on previous error and outcome contingencies¹⁵. Frontocingulate attenuation during decision making is evident across various substances of abuse¹⁶ and is linked with retroactively reported substance use onset⁷. Hypoactive ACC is linked to cognitive and emotional dysfunction in chronic cocaine users, particularly during inhibition and error monitoring^{10, 17–18}. Similarly, individuals with amphetamine use disorders show ACC and/or DLPFC attenuation during decision making involving delay discounting¹⁹ and situations involving high response conflict^{20–21}. Inferior frontal gyrus (IFG), a neighboring region involved in inhibitory control^{22–23}, is heightened in individuals with cocaine use disorder when evaluating monetary reward²⁴, suppressing distracting cocaine cues²⁵, and maintaining emotional responses to negative stimuli²⁶. Thus, stimulant addiction appears to be linked to reduced recruitment of neural resources

dedicated to error monitoring and goal implementation in conjunction with heightened resources needed to inhibit distractors, perhaps to maintain task performance.

Dorsal striatum is linked to action-contingent learning, attaching value to a response following a consequence, leading to more advantageous response selection for future choices^{27–28}. Since stimulant users tend to value drug-related reward more than other goals, rewards, and consequences²⁹, it is not surprising that chronic amphetamine users exhibit dorsal striatum hypoactivation while processing non-drug rewards^{30–31}. Moreover, attenuated dorsal striatum responses during decision making differentiate chronic amphetamine and cocaine users who relapse from those who remain abstinent for one year^{32–33}. Results are far from consistent, however; individuals with cocaine use disorder show greater dorsal striatum responses than CTL while processing non-drug reward feedback³⁴.

Lastly, insular cortex integrates physiological, cognitive, and emotional functions during decision making to avoid negative consequences^{9, 35–36}. Although insular dysfunction is apparent in stimulant use disorder, over- or under-activation appears to differ as a function of task demands. Whereas chronic amphetamine users exhibit insular attenuation during simple and complex decision making tasks involving rewarding and punishing interoceptive stimuli^{31, 37}, individuals with cocaine use disorder show heightened insular responses to non-drug related reward feedback³⁴ (a pattern also evident in heavy cannabis users^{3–4}) but attenuated insular responses to high conflict and error trials¹⁸.

The present study utilizes fMRI data during a Paper-Scissors-Rock (PSR) task to examine decision-making associated with winning, tying, and losing outcomes. OSU exhibit altered insular, IFG, and dorsal striatum activation during decision making than CTL, reflecting divergent processing of reward contingencies⁹. However, given that only approximately 20% of OSU progress to stimulant use disorder², it could be the case that within OSU, those who transition to disorder and develop problem stimulant use (PSU) will exhibit neural patterns that more closely resemble those of chronic stimulant users during reward learning than OSU who eventually desist using stimulants (DSU).

PSR studies of chronic stimulant users guide hypotheses for the current investigation on recent-onset transition to stimulant use disorder. Chronic amphetamine users who relapse show blunted striatal, insular, IFG and ACC responding to PSR outcome feedback³³. Similarly, chronic cocaine users who relapse exhibit lower IFG and striatum activation paired with unstable insular function while making decisions during the PSR task than those who remain abstinent, suggesting reduced neural resources recruited to process stimulus-outcome contingencies³².

Study Aims

Based on prior work in chronic stimulant addiction, our primary aim was to test whether PSU show lower frontocingulate, insular and striatal responses to feedback than DSU, reflecting deficits in outcome monitoring, task maintenance, and reward valuation, consistent with research findings in chronic stimulant addiction. Our secondary aim was to

determine whether blunted brain activation in these regions during decision making were linked to greater future stimulant and comorbid drug use independent of clinical diagnosis.

Methods

Design

Figure 1 illustrates the longitudinal study design: (1) at baseline, OSU completed an interview to evaluate clinical diagnoses and determine initial drug use patterns, and a neuroimaging session; and (2) three years later, OSU completed a follow-up interview to determine changes in clinical status and patterns of drug use.

Participants

The study protocol was approved by the University of California, San Diego institutional review board and complied with the Declaration of Helsinki. Students at local universities were recruited via internet ads, newspapers, and flyers; OSU who met study criteria provided written informed consent to participate. OSU endorsed: (a) >2 off-prescription uses of cocaine and/or pharmaceutical stimulants (amphetamines and/or methylphenidate) in the past six months; (b) no lifetime stimulant dependence; and (c) no interest in drug treatment.

Baseline Interview Session

Lifetime DSM-IV Axis I diagnoses and Axis II antisocial personality disorder (ASPD) were assessed by the Semi-Structured Assessment for the Genetics of Alcoholism II (SSAGA II)³⁸ (see⁹ for participant exclusion criteria). Subjects also completed a measure of verbal intelligence (IQ)³⁹ as well as the Barratt Impulsiveness Scale (BIS-11), Sensation Seeking Scale (SSS), and Beck Depression Inventory (BDI), measures indexing impulsivity, sensation seeking, and depression, respectively^{40–42}.

Baseline Neuroimaging Session

Overview—Participants were instructed to abstain from illicit substance use 72 h prior (abstinence was determined by urine toxicology screen). Subjects then completed the PSR task during fMRI recording after engaging in a practice version of the task outside of the scanner.

PSR paradigm—This task^{9, 32–33} examines how individuals acquire the ability to make decisions associated with advantageous outcomes, wherein: (1) rock beats scissors; (2) paper beats rock; (3) scissors beat paper. Subjects were instructed to play against the computer and attempt to maximize points (1 for a win, 0 for a tie, and –1 for a loss), as they would receive additional payment according to their cumulative point total (each point was worth \$1). Unknown to the subject, probability of beating the computer and thus being reinforced (e.g., subject chooses scissors, computer selects paper, scissors beats paper, subject gains 1 point) was predetermined. A total of 120 trials were presented (six blocks containing 20 trials). Within each block, the three possible selections had pre-determined probabilities of having a winning, tying, or losing outcome. The “preferred response” won on 90% of trials, the “even response” won 50% of the time, and the “worst response” won on 10% of trials. Preferred, even, and worst responses were switched for each of the six blocks.

Figure 2A illustrates an example of one trial. After an initial fixation lasting 2 s, subjects saw a hand forming paper, scissors, and rock on a screen for 1 s and heard the instruction “one, two, three” over headphones. At 3 s into the trial, subjects were then presented with a “Go” sign, providing the cue to select paper, scissors, or rock. Subjects had 3.5 s to respond, after which the trial timed out. Upon responding, the outcome was presented, wherein the subject saw the computer’s response, and heard “you win,” “you lose,” or “a tie”. Nine null trials were interspersed at the beginning (three prior to any relevant trials), middle (three prior to the fourth block), and end of the task (three after all relevant trials were completed) as a temporal jitter.

fMRI image acquisition—One run indexing blood oxygenation level-dependent (BOLD) contrast was collected (randomized fast-event related design) using a Signa EXCITE (GE Healthcare, Milwaukee, Wisconsin) 3.0 Tesla scanner (T2*-weighted EPI scans, TR=2000 ms, TE=32 ms, FOV=230mm³, 64×64 matrix, 30 2.6mm axial slices [1.4 mm gap], flip angle=90°, 290 whole-brain TRs). fMRI volume acquisitions were time-locked to task onset. A high-resolution T1-weighted anatomical image was obtained [spoiled gradient recalled (SPGR), TI=450, TR=8 ms, TE=3 ms, flip angle=12°, FOV=250mm³, 192×256 matrix, 172 sagittally acquired slices with 1mm thickness]. Analysis pathway specifications including slice timing correction, outlier estimation/removal, and motion estimation/correction are detailed in ³.

Multiple regressor analyses—A deconvolution model was created in Analysis of Functional Neuroimages (AFNI) ⁴³, individualized for each participant, comparing decision-making between preferred, even, and worst response selections. Each subject’s behavioral performance determined three regressors of interest for trials in which the participant selected: (a) the preferred response, (b) the tied response, and (c) the worst response (Figure 2B depicts an example of one participant’s performance). The baseline for this model consisted of the inter-trial interval and null trials interspersed between trial blocks.

Regressors of interest were generated to delineate conditions for this model, wherein a 0–1 reference function for each condition was convolved with a gamma variate function⁴⁴ modeling a prototypical hemodynamic response (6–8 s delay) ^{45–46}. Three normalized decision-making predictors (brain activation from trial onset to each participant’s behavioral selection of the preferred, even, and worst response designated for each block) were included in the AFNI program 3dDeconvolve, controlling for motion as well as baseline and linear drift, to estimate goodness of fit between model estimates and BOLD responses for each subject.

Voxels were resampled into 4×4×4mm³ space and whole-brain voxel-wise normalized percent signal change (PSC), the main dependent measure, was determined by dividing the beta coefficient for each of the predictors of interest (preferred, even, and worst responses) by the beta coefficient for the baseline regressor and multiplying by 100. A Gaussian spatial filter (4mm full width half maximum; FWHM) was used to spatially blur PSC values to account for anatomical differences and this output was then normalized to Talairach coordinates (40×48×38 voxel coverage) as defined by AFNI’s built-in atlases. Individual subject PSC-scaled beta weight values for preferred, even, and worst responses for each

voxel included in a whole-brain mask (comprised of 23775 voxels) was extracted for further categorical and dimensional statistical analyses outlined below. Individual voxels meeting a $p < .01$ significance criterion as a result of these statistical tests (linear mixed models and regressions) were further evaluated to determine whether they comprised a significant brain cluster after correction for multiple comparisons (given all voxels included in the whole-brain mask).

Leading neuroimaging programs have recently been criticized for underestimation of spatial autocorrelation in fMRI data, resulting in inadequate implementation of correction for multiple comparisons when determining how many voxels are required to comprise a significant brain cluster⁴⁷. As a consequence of this critique, we revised our laboratory's clustering procedure. First, the updated AFNI 3dFWHMx program was used to more reliably estimate the actual autocorrelation in fMRI data across participants (.44, 1.71, and 10.36) as well as the actual smoothness present in the data after blurring (4.99 mm). Second, we then ran an updated version of AFNI's 3dClustSim that takes these autocorrelation values into account given our voxel size, 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. Given this input, 3dClustSim determined that: (1) our data smoothness approached 6.20mm; and (2) >19 neighboring voxels (or >1216 μ L) were required to comprise a significant brain cluster; this voxelwise cutoff more than doubles the size of the cluster required for significance given similar blurring parameters in our prior work (8 voxels).

Three Year Follow-Up Interview Session

OSU were contacted three years after their baseline assessment (Figure 1). Each participant underwent a standardized interview (phone or in-person) to examine extent of drug use in the three-year interim since the baseline interview, thereby allowing us to identify subjects meeting criteria for new stimulant user groups: PSU or DSU. PSU were a priori defined by: (1) continued stimulant use during the three-year interim (see Table 1); and (2) endorsement of 2+ symptoms of DSM-IV amphetamine and/or cocaine abuse or dependence criteria occurring together 6 contiguous months since the initial visit ($M=4.17$ symptoms; $SD=2.32$; range: 2–9). Percentage of PSU subjects who met criteria for stimulant use disorders were the following: 53% cocaine abuse, 22% cocaine dependence, 42% amphetamine abuse, and 19% amphetamine dependence ($n=3$ met criteria for 2 symptoms of dependence, 1 criterion short to obtain a diagnosis; $n=20$ met criteria for 1 diagnosis; $n=10$ met criteria for 2 diagnoses; and $n=3$ met criteria for 3 diagnoses). In comparison, DSU were defined as having: (1) no 6-month periods of 3+ stimulant uses; and (2) no interim stimulant use disorder symptoms. Figure 1 illustrates that categorical analyses compared PSU and DSU on fMRI data, whereas dimensional analyses included all OSU with usable fMRI and follow-up data, even those who did not meet PSU or DSU group criteria.

Categorical Analyses

Self-report—Group differences in age, verbal IQ, education, drug use sessions, impulsivity, and sensation seeking were evaluated using IBM SPSS Statistics for Windows Version 22 (Armonk, NY) independent sample t -tests. Group differences in gender,

handedness, race/ethnicity, depression (BDI scores 0–9 = no depression; BDI scores 10–14 = mild depression⁴⁸) and drug use recency were explored using SPSS chi-square tests.

Neuroimaging—For each voxel, a linear mixed effects (LME) model in R⁴⁹ was calculated on PSC values with group (PSU, DSU) and decision condition (preferred, even, and worst choices) modeled as fixed factors, and subject modeled as a random factor. For each voxel, degrees of freedom, F , and p values were obtained for each main effect and interaction. Only individual voxels meeting $p < .01$ significance for the F test were considered for inclusion in brain clustering, correcting for multiple comparisons. Cohen's d was calculated to determine effect sizes. All fMRI results were whole-brain extractions.

Dimensional Analyses

Figure 1 illustrates that across all OSU with usable follow-up data, regardless of group status, cumulative stimulant and marijuana uses at baseline as well as interim stimulant and marijuana uses reported at follow-up were log transformed due to skew, standardized, and entered as predictors in multivariate regressions for self-report and neuroimaging data.

Self-report—Multivariate linear regressions were computed in IBM SPSS Statistics for the following dependent variables: age, verbal IQ, education, impulsivity and sensation seeking. A multivariate logistic regression was computed for depression status.

Neuroimaging—A total of three multivariate linear regressions were computed in R (<https://cran.r-project.org/package=rlm>) for each voxel in the whole-brain mask. Dependent variables were PSC for preferred, even, and worst decision trials.

Results

Categorical Analysis

Self-report—Groups did not differ in gender, handedness, race/ethnicity, verbal IQ, education, impulsivity, sensation seeking, or mild depression status (Table 1). Although groups did not differ in baseline stimulant use, PSU endorsed higher interim stimulant uses at follow-up (this was a requirement of PSU group inclusion). Groups did not differ in marijuana-positive urine screens at the fMRI session, cumulative marijuana use at baseline interview, or interim marijuana use reported at the follow-up interview. Although groups did not differ with respect to marijuana use recency at the time of the fMRI scan, a higher percentage of PSU than DSU used stimulants within the week prior to the scan (Table 2).

Neuroimaging—Significant clusters are presented in Table 3. The group main effect (Figure 3A) shows that across all choices, PSU displayed lower activation than DSU in insula, ACC, superior temporal gyrus, inferior parietal lobule, precuneus, and cerebellum. For the group by decision interaction (Figure 3B), PSU exhibited lower activation than DSU in precentral gyrus and midcingulate gyrus when selecting winning and tying choices.

Dimensional Analysis

Self-report—Interim drug use was unrelated to baseline verbal IQ, age and personality when controlling for baseline drug use. However, lower baseline education was associated with higher interim stimulant use (R^2 change = .03, within full model $\beta = -.20$, $t = -2.26$, $p = .03$).

Neuroimaging—Controlling for baseline stimulant and marijuana use, higher interim marijuana use was associated with lower precentral and superior temporal gyri activation for preferred choices (Figure 4 illustrates partial regression plots); no significant clusters emerged for even or worst choices. No significant clusters emerged for interim stimulant uses for preferred, even, or worst choices.

Discussion

The primary goal of the present longitudinal study was to test whether patterns of BOLD activation during decision making could differentiate OSU who developed stimulant use disorders (PSU) three years later from those who desisted using stimulants (DSU). We predicted that PSU would exhibit lower frontocingulate, insular, and striatal responses during decision making related to all types of feedback than DSU, a hypothesis based on findings in chronic amphetamine users who relapsed³³. This hypothesis was partially supported in that PSU exhibited lower insula and ACC activation than DSU when responding to all types of contingencies. Hypoactive ACC responding thus appears to characterize recent-onset as well as chronic stimulant addiction, reflecting blunted error or outcome monitoring^{10, 17–18, 50}. Moreover, insular attenuation in PSU is consistent with reduced insula processing evident in stimulant users across various decision making tasks^{18, 20, 26, 31, 37} and may indicate impaired ability to evaluate stimulus-response contingencies involving negative outcomes. In contrast to our prediction, PSU did not exhibit lower frontal or striatal activation than DSU during the PSR task. It may be the case that patterns of brain activation show greater variability as a function of task context in recent-onset users than chronic stimulant users. Whereas chronic stimulant users exhibit blunted striatal responses across a variety of tasks (e.g., soft brush stroke, breathing occlusion, PSR, delay discounting, incentive salience)^{19, 30–33, 37} two cross-sectional studies indicate that PSU and DSU do not differ in striatal responding during decision making involving pleasant and aversive interoceptive manipulations^{51–52}; however, within the context of a behavioral inhibition task, PSU show greater striatal signal than DSU reflecting heightened prediction error (discrepancy between predicted versus actual outcomes)⁵³. As recent reviews provide compelling evidence that brain mechanisms involved in inhibitory control are implicated in the development of addiction^{6–7, 16}, perhaps paradigms targeting the inability to stop paired with drug or monetary reward would produce more reliable frontostriatal effects than the task utilized for the present study.

In addition to insula and ACC differences between groups, PSU exhibited lower superior temporal gyrus and inferior parietal lobule activation than DSU, findings consistent with research in chronic stimulant users³⁷. Superior temporal gyrus is thought to be involved with integrating past actions with rewarding outcomes to improve future choices³⁶, whereas

inferior parietal lobule is implicated in decision making involving uncertain contingencies⁵⁴. Taken together, PSU appear to recruit reduced resources to link choices with consequences, which may be particularly problematic in situations where reward contingencies are not readily apparent.

The secondary goal of this study was to determine whether baseline brain activation was linked to future patterns of stimulant and comorbid drug use, controlling for baseline drug use. In the present sample, marijuana use was substantial, but did not differ between PSU and DSU at baseline or follow-up, suggesting that group differences reflected in categorical analyses were not due to discrepancies in marijuana consumption. Dimensional analyses, which included all OSU regardless of clinical diagnosis, revealed that higher interim marijuana use was associated with lower precentral gyrus and superior temporal gyrus activation during decision making involving reward. Right precentral gyrus activation during decision making also distinguishes between marijuana users who are actively using and those who are abstinent⁵⁵, although the functional implication of this difference is yet unclear. Superior temporal gyrus results suggest that impaired integration of action-outcome contingencies is linked to excessive future marijuana consumption as well as issues arising from problem stimulant use.

This investigation possesses several strengths including: (a) a longitudinal design; (b) use of a paradigm that has previously examined differences in chronic stimulant users; and (c) no differences in lifetime marijuana use, personality, education or verbal IQ between groups that could otherwise have complicated interpretation of imaging results. However, our investigation is not without its weaknesses: (a) PSU sample size was much smaller than DSU, limiting power to detect small effects; (b) a higher percentage of PSU than DSU had used stimulants the week prior to the neuroimaging scan (although no participants tested positive for stimulants at scan time and agreed to refrain from use for 72 h prior to the scan); and (c) PSU did not differ from DSU as a function of academic achievement or polydrug use and as a result might not be representative or typical of the population of individuals who develop chronic stimulant addiction.

Despite these drawbacks, our findings demonstrate that neural activity during decision making is linked to future stimulant addiction. Young adults who recently transitioned to stimulant use disorder exhibit blunted ACC and insular responding to feedback, replicating patterns evident in chronic stimulant addiction. These patterns of BOLD responding constitute a high-risk addiction profile that could be used in the future to calculate risk scores for individuals experimenting with stimulants using random forest algorithms⁵⁰.

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Figure 1.

Overview of study design and data analyses. At baseline occasional stimulant users (OSU) completed questionnaires, a clinical interview, and a functional magnetic resonance imaging (fMRI) scan. OSU then completed a follow-up clinical interview three years later that included assessment of interim drug use. Only OSU 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 OSU who either 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 OSU and compared relationships between interim stimulant and marijuana use to baseline self-report and fMRI data, controlling for baseline stimulant and marijuana use.

Figure 2. Paper Scissors Rock (PSR) task overview. **(A)** Example of one PSR trial. **(B)** Illustration of the three decision regressors for an individual participant: trials in which the preferred response was selected are contrasted with trials on which the even trials were selected, and then both preferred and even trials were each compared to the worst response selected.

Figure 3.

Categorical analysis: Neuroimaging results. **(A)** The group main effect showed that problem stimulant users (PSU) displayed lower BOLD percent signal change (PSC) than desisted stimulant users (DSU) in middle insula, anterior cingulate cortex (ACC), superior temporal gyrus, inferior parietal lobule, and cerebellum across preferred, even, and worst response selections. **(B)** The group by condition interaction indicated that PSU exhibited lower PSC in cingulate gyrus and precuneus for preferred and tied responses than DSU.

Figure 4.

Dimensional analysis: Neuroimaging results. Partial standardized regression plots show that across OSU participants with follow-up drug use data, higher interim marijuana use was associated with lower percent BOLD percent signal change (PSC) in right precentral gyrus and superior temporal gyrus when making preferred choices. Corrected cluster threshold $t > 2.61$, $p < .01$ two-tailed for > 19 contiguous voxels. Multivariate outliers > 3 SD removed from analysis: precentral gyrus $n=1$ (resulting in 142 df), superior temporal gyrus $n=2$ (resulting in 141 df).

Table 1

Categorical Analysis: Group Demographics

	PSU (n=36)		DSU (n=74)		Statistics	
	Percentage (%)		Percentage (%)		χ^2	p
<i>Female Gender</i>	47.22		41.89	1	0.28	0.60
<i>Marijuana-Positive Urine*</i>	38.89		36.49	1	0.06	0.81
<i>Mild Depression (BDI)</i>	0.00		9.46	1	3.82	0.15
<i>Right Handedness</i>	97.22		94.59	1	0.39	0.54
<i>Caucasian Race/Ethnicity</i>	75.00		72.97	4	1.98	0.74
<hr/>						
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>df</i>	<i>t</i>
<i>Age</i>	20.83	1.61	20.93	1.46	108	0.32
<i>Education</i>	14.67	1.43	14.64	1.37	108	0.11
<i>Verbal IQ</i>	109.56	6.05	108.51	7.79	104	0.70
<i>Impulsivity (BIS-11)</i>	66.67	9.68	65.07	8.53	108	0.88
<i>Sensation Seeking (SSS-V)</i>	24.83	4.90	24.62	4.48	108	0.23
<hr/>						
Baseline Drug Use¹						
<i>Amphetamine</i>	29.83	39.01	20.82	64.85	108	0.77
<i>Cocaine</i>	26.67	41.02	18.55	39.61	108	1.00
<i>Marijuana</i>	802.58	1104.81	846.05	1279.84	108	0.60
<hr/>						
Interim Three-Year Drug Use²						
<i>Amphetamine</i>	95.41	220.91	5.38	28.24	106	6.66
<i>Cocaine</i>	281.46	614.58	8.18	35.78	106	5.49
<i>Marijuana</i>	585.63	937.78	822.10	1986.19	106	0.22

Note:

* Determined by urine screen at the outset of the neuroimaging session.

¹ Lifetime uses of the drug at the time of baseline clinical interview were quantified by the number of discrete sessions consumed.² Number of discrete sessions of drug use from the time of the baseline clinical interview to the time of three year follow-up interview. PSU = problem stimulant users. DSU = desisted stimulant users. IQ = intelligence quotient. BIS-11 = Barratt Impulsiveness Scale. SSS-V = Sensation Seeking Scale. BDI = Beck Depression Inventory.

Table 2

Categorical Analysis: Recency of Drug Use at Baseline Neuroimaging Session

	Past Week	Past Month	Past 6 Months	6–12 Months	>12 Months	Statistics
<i>Stimulants</i>	<i>N</i> (%)	<i>N</i> (%)	<i>N</i> (%)	<i>N</i> (%)	<i>N</i> (%)	$\chi^2(4)=13.93, p=.01$
PSU (<i>n</i> =36)	12 (33%)	14 (39%)	10 (28%)	0	0	
DSU (<i>n</i> =74)	10 (14%)	21 (29%)	27 (36%)	11 (15%)	5 (6%)	
<i>Marijuana</i>	<i>N</i> (%)	<i>N</i> (%)	<i>N</i> (%)	<i>N</i> (%)	<i>N</i> (%)	$\chi^2(4)=3.85, p=.43$
PSU (<i>n</i> =36)	24 (67%)	4 (11%)	3 (8%)	0	5 (14%)	
DSU (<i>n</i> =74)	47 (64%)	7 (9%)	13 (18%)	2 (2%)	5 (7%)	

Note: Recency of drug use was quantified by codes from 1 to 5: 1 = within the past week; 2 = within the past month; 3 = within the past six months; 4 = six to twelve months ago; 5 = greater than one year ago or never tried drug.

Table 3

Categorical Analysis: Neuroimaging Results

Group	# Voxels	x	y	z	L/R	Regions in Cluster	BA	Across All Responses
	25	-40	-5	1	L	Middle Insula	13	DSU > PSU; $d=0.96$
	22	0	43	10	L/R	Anterior Cingulate	32	DSU > PSU; $d=0.84$
	44	-59	-24	11	L	Superior Temporal Gyrus	40/42	DSU > PSU; $d=1.28$
	40	49	-46	21	R	Superior Temporal Gyrus	40	DSU > PSU; $d=0.99$
	47	28	-65	29	R	Precuneus	7	DSU > PSU; $d=0.93$
	30	29	-38	53	R	Inferior Parietal Lobule	40	DSU > PSU; $d=0.83$
	20	3	-66	-6	R	Cerebellum (Culmen)	-	DSU > PSU; $d=0.90$

Group x Condition	# Voxels	x	y	z	L/R	Regions in Cluster	BA	Preferred Response
	22	-7	-10	42	L	Midcingulate Gyrus	24	DSU > PSU; $d=0.62$
	23	4	-33	44	R	Precuneus	7	DSU > PSU; $d=0.74$

Note. PSU = problem stimulant users. DSU = desisted stimulant users. L= left hemisphere. R = right hemisphere. BA = Brodmann Area. Coordinates (x, y, z) reflect center of mass. Voxelwise threshold for group main effect > $F(1,108)=5.58$, $p<.01$ two-tailed for >19 contiguous voxels. Voxelwise threshold for group x decision interaction > $F(2,216)=3.98$, $p<.01$ two-tailed for >19 contiguous voxels. Cohen's d = effect size.