Published in final edited form as:

Addiction. 2014 March ; 109(3): 460–471. doi:10.1111/add.12403.

Striatum and Insula Dysfunction during Reinforcement Learning Differentiates Abstinent and Relapsed Methamphetamine Dependent Individuals

Jennifer L. Stewart, Ph.D.¹, Colm G. Connolly, Ph.D.^{1,2}, April C. May, B.A.¹, Susan F. Tapert, Ph.D.^{1,3}, Marc Wittmann, Ph.D.^{1,3,4}, and Martin P. Paulus, M.D.^{1,3}

¹Department of Psychiatry, University of California San Diego, La Jolla, CA

²Department of Psychiatry, University of California San Francisco, San Francisco, CA

³Psychiatry Service, VA San Diego Healthcare System, La Jolla, CA

⁴Department of Empirical and Analytical Psychophysics, Institute for Frontier Areas of Psychology and Mental Health, Freiburg, Germany

Abstract

Background and aims—Individuals with methamphetamine dependence (MD) exhibit dysfunction in brain regions involved in goal maintenance and reward processing when compared with healthy individuals. We examined whether these characteristics also reflect relapse vulnerability within a sample of MD patients.

Design—Longitudinal, with functional magnetic resonance imaging (fMRI) and clinical interview data collected at baseline and relapse status collected at one-year follow up interview.

Setting—Keck Imaging Center, University of California San Diego, USA

Participants—MD patients (n=60) enrolled in an inpatient drug treatment program at baseline. MD participants remaining abstinent at one year follow-up (Abstinent MD group; n=42) were compared with MD participants who relapsed within this period (Relapsed MD group; n=18).

Measurements—Behavioral and neural responses to a reinforcement learning (Paper-Scissors-Rock) paradigm recorded during an fMRI session at time of treatment.

Findings—The Relapsed MD group exhibited greater bilateral inferior frontal gyrus (IFG) and right striatal activation than the Abstinent MD group during the learning of reward contingencies (Cohen's d range: 0.60–0.83). In contrast, the Relapsed MD group displayed lower bilateral striatum, bilateral insula, left IFG, and left anterior cingulate activation than the Abstinent MD group (Cohen's d range: 0.90–1.23) in response to winning, tying, and losing feedback.

Conclusions—Methamphetamine-dependent individuals who achieve abstinence and then relapse show greater inferior frontal gyrus activation during learning, and relatively attenuated striatal, insular, and frontal activation in response to feedback, compared with methamphetamine-dependent people who remain abstinent.

For correspondence and reprint requests, please contact Jennifer L. Stewart, Laboratory of Biological Dynamics and Theoretical Medicine, Department of Psychiatry, University of California San Diego, 8939 Villa La Jolla Drive, Suite 200, La Jolla, CA, 92037-0985; phone: (858) 534-9440; j6stewart@ucsd.edu.

Declarations of Interest: none.

Keywords

methamphetamine; relapse; decision making; fMRI

Introduction

An estimated 4.7 million Americans (2.1% of the U.S. population) have tried methamphetamine (1), and use of this compound is associated with elevated mortality (2). Methamphetamine addiction presents a societal financial burden and is linked to adverse outcomes such as violence, suicide, cardiovascular disease, and diminished quality of life (3). Consistent with these impairments, research indicates that methamphetamine abuse is associated with behavioral impairments in decision making, illustrated by selection of short term gains at the expense of long term losses and stimulus-bound perseverative responding (4–14). It is argued that addicted individuals make suboptimal decisions due to aberrant physiological feeling states, reduced responsivity to non-drug rewards, and impaired cognitive control as indexed by attenuated processing by the insula, striatum, anterior cingulate (ACC), and prefrontal cortex (15–19). Given prior work on brain dysfunction in substance abusers during decision making, examination of neural and behavioral mechanisms involved in decision-outcome contingencies provides promise in predicting relapse and developing support programs to improve abstinence in methamphetamine dependent (MD) individuals (20).

Research demonstrates that MD individuals exhibit frontostriatal neuronal damage and reduced striatal dopamine receptor binding, both associated with cognitive inflexibility (21–34). In addition to attenuated frontal and insular gray matter density (28, 29), MD individuals display lower frontal, striatum, ACC, and/or insula activation than healthy subjects during various decision making paradigms involving reward, emotion recognition, error processing, vigilance monitoring, and response conflict (5, 6, 9, 10, 12, 14, 35–38). Although extant studies investigating correlates of methamphetamine relapse suggest that brain dysfunction and accompanying behavioral deficits may normalize as a function of abstinence (24, 32, 39–42), further research is warranted to corroborate these findings. Moreover, it is unclear whether neural dysfunction associated with MD and probability of relapse is evident at multiple stages of the decision making process (e.g., during the selection of a choice versus receiving a positive or negative outcome on the basis of that choice).

To address these issues, this investigation examined brain and behavioral performance during decision and outcome phases of a Paper-Scissors-Rock reinforcement learning paradigm shown to activate insula, striatal, and frontal regions thought to be impaired in substance dependence (43–45). Learning the association between an option and the probability that it results in a rewarding outcome involves assessing the discrepancy between the anticipated versus experienced reward. This process involves the striatum, which implements contingencies linking choices with rewarding outcomes (46–48), and the insula and inferior frontal gyrus (IFG), regions that encode change in reward and risk variance during reinforcement (49, 50). Similarly, in healthy subjects ACC has been linked to the integration of rewarding feedback during learning processes (51). Given that impairments in striatal, insular, ACC, and frontal regions are evident in MD individuals and research suggests that these attenuations may be stronger in MD users who relapse (40), this study examines whether these brain regions are linked to methamphetamine relapse.

Neural processing was compared in MD individuals who either remained abstinent or relapsed one year later during two decision phases of a Paper-Scissors-Rock decision

making task: (1) in early trials, wherein decision-outcome contingencies were being acquired; and (2) in late trials, wherein decision-outcome contingencies were being executed. On the basis of extant imaging literature, which has primarily focused on prefrontal and striatal dysfunction in addiction, as well as recent reviews implicating insula and ACC in substance dependence, it was hypothesized that MD users who relapsed within the following year would demonstrate lower activation in these regions across trials during feedback-related decision making than MD individuals who remained abstinent one year later. As an exploratory analysis, we examined whether neural differences in learning decision-outcome contingencies would also differ between groups by examining early versus late trials. Moreover, we predicted that MD users who relapsed would exhibit greater perseverative behavioral responding as indexed by a pattern of win-stay responses (e.g., if the last decision resulted in a win, using the same decision on the current trial) than users who remained abstinent.

Methods

Subjects

The study protocol was approved by the UCSD Human Research Protections Program and carried out in accordance with the Declaration of Helsinki. Sixty-five subjects meeting DSM-IV MD criteria within the past year were recruited from 28-day inpatient Alcohol and Drug Treatment Programs at the San Diego Veterans Affairs (VA) Medical Center and Scripps Green Hospital (La Jolla, CA). All subjects gave written informed consent to participate in a clinical interview session, a functional magnetic resonance imaging (fMRI) session, and a brief follow-up phone interview one year later to assess abstinence from methamphetamine and other substances. Follow-up interviews asked whether individuals had relapsed, and if so, the date of relapse for each substance used. Participants were contacted approximately one year after the clinical interview session. Several approaches that have been successful in large-scale longitudinal studies were used (52). For example, individuals were contacted by telephone or mail 12 months after the initial evaluation, using addresses of friends or family members, VA records, or the Department of Motor Vehicle records to locate them. For veterans the VA is the principal care center where they receive treatment and help for all medical ailments. Therefore veterans enter the VA system regularly and repeatedly and thus can more easily be tracked. Follow-up calls were completed for 60 out of 65 subjects (92% follow-up rate; 5 were unreachable) and as a result, 60 subjects with longitudinal data were included in the present analysis (47M, 13F; age: $M = 37.8$ years, $SD = 10.4$, range 19–55; ethnicity: 70% Caucasian, 13% African American, 8% Pacific Islander, 5% Asian, 2% American Indian, 2% other). Subjects underwent urine toxicology screenings for the presence of drugs (a mandatory procedure of program participation) and were experiencing no symptoms of substance withdrawal at the time of scanning (for 52/60 subjects with recency data: days of abstinence from methamphetamine $M = 33.9$, $SD = 20.1$, range = 15–119 days). Forty-two subjects reported remaining abstinent from drugs (with the exception of nicotine) from the time of inpatient treatment to one-year follow-up (Abstinent MD group), whereas the remaining 18 subjects reported that they relapsed within the past twelve months (Relapsed MD group). Groups did not differ on days since last methamphetamine use (Abstinent MD: $M = 29.1$ $SD = 19.0$; Relapsed MD: $M = 27.5$, $SD = 14.5$; $t(52) = 0.3$, $p = .76$).

Lifetime DSM-IV Axis I diagnoses (including substance abuse and dependence; DSM-IV) (53) and Axis II antisocial personality disorder (ASPD) were assessed by experienced interviewers using the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) (54), a detailed structured clinical interview including timeline follow-back methods to quantify lifetime drug use based on the number of distinct sessions drugs were

used. Diagnoses were based on consensus meetings with a clinician specialized in substance use disorders (MPP) and trained study personnel. The following were exclusion criteria: (1) ASPD; (2) current (and past 6 months) drug-independent Axis I anxiety and unipolar depressive disorders; (3) lifetime psychotic disorders; (4) severe medical disorders; (5) current use of medications affecting the hemodynamic response such as antihypertensives, insulin, and thyroid medication; (6) current positive urine toxicology test for any substance other than nicotine; and (7) head injuries or loss of consciousness > 5 min. A total of 59/60 subjects reported right handedness. During the clinical interview session: (1) the North American Adult Reading Test (55), a measure of verbal IQ, was administered to determine whether level of intelligence predicted relapse; (2) lifetime uses of amphetamine, cocaine, and marijuana were calculated; and (3) questionnaires indexing characteristics previously associated with methamphetamine use were administered (26, 38, 56) to determine whether personality measures alone could predict relapse. The Beck Depression Inventory (BDI) (57), Barratt Impulsivity Scale (BIS) (58), and Sensation Seeking Scale (SSS-V) (59) were used to index depression, impulsivity and sensation seeking, respectively.

Paper-Scissors-Rock Task

The Paper-Scissors-Rock task (43–45) examines how individuals acquire the ability to make decisions associated with advantageous outcomes (please see Figure 1 and refer to 46–48 for more details). This task is based on the well-known Paper-Scissors-Rock game, 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). Players were told that 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 for each response option. A total of 120 trials were presented, consisting of six blocks containing 20 trials each. Within each block, the three possible selections had pre-determined probabilities of having a winning, tying, or losing outcome. The “preferred response” wins on 90% of trials, the “even response” wins 50% of the time, and the “worst response” wins on 10% of trials. Thus, if rock was the preferred response and paper was the worst response in a particular block, then selecting rock would result in a win 90% of the time and selecting paper would result in a win 10% of the time. Unbeknownst to the subject, preferred, even, and worst responses were switched for each of six blocks presented.

fMRI Image Acquisition

A fMRI run sensitive to blood oxygenation level-dependent (BOLD) contrast was collected in a randomized fast-event related design using a Signa EXCITE (GE Healthcare, Milwaukee, Wisconsin) 3.0 Tesla scanner (T2*-weighted echo planar imaging (EPI) scans, TR=2000 ms, TE=32 ms, FOV=23cm, 64×64 matrix, 30 2.6mm axial slices with 1.4 mm gap, flip angle=90°, 290 whole-brain acquisitions). fMRI volume acquisitions were time-locked to task onset. A high-resolution T1-weighted image [spoiled gradient recalled (SPGR), TI=450, TR=8 ms, TE=3 ms, flip angle=12°, FOV=25cm, 256×256 matrix, 172 sagittally acquired slices with 1mm thickness] was obtained for anatomical reference.

Behavioral Analysis

Responses were obtained using the first three buttons on a response box recorded during each trial to determine response selection (preferred, even, and worst). Two linear mixed effects (LME) analyses were performed in R (60). The first LME examined group (Abstinent MD, Relapsed MD) and decision time (early trials, late trials) across blocks, with probability of preferred response selection as the dependent variable. The second LME compared group and outcome (wins, ties, losses), with total number of each outcome across

blocks as the dependent variable. Subjects were treated as random effects, whereas group, decision time, and outcome were modeled as fixed effects.

fMRI Data Analysis

Preprocessing—Functional analyses were conducted using AFNI (61). Following reconstruction, differences in slice acquisition timing were corrected using Fourier interpolation. The time-series were then motion corrected (least-squares alignment using three rotational and three translational parameters). EPI datasets were aligned to the T1-weighted anatomical using local Pearson correlation (62). To relate EPI changes to task characteristics, a multivariate regressor approach, described below, was used. Motion regressors were included in deconvolutions described below to account for EPI intensity changes possibly due to motion artifacts. Data were inspected to determine successful image alignment and existence of remaining artifacts.

Deconvolution: Decision phase—Based on subjects' learning curves (frequency of preferred response selection as a function of trial position after each switch), groups of trials across blocks during the decision phase of the task depicted in Figure 1 (from trial onset until response selection, as opposed to the outcome phase) were separated into early trials, defined as trials 1–8, when contingencies (selection of the preferred response, avoidance of the worst response) were being learned, and late trials, defined as trials 13–20, when contingencies had been established. Based on the behavioral performance of each subject, trials were also divided into those resulting in wins, ties, and losses. Deconvolution was then performed, wherein three motion regressors, a baseline and linear drift regressor, two normalized decision time regressors (early trials, late trials), and three normalized outcome regressors (wins, ties, losses) were convolved with a hemodynamic response function. The baseline for the decision phase consisted of the inter-trial interval and null trials interspersed between trial blocks.

Post-deconvolution processing—Resultant beta values for regressors of interest were converted to a percent signal change score relative to baseline, which served as the activation measure. Voxels were resampled into $4 \times 4 \times 4$ mm³. Images were spatially filtered using a Gaussian Spatial Filter (full-width-half-maximum 4.2 mm) to account for individual anatomical differences. Anatomical images were manually talairached and echoplanar images were transformed into Talairach space.

Group analysis: Decision phase—For each voxel, a LME analysis was computed, wherein subjects were treated as random effects and group (Abstinent MD, Relapsed MD) and decision time (early trials, late trials) were modeled as fixed effects. The dependent variable was percent signal change from baseline.

Group analysis: Outcome phase—For each voxel, a second LME analysis was computed, wherein subjects were treated as random effects and group and outcome (wins, ties, losses) were modeled as fixed effects. The dependent variable was percent signal change from baseline.

Extraction of significant LME results—A threshold adjustment method based on Monte-Carlo simulations (AFNI's program Alpha Sim) guarded against identifying false positive areas of activation (considering whole brain voxel size and 4mm smoothness). For main effects and interactions involving group, AlphaSim identified a minimum cluster volume of 960 μ L (15 contiguous voxels, each voxel less than $p < .00001$ uncorrected) in conjunction with a cluster significance of $p < .002$ to result in a voxel-wise probability of $p < .05$ corrected for multiple comparisons. In addition to whole-brain analyses, individual a-

priori region of interest masks were used to extract significant activation from bilateral striatum, insula, and ACC. The voxelwise threshold for effects of interest were based on the following LME degrees of freedom and F values: (1) Decision phase group main effect and group by decision time interaction: $F(1,58)=4.01$; (2) Outcome phase group main effect: $F(1,58) = 4.01$ and group by outcome interaction: $F(2,116)=3.08$. Independent t-tests were calculated between groups for all clusters emerging as significant in LME analyses. Cohen's d effect sizes were also calculated for significant results involving group differences.

Results

Subject Characteristics

Groups did not differ on the majority of demographic or personality variables (see Table 1). However, Relapsed MD endorsed significantly higher rates of marijuana dependence and marginally greater rates of alcohol dependence than Abstinent MD.

Behavioral Data

Group means for behavioral performance variables are listed in Table 1. LME results (see Figure 2) demonstrated that although a main effect of decision time emerged wherein subjects selected more preferred responses during late trials ($M=44.2\%$, $SE=1.8\%$) than early trials ($M=35.4\%$, $SE=1.0\%$; $F(1,91)=18.2$, $p<.001$), groups did not differ in percentage of preferred response selection across trials or between early and late trials (both $p>.34$). Similarly, although groups achieved similar numbers of wins, ties and losses ($p=.10$), number of wins ($M=44.2$, $SE=1.1$) and ties ($M=41.5$, $SE=1.0$) received was significantly higher than losses ($M=34.2$, $SE=0.8$) across subjects ($F(2,106)=34.2$, $p<.001$). Finally, although number of non-random perseverative choice sequences as indexed by win-stay responses did not differ between groups, within Relapse MD, a higher number of win-stay responses was associated with greater (log-transformed) lifetime uses of methamphetamine ($r=.46$, $p=.05$, $R^2=.21$), a correlation significantly stronger for Relapsed MD than Abstinent MD ($r=-.12$, $p=.47$; $z=2.03$, $p=.04$).

fMRI Data

Decision phase—For the main effect of group, Relapsed MD exhibited greater right IFG activation ($d=0.92$) than Abstinent MD across trials ($p=.004$), an effect that remained significant when individuals with current marijuana dependence were removed from analysis ($p=.03$) (see Figure 3A). For the group by decision interaction (Table 2), Relapsed MD exhibited greater bilateral IFG and uncus activation as well as higher left middle temporal gyrus and right caudate, thalamus, parahippocampal gyrus, and hippocampus activation than Abstinent MD during early trials (see Figure 3B), findings that remained at least marginally significant after subjects with comorbid marijuana dependence were removed from analysis.

Outcome phase—The group main effect (Table 3 and Figure 4) revealed that Relapsed MD displayed lower bilateral insula, striatum, thalamus, posterior cingulate, and precuneus activation than Abstinent MD across winning, tying and losing outcomes, findings that remained significant after removal of subjects with marijuana dependence from analyses. Relapsed MD also exhibited lower left ACC activation than Abstinent MD to feedback (see Figure 5A). For the group by outcome interaction (Table 4), Relapsed MD displayed lower right cingulate gyrus activation to ties and lower right anterior insula activation (Figure 5B) to ties and losses than Abstinent MD.

Discussion

This study focused on brain processing during reinforcement-related decision-making in MD individuals who subsequently relapsed versus those that remained abstinent during a one-year follow up interval. Consistent with our first prediction, Relapsed MD exhibited lower frontal, insula, striatum, and ACC activation in response to outcomes than Abstinent MD, which may reflect engaging relatively fewer neural processing resources when processing feedback in those individuals who resume methamphetamine consumption. These findings are consistent with dysfunction reported in these brain regions for methamphetamine abusers (5, 6, 9, 10, 12, 14, 35–38), including those who relapse (40). Second, in contrast to attenuated striatal activation evident in response to feedback, Relapsed MD demonstrated right striatal hyperactivation during learning of decision-outcome contingencies when compared to Abstinent MD, which may reflect the fact that relapsed individuals engage relatively more neural processing resources when attempting to establish the reinforcement contingencies. Taken together, results support the assertion that Relapsed MD may possess a dysregulated reward system that could be related to drug consumption despite negative consequences (63). Finally, although we predicted that Relapsed MD would show greater perseverative responding than Abstinent MD as indexed by a higher number of win-stay responses (8, 14). This prediction was not supported. However, within Relapsed MD, greater perseverative responding was linked to higher lifetime methamphetamine use, suggesting that chronicity of use is linked to behavioral impairments.

In addition to group differences in insular, frontal and striatal regions, Relapsed MD demonstrated altered activation in regions important for memory processing during decision making such as posterior cingulate gyrus, parahippocampal gyrus and associated structures (uncus), hippocampus, and middle temporal gyrus. Given that reward fluctuations are linked to greater parahippocampal and hippocampal activation during decision making (64) and that posterior cingulate gyrus may represent affective states developed on the basis of prior patterns of reward and punishment (65), heightened activation in these regions during early trials when reward contingencies are being learned and/or when receiving valenced feedback suggest that Relapsed MD may need to devote greater neural resources to maintaining the preferred response in memory. Given that MD patients exhibit gray matter deficits in the hippocampus and posterior cingulate gyrus (66), show greater posterior cingulate and hippocampal gyrus activation to difficult versus easy decisions than healthy control subjects (10), and display heightened posterior cingulate glucose metabolism at rest (37, 38), over-recruitment of brain regions involved in memory may be necessary to process and remember complex information in MD who have difficulty remaining abstinent from drugs.

Although this longitudinal study possesses many merits, including examination of self-report, behavioral, and neural indices of relapse vulnerability, it also has several limitations. First, although Relapsed MD endorsed higher rates of comorbid marijuana dependence at the time of the fMRI session than Abstinent MD, given the relatively small sample of Relapsed MD and Abstinent MD who met criteria for marijuana dependence, the present investigation could not reliably compare brain activation, behavioral performance and personality characteristics in those with versus without these comorbid diagnoses. However, neural differences between Abstinent and Relapsed MD largely remained significant after removing individuals with comorbid marijuana dependence from analyses, suggesting that attenuated fronto-cingulate, striatal, and insular activation to feedback in Relapsed MD is not primarily related to concurrent problems with marijuana use. Although recent work suggests that polysubstance abuse is not a robust predictor of methamphetamine relapse (67), additional investigation is warranted. Second, although this study benefits from a longitudinal design with respect to self-reported drug use, we did not collect additional

fMRI data at one-year follow-up. Thus, although our findings indicate that brain dysfunction in MD individuals reflects relapse vulnerability we cannot determine whether brain activation “normalizes” further in MD individuals who remained abstinent for one year. Future research is needed to address this issue. Third, self-report was utilized as the only measure of relapse. Future investigations of relapse should incorporate urine screens at one-year follow-up to verify abstinence. Fourth, it is possible that self-assessment and behavioral assessments are not sensitive enough to detect future behavioral changes. Specifically, the momentary assessment of mood and/or cognitive function may be highly context-specific and may not translate to how individuals behave when exposed to the possibility of drug taking behavior. On the other hand, the degree to which the brain engages in different behavioral processes may be relatively context-independent, i.e. may provide a relatively stable biomarker quantifying the degree of neural processing for an individual. Despite these limitations, this study demonstrates that brain activation during reward learning differentiates abstinent and relapsed MD individuals. It will be important to determine whether training programs can be developed to repair deficits in reward sensitivity within the context of methamphetamine treatment in order to prevent future relapse.

Acknowledgments

This work was supported by a grant from the National Institute on Drug Abuse (Grant No. R01 DA018307 to Martin Paulus).

References

1. Anglin MD, Burke C, Perrochet B, Stamper E, Dawud-Noursi S. History of the methamphetamine problem. *J PsychoactiveDrugs*. 2000; 32(2):137–141.
2. Kuo CJ, Liao YT, Chen WJ, Tsai SY, Lin SK, Chen CC. Causes of death of patients with methamphetamine dependence: A record-linkage study. *Drug Alcohol Rev*. 2010
3. Gonzales R, Mooney L, Rawson RA. The methamphetamine problem in the United States. *Annu Rev Public Health*. 2010; 31:385–398. [PubMed: 20070191]
4. Ghahremani DG, Tabibnia G, Monterosso J, Helleman G, Poldrack RA, London ED. Effect of modafinil on learning and task-related brain activity in methamphetamine-dependent and healthy individuals. *Neuropsychopharmacology*. 2011; 36(5):950–959. [PubMed: 21289606]
5. Hoffman WF, Schwartz DL, Huckans MS, McFarland BH, Meiri G, Stevens AA, et al. Cortical activation during delay discounting in abstinent methamphetamine dependent individuals. *Psychopharmacology (Berl)*. 2008; 201(2):183–193. [PubMed: 18685833]
6. Monterosso JR, Ainslie G, Xu J, Cordova X, Domier CP, London ED. Frontoparietal cortical activity of methamphetamine-dependent and comparison subjects performing a delay discounting task. *Hum Brain Mapp*. 2007; 28(5):383–393. [PubMed: 16944492]
7. Monterosso JR, Aron AR, Cordova X, Xu J, London ED. Deficits in response inhibition associated with chronic methamphetamine abuse. *Drug Alcohol Depend*. 2005; 79(2):273–277. [PubMed: 15967595]
8. van der Plas EA, Crone EA, van den Wildenberg WP, Tranel D, Bechara A. Executive control deficits in substance-dependent individuals: a comparison of alcohol, cocaine, and methamphetamine and of men and women. *J Clin Exp Neuropsychol*. 2009; 31(6):706–719. [PubMed: 19037812]
9. Kim YT, Song HJ, Seo JH, Lee JJ, Lee J, Kwon DH, et al. The differences in neural network activity between methamphetamine abusers and healthy subjects performing an emotion-matching task: functional MRI study. *NMR Biomed*. 2011; 24(10):1392–1400. [PubMed: 21472808]
10. Nestor LJ, Ghahremani DG, Monterosso J, London ED. Prefrontal hypoactivation during cognitive control in early abstinent methamphetamine-dependent subjects. *Psychiatry Res*. 2011; 194(3): 287–295. [PubMed: 22047731]

11. King G, Alicata D, Cloak C, Chang L. Neuropsychological deficits in adolescent methamphetamine abusers. *Psychopharmacology (Berl)*. 2010; 212(2):243–249. [PubMed: 20640405]
12. Salo R, Ursu S, Buonocore MH, Leamon MH, Carter C. Impaired prefrontal cortical function and disrupted adaptive cognitive control in methamphetamine abusers: a functional magnetic resonance imaging study. *Biol Psychiatry*. 2009; 65(8):706–709. [PubMed: 19136097]
13. Kalechstein AD, Newton TF, Green M. Methamphetamine dependence is associated with neurocognitive impairment in the initial phases of abstinence. *J Neuropsychiatry Clin Neurosci*. 2003; 15(2):215–220. [PubMed: 12724464]
14. Paulus MP, Hozack N, Frank L, Brown GG, Schuckit MA. Decision making by methamphetamine-dependent subjects is associated with error-rate-independent decrease in prefrontal and parietal activation. *Biol Psychiatry*. 2003; 53(1):65–74. [PubMed: 12513946]
15. Naqvi NH, Bechara A. The insula and drug addiction: an interoceptive view of pleasure, urges, and decision-making. *Brain Struct Funct*. 2010; 214(5–6):435–450. [PubMed: 20512364]
16. Garavan H, Hester R. The role of cognitive control in cocaine dependence. *Neuropsychol Rev*. 2007; 17(3):337–345. [PubMed: 17680368]
17. Volkow ND, Fowler JS, Wang GJ, Baler R, Telang F. Imaging dopamine's role in drug abuse and addiction. *Neuropharmacology*. 2009; 56(Suppl 1):3–8. [PubMed: 18617195]
18. Goldstein RZ, Volkow ND. Drug addiction and its underlying neurobiological basis: neuroimaging evidence for the involvement of the frontal cortex. *Am J Psychiatry*. 2002; 159(10):1642–1652. [PubMed: 12359667]
19. Paulus MP, Tapert SF, Schulteis G. The role of interoception and alliesthesia in addiction. *Pharmacol Biochem Behav*. 2009; 94(1):1–7. [PubMed: 19698739]
20. Reske M, Paulus MP. Predicting treatment outcome in stimulant dependence. *Ann N Y Acad Sci*. 2008; 1141:270–283. [PubMed: 18991963]
21. Alicata D, Chang L, Cloak C, Abe K, Ernst T. Higher diffusion in striatum and lower fractional anisotropy in white matter of methamphetamine users. *Psychiatry Res*. 2009; 174(1):1–8. [PubMed: 19782540]
22. Chang L, Ernst T, Speck O, Patel H, DeSilva M, Leonido-Yee M, et al. Perfusion MRI and computerized cognitive test abnormalities in abstinent methamphetamine users. *Psychiatry Res*. 2002; 114(2):65–79. [PubMed: 12036507]
23. Chang L, Cloak C, Patterson K, Grob C, Miller EN, Ernst T. Enlarged striatum in abstinent methamphetamine abusers: a possible compensatory response. *Biol Psychiatry*. 2005; 57(9):967–974. [PubMed: 15860336]
24. Ernst T, Chang L. Adaptation of brain glutamate plus glutamine during abstinence from chronic methamphetamine use. *J Neuroimmune Pharmacol*. 2008; 3(3):165–172. [PubMed: 18521756]
25. Kim SJ, Lyoo IK, Hwang J, Sung YH, Lee HY, Lee DS, et al. Frontal glucose hypometabolism in abstinent methamphetamine users. *Neuropsychopharmacology*. 2005; 30(7):1383–1391. [PubMed: 15726115]
26. Lee B, London ED, Poldrack RA, Farahi J, Nacca A, Monterosso JR, et al. Striatal dopamine d2/d3 receptor availability is reduced in methamphetamine dependence and is linked to impulsivity. *J Neurosci*. 2009; 29(47):14734–14740. [PubMed: 19940168]
27. McCann UD, Kuwabara H, Kumar A, Palermo M, Abbey R, Brasic J, et al. Persistent cognitive and dopamine transporter deficits in abstinent methamphetamine users. *Synapse*. 2008; 62(2):91–100. [PubMed: 17992686]
28. Nakama H, Chang L, Fein G, Shimotsu R, Jiang CS, Ernst T. Methamphetamine users show greater than normal age-related cortical gray matter loss. *Addiction*. 2011; 106(8):1474–1483. [PubMed: 21438934]
29. Schwartz DL, Mitchell AD, Lahna DL, Luber HS, Huckans MS, Mitchell SH, et al. Global and local morphometric differences in recently abstinent methamphetamine-dependent individuals. *Neuroimage*. 2010; 50(4):1392–1401. [PubMed: 20096794]
30. Tobias MC, O'Neill J, Hudkins M, Bartzokis G, Dean AC, London ED. White-matter abnormalities in brain during early abstinence from methamphetamine abuse. *Psychopharmacology (Berl)*. 2010; 209(1):13–24. [PubMed: 20101394]

31. Volkow ND, Chang L, Wang GJ, Fowler JS, Ding YS, Sedler M, et al. Low level of brain dopamine D2 receptors in methamphetamine abusers: association with metabolism in the orbitofrontal cortex. *Am J Psychiatry*. 2001; 158(12):2015–2021. [PubMed: 11729018]
32. Volkow ND, Chang L, Wang GJ, Fowler JS, Franceschi D, Sedler M, et al. Loss of dopamine transporters in methamphetamine abusers recovers with protracted abstinence. *J Neurosci*. 2001; 21(23):9414–9418. [PubMed: 11717374]
33. Salo R, Fassbender C. Structural, functional and spectroscopic MRI studies of methamphetamine addiction. *Curr Top Behav Neurosci*. 2012; 11:321–364. [PubMed: 22094881]
34. Jan RK, Kydd RR, Russell BR. Functional and structural brain changes associated with methamphetamine abuse. *Brain Sciences*. 2012; 2:434–482.
35. Payer DE, Lieberman MD, London ED. Neural correlates of affect processing and aggression in methamphetamine dependence. *Arch Gen Psychiatry*. 2011; 68(3):271–282. [PubMed: 21041607]
36. Payer DE, Nurmi EL, Wilson SA, McCracken JT, London ED. Effects of methamphetamine abuse and serotonin transporter gene variants on aggression and emotion-processing neurocircuitry. *Translational psychiatry*. 2012; 2:e80. [PubMed: 22832817]
37. London ED, Berman SM, Voytek B, Simon SL, Mandelkern MA, Monterosso J, et al. Cerebral metabolic dysfunction and impaired vigilance in recently abstinent methamphetamine abusers. *Biol Psychiatry*. 2005; 58(10):770–778. [PubMed: 16095568]
38. London ED, Simon SL, Berman SM, Mandelkern MA, Lichtman AM, Bramen J, et al. Mood disturbances and regional cerebral metabolic abnormalities in recently abstinent methamphetamine abusers. *Arch Gen Psychiatry*. 2004; 61(1):73–84. [PubMed: 14706946]
39. Clark VP, Beatty GK, Anderson RE, Kodituwakku P, Phillips JP, Lane TD, et al. Reduced fMRI activity predicts relapse in patients recovering from stimulant dependence. *Hum Brain Mapp*. 2012
40. Paulus MP, Tapert SF, Schuckit MA. Neural activation patterns of methamphetamine-dependent subjects during decision making predict relapse. *Arch Gen Psychiatry*. 2005; 62(7):761–768. [PubMed: 15997017]
41. Simon SL, Dacey J, Glynn S, Rawson R, Ling W. The effect of relapse on cognition in abstinent methamphetamine abusers. *J Subst Abuse Treat*. 2004; 27(1):59–66. [PubMed: 15223095]
42. Salo R, Nordahl TE, Galloway GP, Moore CD, Waters C, Leamon MH. Drug abstinence and cognitive control in methamphetamine-dependent individuals. *J Subst Abuse Treat*. 2009; 37(3):292–297. [PubMed: 19339145]
43. Paulus MP, Feinstein JS, Leland D, Simmons AN. Superior temporal gyrus and insula provide response and outcome-dependent information during assessment and action selection in a decision-making situation. *Neuroimage*. 2005; 25(2):607–615. [PubMed: 15784440]
44. Paulus MP, Feinstein JS, Tapert SF, Liu TT. Trend detection via temporal difference model predicts inferior prefrontal cortex activation during acquisition of advantageous action selection. *Neuroimage*. 2004; 21(2):733–743. [PubMed: 14980576]
45. Stewart AT, Flagan TM, May AC, Reske M, Simmons AN, Paulus MP. Young adults at risk for stimulant dependence show reward dysfunction during reinforcement-based decision making. *Biol Psychiat*. in press
46. Delgado MR, Miller MM, Inati S, Phelps EA. An fMRI study of reward-related probability learning. *Neuroimage*. 2005; 24(3):862–873. [PubMed: 15652321]
47. Knutson B, Cooper JC. Functional magnetic resonance imaging of reward prediction. *Curr Opin Neurol*. 2005; 18(4):411–417. [PubMed: 16003117]
48. O'Doherty J, Dayan P, Schultz J, Deichmann R, Friston K, Dolan RJ. Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science*. 2004; 304(5669):452–454. [PubMed: 15087550]
49. Li J, McClure SM, King-Casas B, Montague PR. Policy adjustment in a dynamic economic game. *PLoS One*. 2006; 1:e103. [PubMed: 17183636]
50. Preusschoff K, Quartz SR, Bossaerts P. Human insula activation reflects risk prediction errors as well as risk. *J Neurosci*. 2008; 28(11):2745–2752. [PubMed: 18337404]
51. Santesso DL, Dillon DG, Birk JL, Holmes AJ, Goetz E, Bogdan R, et al. Individual differences in reinforcement learning: behavioral, electrophysiological, and neuroimaging correlates. *Neuroimage*. 2008; 42(2):807–816. [PubMed: 18595740]

52. Twitchell GR, Hertzog CA, Klein JL, Schuckit MA. The anatomy of a follow-up. *Br J Addict.* 1992; 87(9):1327–1333. [PubMed: 1392554]
53. Association, AP. *Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition.* Washington D.C.: American Psychological Association; 1994.
54. Bucholz KK, Cadoret R, Cloninger CR, Dinwiddie SH, Hesselbrock VM, Nurnberger JI Jr, et al. A new, semi-structured psychiatric interview for use in genetic linkage studies: a report on the reliability of the SSAGA. *J Stud Alcohol.* 1994; 55(2):149–158. [PubMed: 8189735]
55. Uttl B. North American Adult Reading Test: age norms, reliability, and validity. *J Clin Exp Neuropsychol.* 2002; 24(8):1123–1137. [PubMed: 12650237]
56. Ersche KD, Turton AJ, Pradhan S, Bullmore ET, Robbins TW. Drug addiction endophenotypes: impulsive versus sensation-seeking personality traits. *Biol Psychiatry.* 2010; 68(8):770–773. [PubMed: 20678754]
57. Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry.* 1961; 4:561–571. [PubMed: 13688369]
58. Patton JH, Stanford MS, Barratt ES. Factor structure of the Barratt impulsiveness scale. *J Clin Psychol.* 1995; 51(6):768–774. [PubMed: 8778124]
59. Zuckerman M. Item revisions in the Sensation Seeking Scale form V (SSS-V). *Pers Indiv Differ.* 1996; 20:515.
60. Pinheiro J, Bates D, DebRoy S, Sarkar D. Team RDC. *nlme: Linear and Nonlinear Mixed Effects Models.* 2011
61. Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res.* 1996; 29(3):162–173. [PubMed: 8812068]
62. Saad ZS, Glen DR, Chen G, Beauchamp MS, Desai R, Cox RW. A new method for improving functional-to-structural MRI alignment using local Pearson correlation. *Neuroimage.* 2009; 44(3): 839–848. [PubMed: 18976717]
63. Volkow ND, Wang GJ, Fowler JS, Tomasi D, Telang F, Baler R. Addiction: decreased reward sensitivity and increased expectation sensitivity conspire to overwhelm the brain's control circuit. *Bioessays.* 2010; 32(9):748–755. [PubMed: 20730946]
64. Elliott R, Dolan RJ, Frith CD. Dissociable functions in the medial and lateral orbitofrontal cortex: evidence from human neuroimaging studies. *Cereb Cortex.* 2000; 10(3):308–317. [PubMed: 10731225]
65. Bechara A. Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. *Nat Neurosci.* 2005; 8(11):1458–1463. [PubMed: 16251988]
66. Thompson PM, Hayashi KM, Simon SL, Geaga JA, Hong MS, Sui Y, et al. Structural abnormalities in the brains of human subjects who use methamphetamine. *J Neurosci.* 2004; 24(26):6028–6036. [PubMed: 15229250]
67. Dean AC, London ED, Sugar CA, Kitchen CM, Swanson AN, Heinzerling KG, et al. Predicting adherence to treatment for methamphetamine dependence from neuropsychological and drug use variables. *Drug Alcohol Depend.* 2009; 105(1–2):48–55. [PubMed: 19608354]

Figure 1.
Illustration of Paper-Scissors-Rock paradigm.

Figure 2.

Abstinent and Relapsed Methamphetamine Dependent (MD) groups demonstrated similar behavioral acquisition (during early trials) and execution (during late trials) of the preferred response across blocks ($p > .34$).

Figure 3.

Decision phase fMRI results: (A) Main effect of group wherein the Relapsed Methamphetamine Dependent (MD) group exhibited greater right inferior frontal gyrus (IFG) activation while making decisions across early and late trials than the Abstinent MD group. (B) Group by decision interaction wherein Relapsed MD exhibited greater bilateral IFG and uncus and right striatum, hippocampus, thalamus, and parahippocampal gyrus activation than Abstinent MD while making decisions during early trials. Groups did not differ in activation during late trials. BA = Brodmann Area. The y-axis reflects percent signal change relative to baseline. Error bars reflect ± 1 standard error.

Figure 4.

Outcome phase fMRI results: Main effect of group wherein the Relapsed Methamphetamine Dependent (MD) group showed lower bilateral insula and caudate activation than the Abstinent MD group across winning, tying, and losing outcomes. The y-axis reflects percent signal change relative to baseline. Error bars reflect ± 1 standard error.

Figure 5.

Outcome phase fMRI results: (A) Main effect of group wherein the Relapsed Methamphetamine Dependent (MD) group showed lower left anterior cingulate (ACC) activation than the Abstinent MD group across winning, tying, and losing outcomes. (B) Group by outcome interaction, wherein the Relapsed Methamphetamine (MD) group exhibited lower right anterior insula activation than the Abstinent MD group in response to ties and losses. The y-axis reflects percent signal change relative to baseline. Error bars reflect ± 1 standard error.

Table 1

Subject Characteristics as a function of One Year Follow-Up Group Status

Characteristics at Time of fMRI Session	Abstinent MD (n=42)		Relapsed MD (n=18)		Group Statistics	
	M (SD)		M (SD)		df	t p
Age (Years)	37.8 (10.9)		37.9 (9.4)		57	0.1 0.97
Verbal IQ	108.9 (9.8)		109.9 (7.5)		56	0.4 0.70
Education (Years)	12.9 (1.8)		13.3 (1.5)		58	1.0 0.33
Methamphetamine Use (Years)	13.7 (10.0)		13.3 (8.9)		58	-0.2 0.87
Lifetime Methamphetamine Use (Sessions)	10433.93 (14900.2)		9221.7 (12596.4)		58	-0.3 0.76
Lifetime Cocaine Use (Sessions)	1593.1 (2805.3)		2835.0 (6438.9)		58	1.0 0.30
Lifetime Marijuana Use (Sessions)	5962.4 (9646.7)		5006.7 (9031.0)		58	-0.4 0.72
Number of Weeks Used Alcohol in Past 6 Months	10.6 (10.7)		11.0 (11.0)		55	-0.1 0.90
Number of Current Alcohol Drinks Per Week	19.1 (29.9)		30.0 (56.1)		55	-1.0 0.45
Beck Depression Inventory (BDI)	7.8 (7.4)		7.1 (7.0)		54	-0.3 0.75
Barratt Impulsivity Total (BIS)	76.3 (12.7)		77.6 (10.0)		45	0.3 0.75
Sensation Seeking Total (SSS)	22.9 (5.9)		22.7 (6.2)		50	-0.1 0.94
Lifetime Conduct Disorder Symptoms	1.3 (1.3)		1.4 (1.6)		58	0.1 0.89
Lifetime ASPD Symptoms	1.2 (1.5)		0.9 (1.2)		58	-0.7 0.49
Lifetime ADHD Symptoms	3.8 (5.2)		4.0 (6.1)		58	0.1 0.91
<i>Paper-Scissors-Rock Behavioral Performance</i>	<i>M (SD)</i>		<i>M (SD)</i>		<i>df</i>	<i>t p</i>
Probability Preferred Response Selection, Early Trials (%)	34.8 (7.1)		36.0 (7.2)		58	-0.4 0.70
Probability Preferred Response Selection, Late Trials (%)	42.8 (13.0)		45.5 (12.7)		58	-0.7 0.50
Win-Stay Responses	.03 (.02)		.03 (.02)		56	-0.1 0.96
Total Wins	44.1 (7.8)		44.3 (7.6)		58	-0.1 0.95
<i>Gender, Ethnicity, Comorbid Substance Use</i>	<i>Abstinent MD (n=42)</i>		<i>Relapsed MD (n=18)</i>		<i>df</i>	χ^2 p
% Women	21%		22%		1	0.0 0.95
% Caucasian	71%		67%		1	0.1 0.71
% Current Nicotine Dependence	52%		33%		1	1.8 0.18
% Current Alcohol Dependence	10%		28%		1	3.3 0.07

Characteristics at Time of fMRI Session	Abstinent MD (n=42)		Relapsed MD (n=18)		Group Statistics	
	M (SD)		M (SD)		t	p
% Current Cocaine Dependence	14%		11%		1	0.74
% Current Marijuana Dependence	5%		28%		1	0.01

Note: IQ = intelligence quotient. BDI = Beck Depression Inventory. BIS = Barratt Impulsivity Scale. SSS = Sensation Seeking Scale. ADHD = attention deficit hyperactivity disorder. ASPD = antisocial personality disorder. Data were missing for the following number of subjects: age=1, verbal IQ=2, alcohol use=3, BDI=4, BIS=13, and SSS=8. A total of 2 subjects had win-stay behavioral responses that were >3 SD from the mean and as a result were removed from analysis.

Table 2

Imaging Results for the Group by Decision Interaction, Decision Phase

Volume (μL)	#Voxels/ Cluster	x	y	z	Hem	Regions in Cluster	BA	Early Trials	Late Trials	Cohen's d	With/Without Marijuana Dependence (p)
<i>Frontal Cortex/Limbic</i>											
3072	48	-20	1	-21	L	Inferior Frontal Gyrus, Uncus	47, 34	R > A	ns	0.60	.04 / .10
17,152	268	32	-23	-9	R	Inferior Frontal Gyrus, Uncus, Parahippocampal Gyrus, Caudate, Hippocampus, Thalamus	47, 36	R > A	ns	0.83	.01 / .03
<i>Temporal Cortex</i>											
3520	55	-42	10	-31	L	Middle/Inferior Temporal Gyrus	38	R > A	ns	0.64	.02 / .08
1280	20	-47	-15	-11	L	Middle Temporal Gyrus	21	R > A	ns	0.67	.03 / .07

Note: R = Relapsed Methamphetamine Dependent. A = Abstinent Methamphetamine Dependent. ns = non-significant. Hem = Hemisphere. L = left hemisphere. R = right hemisphere. BA = Brodmann Area. With/Without Marijuana Dependence = independent t-test p-values for group comparisons including versus excluding $n=7$ subjects (n=5 Relapsed group; n=2 Abstinent group) with current marijuana dependence. Talairach coordinates reflect center of mass.

Table 3

Imaging Results for the Group Main Effect, Outcome Phase

Volume (μL)	#Voxels/ Cluster	x	y	z	Hem	Regions in Cluster	BA	Group Difference	Cohen's d	With/Without Marijuana Dependence (p)
<i>Insular Cortex/Limbic</i>										
64128	1002	11	-11	10	L/R	Thalamus, Insula, Caudate, Putamen, Lentiform Nucleus	13	A > R	1.35	.001 / .01
4736	74	-35	4	8	L	Anterior/Middle Insula *	13	A > R	1.23	.001 / .01
2880	45	37	-23	17	R	Middle Insula *	13	A > R	1.10	.001 / .01
2176	34	-11	4	10	L	Caudate *	-	A > R	0.98	.01 / .02
1152	18	14	-2	15	R	Caudate *	-	A > R	0.97	.01 / .04
<i>Cingulate Cortex</i>										
12096	189	-6	-59	22	L/R	Posterior Cingulate	31	A > R	1.01	.01 / .01
3648	57	-3	-28	38	L/R	Cingulate Gyrus	31	A > R	0.80	.01 / .05
2304	36	6	4	44	R	Cingulate Gyrus	24	A > R	1.09	.001 / .01
1344	21	-11	31	21	L	Anterior Cingulate *	32	A > R	0.90	.01 / .01
<i>Frontal Cortex</i>										
7744	121	-5	35	31	L/R	Medial Frontal Gyrus	9	A > R	0.97	.001 / .01
1856	29	-45	1	42	L	Middle Frontal Gyrus	6	A > R	0.94	.001 / .03
1792	28	-51	8	22	L	Inferior Frontal Gyrus	44	A > R	1.09	.001 / .004
1408	22	-4	-7	55	L	Medial Frontal Gyrus	6	A > R	0.81	.01 / .03
1088	17	-29	45	18	L	Superior Frontal Gyrus	10	A > R	0.82	.004 / .01
960	15	21	43	27	R	Superior Frontal Gyrus	10	A > R		
<i>Temporal Cortex</i>										
3200	50	-50	1	-7	L	Superior Temporal Gyrus	38	A > R	1.26	.001 / .001
1024	16	-64	-30	-2	L	Middle Temporal Gyrus	21	A > R	0.89	.01 / .02
1280	20	38	-78	-11	R	Fusiform Gyrus	19	A > R	0.92	.003 / .01
<i>Parietal Cortex</i>										
1792	28	-57	-43	27	L	Supramarginal Gyrus	40	A > R	1.16	.001 / .01
1088	17	-33	-56	43	L	Inferior Parietal Lobule	7	A > R	0.86	.01 / .02
1024	16	-2	-59	41	L	Precuneus	7	A > R	0.73	.01 / .02
3136	49	12	-73	39	R	Precuneus	7	A > R	0.98	.002 / .01

Volume (μL)	#Voxels/ Cluster	x	y	z	Hem	Regions in Cluster	BA	Group Difference	Cohen's d	With/Without Marijuana Dependence (p)
2240	35	36	-41	42	R	Inferior Parietal Lobule	40	A > R	0.83	.01 / .05
<i>Occipital Cortex</i>										
3328	52	20	-74	14	R	Cuneus	17	A > R	1.06	.001 / .003
1024	16	15	-93	-7	R	Lingual Gyrus	17	A > R	1.13	.001 / .003
<i>Cerebellum</i>										
11968	187	-17	-65	-16	L/R	Declive	-	A > R	1.32	.001 / .001
3328	52	29	-63	-23	R	Culmen	-	A > R	1.16	.001 / .001
2880	45	-32	-78	-24	L	Uvula	-	A > R	1.19	.001 / .003

Note:

* Mask restricted to significant activation in that particular region of interest (insula, striatum, and anterior cingulate).

R = Relapsed Methamphetamine Dependent. A = Abstinent Methamphetamine Dependent. Hem = Hemisphere. L = left hemisphere. R = right hemisphere. BA = Brodmann Area. With/Without Marijuana Dependence = independent t-test p-values for group comparisons including versus excluding $n=7$ subjects ($n=5$ Relapsed group; $n=2$ Abstinent group) with current marijuana dependence. Talairach coordinates reflect center of mass.

Table 4

Imaging Results for the Group by Decision Interaction, Decision Phase

Volume (µL)	#Voxels/ Cluster	x	y	z	Hem	Regions in Cluster	BA	Wins	Ties	Losses	Cohen's d	With/Without Marijuana Dependence (p)
<i>Cingulate Cortex</i>												
1472	23	3	5	30	R	Cingulate Gyrus	24	ns	A > R	ns	0.84	.01 / .04
<i>Insular Cortex</i>												
2112	33	32	7	7	R	Anterior Insula	13	ns	A > R	A > R	0.85; 0.63	Ties=.01 / .09 Losses=.03 / .20

Note: R = Relapsed Methamphetamine Dependent. A = Abstinent Methamphetamine Dependent. ns = non-significant. Hem = Hemisphere. L = left hemisphere. R = right hemisphere. BA = Brodmann Area. With/Without Marijuana Dependence = independent t-test p-values for group comparisons including versus excluding n=7 subjects (n=5 Relapsed group; n=2 Abstinent group) with current marijuana dependence. Talairach coordinates reflect center of mass.