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Individualized relapse prediction: personality measures and striatal and insular activity during reward-processing robustly predict relapse*

Joshua L. Gowin[1,2], **Tali M. Ball**[1], **Marc Wittmann**[1,3], **Susan F. Tapert**[1,4], and **Martin P. Paulus**[1,5,6]

[1]Psychiatry, University of California San Diego, La Jolla, CA [2]Section on Human Psychopharmacology, Laboratory of Clinical and Translational Studies, National Institute on Alcohol Abuse and Alcoholism, Bethesda, Maryland [3]Empirical and Analytical Psychophysics, Institute for Frontier Areas of Psychology and Mental Health, Freiburg, Germany [4]Psychology Service, VA San Diego Healthcare System, La Jolla, CA [5]Psychiatry Service, VA San Diego Healthcare System, La Jolla, CA [6]Laureate Institute for Brain Research

Abstract

Background—Nearly half of individuals with substance use disorders relapse in the year after treatment. A diagnostic tool to help clinicians make decisions regarding treatment does not exist for psychiatric conditions. Identifying individuals with high risk for relapse to substance use following abstinence has profound clinical consequences. This study aimed to develop neuroimaging as a robust tool to predict relapse.

Methods—68 methamphetamine-dependent adults (15 female) were recruited from 28-day inpatient treatment. During treatment, participants completed a functional MRI scan that examined brain activation during reward processing. Patients were followed 1 year later to assess abstinence. We examined brain activation during reward processing between relapsing and abstaining individuals and employed three random forest prediction models (clinical and personality measures, neuroimaging measures, a combined model) to generate predictions for each participant regarding their relapse likelihood.

Results—18 individuals relapsed. There were significant group by reward-size interactions for neural activation in the left insula and right striatum for rewards. Abstaining individuals showed

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Corresponding author: J.L. Gowin, Address: 10 Center Dr., Building 10-CRC, Rm 1-5330, Bethesda, MD 20892, joshua.gowin@nih.gov, tel: +1 301 451 6968.

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increased activation for large, risky relative to small, safe rewards, whereas relapsing individuals failed to show differential activation between reward types. All three random forest models yielded good test characteristics such that a positive test for relapse yielded a likelihood ratio 2.63, whereas a negative test had a likelihood ratio of 0.48.

Conclusions—These findings suggest that neuroimaging can be developed in combination with other measures as an instrument to predict relapse, advancing tools providers can use to make decisions about individualized treatment of substance use disorders.

1. Introduction

Relapse is a vexing problem in addictive disorders and, typically, only 40 to 60% of individuals with addictive disorders are able to maintain abstinence for more than a year after initiating treatment (Hunt et al., 1971; McLellan et al., 2000). Since numerous studies have suggested that treatment can lower relapse rates (Baker et al., 2001; Irvin et al., 1999; Kosten and O'Connor, 2003; Lancaster et al., 2006; Schmitz et al., 2001), identifying treatment-seeking patients at greatest risk of relapse could help clinicians to appropriate more resources to those individuals to more effectively reduce relapse rates. Previous studies have shown that demographic (e.g., lower socioeconomic status; Mclellan et al., 1994), social (e.g., lack of family support; National Institute of Drug Abuse, 1999), and neuroimaging measures (Janes et al., 2010; Paulus et al., 2005; e.g., failure to show differential activation during risky and safe decisions; Gowin et al., 2014a), can indicate relapse likelihood. More recent investigations have used machine learning techniques to predict individual outcomes (Connor et al., 2007; Weinstein et al., 2009). To date, few such studies have used brain imaging measures and have focused on making individually specific predictions. There is some indication that the combination of imaging and sophisticated analytic approaches may provide sufficient prediction accuracy that would allow one to develop prognostic tests of relapse. Such tests could aid a clinician in providing a patient-specific risk assessment that could be used to objectively communicate risk to the patient or change the course of treatment to reduce risk status.

One proposed marker of substance use disorders (SUDs), including methamphetamine dependence (MD; May et al., 2013; Schouw et al., 2013; Stewart et al., 2014), is altered neural response of the limbic reward system (Koob, 2013; Volkow and Fowler, 2000). There are two prominent hypotheses on how the response changes: individuals with SUDs may have hyper- or hypo-activation in response to rewarding stimuli, reflecting either enhanced incentive salience or reward deficiency, respectively. The incentive salience hypothesis derives from evidence that repeated pairing of a cue with a rewarding substance leads to enhanced dopaminergic responding, and drug-craving, when shown the cue (Berridge, 2012). The reward deficiency hypothesis derives from evidence that individuals with SUDs have impaired function of the dopamine reward system, and thus have lower response to rewards such as food, and may use substances to enhance dopamine signaling (Blum et al., 2012). A recent review suggests that the presence of drug cues may modulate reward circuitry activation, where drug cues enhance reward circuitry activation relative to controls, but natural rewards produce lower levels of activity (Leyton and Vezina, 2013; Limbrick-Oldfield et al., 2013). Corroborating this, several studies using monetary or food rewards

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have shown that individuals with SUDs relative to controls show decreased activation in the striatum, amygdala and insula when viewing or receiving rewards (Ihssen et al., 2011; Jia et al., 2011; Konova et al., 2012; Peters et al., 2011). The ability to stimulate reward circuitry through natural rewards may diminish the desire to stimulate it through substance use, potentially reducing the risk of relapse. It remains unclear whether processing of non-drug rewards during early abstinence can distinguish between individuals who will relapse or remain abstinent.

In a previous study, we examined early-abstinent MD during the decision phase of a risk-taking task and showed that a lack of differentiation between safe and risky options distinguished individuals who would relapse (Gowin et al., 2014a). That study attempted to identify processing differences between individuals who relapse versus abstain (i.e., disrupted risky decision-making). Here, we use data from the same sample to focus on a different question: can neuroimaging be developed as a practical prediction tool to identify individuals at risk of relapse? Improving diagnosis of SUDs is a critical issue to the field (Volkow and Baler, 2013). To address this question, we use a novel statistical model to determine how well neuroimaging can be used to predict clinical outcomes in combination with clinical, demographic and behavioral measures. We wanted to address a problem in neuroimaging prediction models identified by Whelan and Garavan (2013); they showed that the failure of neuroimaging studies to use out-of-sample data disposes them to inflate prediction estimates. We reduced the risk of inflated estimates by using random forest (Breiman, 2001), a robust model that employs a training and testing set. We hypothesized that those individuals who have the greatest difficulty in differentially processing levels of reward, i.e., the neural activation difference to small versus large rewards, might be at greatest risk for relapse. Moreover, we aimed to examine whether a machine learning approach, i.e., random forest, using neural activation during reward could be used to develop a robust test to assess relapse risk of individual participants. Support for the hypotheses and evidence for a robust test would integrate reward-processing dysfunctions with a practically useful tool that would make a significant contribution to addiction medicine.

2. Materials and Methods

2.1 Sample

Sixty-eight (fifteen female) MD individuals were recruited through 28-day inpatient drug treatment programs at the Veterans Affairs San Diego Healthcare System and Scripps Green Hospital (La Jolla, CA). Both treatment programs employ 12-step models, daily education and exercise, and require participants to attend Narcotics Anonymous meetings. All participants completed the 28-day program and consented to participate in a clinical interview, a brain scan, and a follow-up phone interview one year later. Participants had ceased using methamphetamine an average of 32.9 ± 2.4 (mean ± SEM) days prior to study procedures (range: 15 – 119), which occurred during the third or fourth week of treatment.

2.2 Clinical Assessments

Lifetime DSM-IV Axis I diagnoses, substance use and Axis II antisocial personality disorder were assessed during the second week of treatment using the Semi Structured Assessment

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for the Genetics of Alcoholism (SSAGA; Bucholz et al., 1994; Hesselbrock et al., 1999). All participants met criteria for primary dependence on methamphetamine. The following were exclusion criteria for all groups: (1) antisocial personality disorder; (2) current (past 6 months) Axis I panic disorder, social phobia, posttraumatic stress disorder, major depressive disorder; (3) lifetime bipolar disorder, schizophrenia, and obsessive compulsive disorder; (4) current severe medical disorders requiring inpatient treatment or frequent medical visits; (5) use of medications that affect the hemodynamic response within the past 30 days; (6) current positive urine toxicology test; and (7) history of head injuries with loss of consciousness for longer than 5 minutes. Participants completed the Beck Depression Inventory (BDI; Beck et al., 1961).

One-year follow-up consisted of an interview based on the substance use portion of the SSAGA, a well-validated measure for the assessment of substance use metrics (Bucholz et al., 1994; Hesselbrock et al., 1999). Participants were asked whether, and when, they had used any of the following substances in the past year: sedatives, hallucinogens, stimulants, marijuana, cocaine or opiates. Since treatment was abstinence-based, relapse was defined as any use of these substances. Based on interview responses, forty-five participants (11 female) reported abstinence from drugs (except nicotine). Eighteen participants (4 female) reported at least one substance use during the year (i.e. relapsed). Five participants (7.4%) could not be tracked; these participants were similar to the remaining sample in age, education and lifetime methamphetamine use. Characteristics are summarized in Table 1.

2.3 Temperament and neurocognitive assessment

During the second week of treatment, participants completed the Barratt Impulsiveness Scale (BIS; Patton et al., 1995), NEO Five-Factor Inventory (McCrae and Costa, 2004), Temperament and Character Inventory (TCI; Cloninger, 1987), Sensation Seeking Scale (SSS-V; Zuckerman, 1996) and North American Adult Reading Test (Uttl, 2002) to measure verbal intelligence (VIQ).

2.4 Neuroimaging task

The Risky Gains Task (RGT) has been used in prior studies (Gowin et al., 2014b; Paulus et al., 2003) and is briefly described here. The goal of the RGT was to earn as much money as possible. Participants selected one of three options—20¢, 40¢ or 80¢—on each trial. The options appeared one at a time in ascending order for 1 second each. Participants were told 20¢ was the safe option (guaranteed gain of 20¢) and 40¢ and 80¢ were risky options (choosing 40¢ or 80¢ resulted in a chance of either gaining or losing 40¢or 80¢, respectively). The trial ended and feedback was given immediately after the participant won or lost, but all trials lasted 3.5 seconds. The task contained 96 trials. Unbeknownst to participants, the number of loss trials (-40¢ and -80¢) was set so that choosing the same option on each trial would earn the same final payment; choosing risky versus safe provided no advantage. Participants were excluded if they chose the same option on every trial because neuroimaging regressors could not be computed for the unchosen option (N=2).

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2.5 Functional magnetic resonance imaging

Scans were conducted during the second or third week of treatment. Subjects completed a questionnaire based on the Semi-Structured Assessment for Drug Dependence and Alcoholism (Pierucci-Lagha et al., 2005) prior to scanning to confirm the absence of withdrawal symptoms; no subjects reported withdrawal symptoms. Smokers were allowed to smoke, but nicotine levels were not measured. A fMRI run sensitive to blood-oxygenation level dependent (BOLD) contrast was collected using a Signa EXCITE 3T scanner (GE Healthcare, Milwaukee, Wisconsin, T2*-weighted echo planar imaging; TR=2000ms, TE=32ms, FoV=230×230 mm^2, 64×64 matrix, 30 2.6-mm axial slices with 1.4mm gap, flip angle=90°, total duration: 8min, 32sec, 3.59×3.59×2.6 mm^3 voxels). Six resting trials (6-10 sec) were collected at preset points during the task and used as part of baseline, along with inter-trial intervals. A high-resolution, T-1 weighted image was collected during the same session for anatomical reference.

Data were preprocessed using Analysis of Functional Neurolmages (AFNI) software (Cox, 1996). Echo planar images were aligned to anatomical images. Images were spatially smoothed using a 4 mm Gaussian filter and normalized to Talairach space. Preprocessed data were analyzed with a multiple regression model using AFNI's 3dDeconvolve. Regressors for safe (+20) and risky (+40, +80) decisions were defined as starting at trial onset and ending when a) the subject made a response or b) a punishment (-40¢, -80¢) was delivered (no jitter occurred between phases to keep subjects engaged with the sequence of actions). Regressors for wins (+20¢, +40¢, +80¢) and losses (-40¢, -80¢) were defined as starting when the outcome appeared and ending at the onset of the next trial. Motion and drift across the run were included as regressors of non-interest. Following deconvolution, percent signal change (PSC) was calculated by dividing the regressors by baseline activation, which was calculated during six null trials interspersed in the task. Group analyses focused on reward-processing (the decision phase of this task was analyzed in a previous manuscript: Gowin et al., 2014a).

2.6 Linear mixed effects model of reward processing (standard analysis pathway)

To determine if MD who went on to relapse showed different neural activation patterns relative to MD with continued abstinence, a linear mixed-effects (LME) analysis was conducted with R software (http://www.r-project.org; *nlme* package). Group (relapse, abstinent) and reward type (+20¢, +40¢, and +80¢) were fixed effects in the model and individual participants were random effects. LME analysis examined the main effect of group and the group by reward interaction. Analyses were performed voxel-wise across the entire brain (total voxels = 72,960, final voxel size = 4×4×4mm). A volume threshold adjustment was performed based on AFNI's AlphaSim to prevent type-l errors. An *a priori* per-voxel threshold of p=0.05 in a cluster of 768μL (12 contiguous voxels) resulted in an *a posteriori* cluster-wise p=0.05.

To test whether any variables could predict time to relapse, a Cox proportional hazards model was used. The dependent variable was the number of days between assessment and relapse. The independent variables were the total number of methamphetamine uses (log-transformed due to positive skew) and the difference in activation between a large, risky

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(mean of +40¢ and +80¢) and small, safe win (+20¢) in the right putamen and the right caudate (chosen based on LME results).

2.7 Random forest prediction model (predictive test analysis pathway)

Random forest is a machine-learning tool that uses predictor variables to classify members of a sample into categories (e.g., relapse or abstinent). The forest is constructed from a multitude of decision-trees (Breiman, 2001). While a single decision tree is susceptible to noise, the average of many trees, obtained by a forest, is not, so long as the trees are uncorrelated. Random forest performs as well or better than alternative classification techniques in terms of accuracy and robustness (i.e., even in the presence of noise, the model does not overfit to a given sample; Breiman, 2001). In the present study, random forest models were computed using R (*randomForest* library) to determine if neuroimaging variables, clinical and personality variables, or a combination of the two could predict relapse at the individual level.

The random forest method used here involves four steps (Ball et al., 2013; Breiman, 2001; Genuer et al., 2010; Strobl et al., 2009). First, 2,000 decision trees were grown, each using a different, randomly-selected subsample of participants and independent variables. Each tree was grown using a different bootstrap sample of all participants (about two-thirds of the total sample), constituting the training set for that particular tree. At each node of a tree, the model randomly sampled a small number of the total available variables. Specifically, the square root of the total number of available variables was sampled. An optimal split point was determined for each node (e.g., a score greater than 5 on the BDI classifies as relapse) at each node. The tree was grown, without pruning, to the largest extent possible. The tree ends with each participant in the training set classified as relapse or abstinent.

Second, participants in the test set were run through the decision tree to evaluate how well it classified new subjects. The accuracy with which the tree classifies the test set provides a running estimate of classification error and helps determine the extent that each variable contributes to correct classification. Across the 2000 trees in the forest, each participant was part of the test set about a third of the time (i.e., ≈666 times). The average number of times that each participant was misclassified when they were a part of the test set provides the error estimate of the forest. Since the error estimate for random forest models has proven to be unbiased in many tests, there is no need for cross-validation on a separate test set (Breiman, 2001; Breiman and Cutler, 2001). Each tree casts a vote for the outcome of each participant, and the classification of a particular subject was determined by the vote endorsed by the majority of the trees. For example, if 51% of trees voted that Subject X would relapse, then Subject X was classified as someone who would relapse.

Third, the variables that contributed most to decision-tree accuracy were identified based on permutation importance scores (Ball et al., 2013; Genuer et al., 2010). Permutation importance is defined by the mean decrease in classification accuracy when values of a variable are randomly permuted across all trees (Breiman, 2001). For example, the values for variable X for each participant were randomly permuted. If the difference between the model's performance with the true values and the model's performance with the permuted values of variable X is large, variable X would have a high permutation importance score,

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signifying that it carried important information that helped accurately classify participants. Median permutation scores were based on 500 repetitions of the random forest analysis to provide stable estimates.

Fourth, the most important variables were identified and retained for a final, more parsimonious model, which is a common step when the number of variables is high (Breiman and Cutler, 2001). Since negative scores are due to random variation around zero (Strobl et al., 2009), only variables with a permutation score higher than the absolute value of the most negative score were included in the final model to guard against including variables that predicted no better than chance. Further, the number of variables in the final model was restricted to a maximum of 10, following the method of Nicodemus and colleagues (2010) and because visual inspection of the Scree plot showed variable importance diminished after the tenth variable. The classification of each participant based on the final model was used to determine diagnostic test characteristics, such as accuracy, sensitivity, specificity and likelihood ratios.

The neuroimaging only model examined the difference in percent signal change between large, risky (mean of +40¢ and +80¢) and small, safe rewards (+20¢) as well as losses (mean of -40¢ and -80¢). The entire brain (excluding cerebellum) was segmented based on anatomy into 72 distinct regions, and the average voxel-wise difference in signal change was calculated for each region, yielding 144 independent variables. The construction of the mask used for segmentation was described in a previous report (Ball et al., 2013; Fonzo et al., 2013) and is recapitulated here. Grey matter probability maps were generated based on high resolution Tl images of 43 healthy adults. Probability maps were transformed to Talairach (Talairach and Tournoux, 1988) coordinates and regions were defined using the Talairach atlas. The 144 neuroimaging variables then went through the four steps described above.

A second model used only clinical (lifetime methamphetamine use, lifetime cocaine use, lifetime cannabis use, time since last drug use before treatment, years of drug use, BDI, current number of cigarettes/day), demographic (age, gender, years of education), behavioral (total proportion of risky options, proportion of risky options following a previous loss) and psychometric measures (BIS, NEO, SSS, TCI, VIQ). Finally, a third, combined model used all of the variables from the previous two models.

Classification accuracy, sensitivity, specificity, and positive and negative likelihood ratios were determined for the output of all three models. The proportion of trees voting for relapse for each participant was used to generate receiver operating characteristic (ROC) curves for each model, and the area under the curve (AUC) was calculated. The AUC for an ROC curve is one of the best ways to estimate the predictive accuracy of a diagnostic test, where 1 indicates perfect discriminative ability and 0.5 (i.e., the reference line) indicates no discriminative ability. McNemar's test was used to statistically compare the three models to each other.

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3. Results

3.1 Group characteristics

There were no significant differences between the group that relapsed and the group that remained abstinent in demographics or drug use history (p>.05; Table 1). Mean number of days to relapse among MD who relapsed was 175.1 (SEM=29.3). A chi-squared analysis showed that the relapse group (21%) had a higher prevalence of current marijuana dependence relative to the abstinent group (4%), but the small number of participants meeting this criteria (N=6) precludes a subgroup analysis. MD who relapsed chose the risky option a similar proportion of times (mean= 0.48, SD=.29) compared to those who remained abstinent (mean= 0.49, SD=.20; $F_{1, 61}$ = .09, p=.76).

3.2 Linear mixed effects model of outcome

LME analysis indicated significant group (abstinent, relapse) by reward magnitude (+20¢, +40¢, and +80¢) effects in the right putamen, right caudate, left anterior insula and several other regions (Table 2). In the putamen, caudate, and anterior insula, MD who remained abstinent showed increasedactivation during 80¢ relative to 20¢ wins, whereas MD who relapsed showed reduced activity during 80¢ relative to 20¢ wins (see Figure 1).

3.3 Time to relapse prediction

The Cox proportional hazards model significantly predicted time to relapse (-2 log likelihood=129.8, χ^2 (3) =13.3, p=0.004). Individuals with less differentiation between large, risky and small, safe rewards in the putamen (b=-.66, p=.04), and individuals with higher lifetime methamphetamine usage (b=-.60, p=0.03), were likely to relapse sooner.

3.4 Individual outcome prediction models (Random Forest)

3.4.1 Clinical and Personality Variables Only—According to the random forest procedure outline above, nine variables met inclusion criteria for the final model: NEO Neuroticism, BDI total score, SSS boredom susceptibility, SSS thrill and adventure seeking, SSS total, BIS motor impulsivity, BIS perseverance, TCI harm avoidance and log-transformed lifetime cocaine uses. Student's t-tests showed that the groups did not differ significantly on any of these variables (see Figure 2; all p> 0.05), suggesting that the random forest model detected relapse likelihood using higher-order interactions between the variables. The AUC for the ROC curve was 0.74. A positive test for relapse indicated a 2.87 increase in risk (+LR= 2.87, 95% confidence interval: 1.52, 5.40), whereas a negative test indicated decreased risk by 2.32 (-LR = 0.43, 95% CI: 0.22, 0.85). Since the confidence intervals did not overlap with 1 or each other, the model predicts outcomes better than chance (p<0.05).

3.4.2 Neuroimaging Variables Only—Eight regions met criteria for inclusion in the final model, and all of them were related to brain processing differences between small, safe and large, risky rewards. These regions included left and right transverse temporal gyrus, right inferior temporal gyrus, right posterior insula, right postcentral gyrus, right medial globus pallidus, right putamen, and left nucleus accumbens. Specifically, in all eight regions MD who relapsed had lower differential activation between large, risky and small, safe

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rewards relative to MD who remained abstinent (Figure 2). The AUC for the ROC plot was 0.73. A positive test for relapse indicated a 2.63 increase in risk (+LR=2.63, 95% CI: 1.36, 5.07), whereas a negative test indicated decreased risk by 1.98 (-LR= 0.51, 95% CI: 0.28, 0.93). Since the confidence intervals did not overlap with 1 or each other, the model predicts outcomes better than chance ($p<0.05$).

3.4.3 Combined Model—Ten variables met criteria for inclusion in the final combined model: SSS thrill and adventure seeking, the eight brain regions listed in the brain-only model, and the cingulate gyrus. The AUC for the ROC plot was 0.71. A positive test for relapse indicated a 3.28 increase in risk (+LR=3.28, 95% CI: 1.59, 6.79), whereas a negative test indicated decreased risk by 2.08 (-LR=0.48, 95% CI: 0.26, 0.87). Since the confidence intervals did not overlap with 1 or each other, the model predicts outcomes better than chance ($p<0.05$).

3.4.4 Model comparisons—Figure 3 and Table 3 show model performance and test characteristics. Each model produced sensitivity greater than 0.6 and specificity approaching 0.8, such that nearly four of five individuals with a negative test remained abstinent, while three of five individuals with a positive test relapsed. McNemar's test showed that none of the three models differed significantly from each other ($p>.22$). Please see Supplementary Material for more information[1].

4. Discussion

We examined whether brain activation during reward-processing can accurately predict which methamphetamine-dependent individuals will relapse in the year following treatment. Our results suggest that the degree to which the striatum differentially processes large, risky versus small, safe rewards is a robust predictor of relapse. In particular, those individuals who show brain activation that fails to differentiate reward magnitudes relapsed sooner. The present results complement our previous study, which showed that altered risk-processing may be a mechanism driving relapse (Gowin et al., 2014a), by demonstrating that in addition to elucidating processing differences, neuroimaging may also be developed as a practical test to distinguish individuals at risk of relapse from those likely to remain abstinent. Therefore, the current results may have more clinical utility in evaluating treatment-seeking MD. The random forest models had AUCs over 0.7, which is good for discriminating between individuals who will relapse or remain abstinent, considering they did not differ on any demographic or personality measures. This specificity and sensitivity improves greatly over chance. The high AUCs, robustness of the model, and use of separate training and test sets (to reduce over-fitting; Breiman, 2001) provide evidence that this could be developed as a test to predict relapse status.

Both the linear-mixed effects and random forest models identified the striatum and insula as regions which differentiated individuals who relapsed from those who remained abstinent, supporting the hypothesis that reward processing may indicate substance dependence status (Gowin et al., 2013; Volkow and Fowler, 2000). Indeed, three of the eight brain regions

[1]Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:…

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identified by the random forest model are part of the striatum, indicating that the function of this region plays an important role in sustained abstinence. In the putamen clusters identified by both models, individuals who showed an increase in activation during large, risky relative to small, safe wins were more likely to maintain abstinence, and maintain it longer. This is consistent with our previous study, which showed that greater differentiation between safe and risky options in the insula was associated with greater likelihood to maintain abstinence; individuals who relapse may generally fail to appreciate differences in value and probability (Gowin et al., 2014a). The identification by our study that appropriate reward-processing in the striatum as a function that contributes to recovery from substance use disorders corroborates previous work that reward processing plays a role in mental health and addition (Balodis and Potenza, 2015; Knutson and Heinz, 2015). Another study suggests that posterior insula, putamen and caudate may jointly contribute to decisions to wait for larger rewards rather than take smaller gains sooner (Wittmann et al., 2007). Given the insula's role in decision-making (Bechara, 2004; Craig, 2009; Ernst et al., 2002; Wittmann et al., 2007), it would be plausible that the striatum assesses value and interacts with the insula to contribute to decisions about reward, including the immediate pleasure of substance use versus the gradual enjoyment of sustained abstinence.

The random forest neuroimaging model and linear mixed-effects analysis of brain activation revealed some similar and some discrepant findings. The similar findings were discussed in the previous paragraph. Discrepantly, the random forest model identified a few different brain regions (e.g., globus pallidus) and was able to construct a predictive model using clinical and personality variables, whereas linear tests did not find any significant differences between the two groups on the same measures. This is likely due to the random forest models ability to detect higher-order interactions among variables. For example, even though standard linear t-tests failed to identify any differences on clinical and personality variables between the group that relapsed the one that remained abstinent, the random forest model used a combination of the same variables to predict relapse significantly better than chance. Further, since most analyses in neuroimaging use a variant of a linear model, it is worth noting linear models of brain activation make many comparisons and report all areas that survive a threshold. Analyses by Whelan and Garavan (2013) have shown that this approach leads to a high likelihood of overfitting. Random forest reduces the risk of overfitting by using a training and test set. Thus, regions which by chance have high significance in the training set will fail to replicate in the test set, giving a more accurate estimate of their importance. The robustness of the random forest model suggests that these findings are more likely to replicate in new samples.

The clinical and personality model performed similarly to the neuroimaging model. The combined model used mostly neuroimaging variables and showed improved specificity and accuracy relative to both models, possibly supporting our hypothesis that neuroimaging variables explain additional variance relative to clinical and personality variables. Despite the similar performance of the models, there may be advantages for developing diagnostic tests that include neuroimaging. First, neuroimaging does not rely on self-report, which can be unreliable among individuals with substance use disorders (Brown et al., 1992). Second, fMRI measures may be orthogonal to behavioral and clinical data, possibly reducing collinearity and creating stronger models (Breiman, 2001). Whatever advantages

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neuroimaging may provide should be weighed against the additional costs and workload it requires. One way to improve neuroimaging models would be to include additional tasks that assess other cognitive systems (e.g., stress) aside from reward processing to get a more comprehensive view of brain function. Lastly, neuroimaging may better indicate the neurobiological status (e.g., reduced striatal D_2 receptors; Volkow et al., 2002) of the underlying disease. As more refined models are developed, future studies should perform a cost-benefit analysis for neuroimaging as a predictive tool.

There are several limitations to the present study. A 29% relapse rate is lower than the normal range of 40-60% (McLellan et al., 2000), and drug use and relapse were assessed via self-report and not verified by urine toxicology. Nonetheless, since individuals with antisocial personality disorder were excluded and participants stood to gain nothing by lying, we believe the likelihood of intentional deception to be low. Further, since relapse was assessed using the same method (i.e., SSAGA) as the initial diagnosis of MD, we believe the diagnosis of relapse is roughly as reliable as the initial diagnosis. We also excluded individuals with co-morbid psychiatric conditions, which have been shown to contribute to relapse (McLellan et al., 2000; National Institute of Drug Abuse, 1999). There may also have been a selection bias since we only studied individuals who were willing to undergo an MRI scan and study procedures. Excluding co-morbid diagnoses and including individuals able to complete an MRI scan may have lowered relapse rates and reduced generalizability, a possibility that should be clarified in future studies. Future studies may improve upon these methods by validating relapse through urine-toxicology or, if using self-report, performing a calendar-supported timeline-follow back assessment of substance use. Although participants in this sample had a primary diagnosis of methamphetamine dependence, many met criteria for dependence on other substances as well, so our results may not be methamphetamine specific but reflect polysubstance use. Also, the majority of the participants were recruited through a Veterans Affairs hospital, so the findings may not generalize to other populations of methamphetamine-dependent individuals. Finally, although we used a robust technique that employed out-of-sample data, these findings need to be replicated to confirm their validity.

The random forest model built with neuroimaging data generated accurate predictions of which individuals would relapse. Since anatomical regions were used, it would be easy to collect the same variables in new samples to test the replicability of these findings. Further studies may validate that neuroimaging can be used as a tool to predict relapse, providing an essential advance in the way treatment providers make decisions about individualized treatment of substance use disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

We did fMRI on abstinent methamphetamine-dependent individuals and determined who relapsed.

We used a robust classification technique called random forest to generate individual-level predictions.

The random forest model was consistent with a standard linear model.

Our models performed well, with specificity, sensitivity and ROC AUC around 0.7.

Our results suggest that neuroimaging can be developed to predict individual clinical outcomes.

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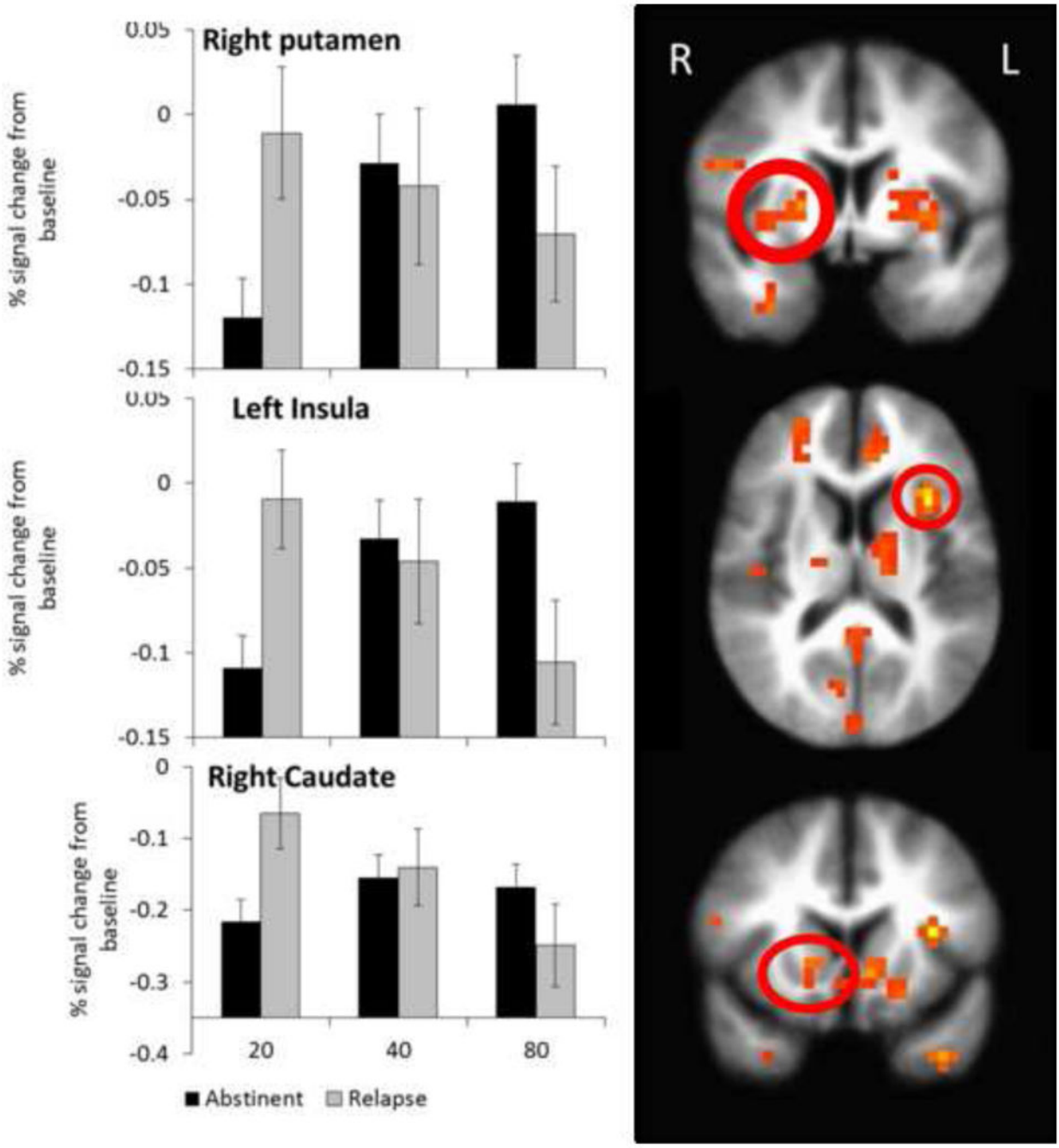

Figure 1.

Group by reward interaction in the striatum and insula. The linear mixed effects model revealed a significant group by reward size effect in the right striatum and left anterior insula. The group that remained abstinent showed greater activation for a large, risky relative to a small, safe rewards, while the group that relapsed showed decreased activation during large, risky relative to small, safe rewards. The right putamen cluster overlaps substantially with the brain region identified in the random forest model as predicting relapse status. Bars represent mean and error bars represent SEM.

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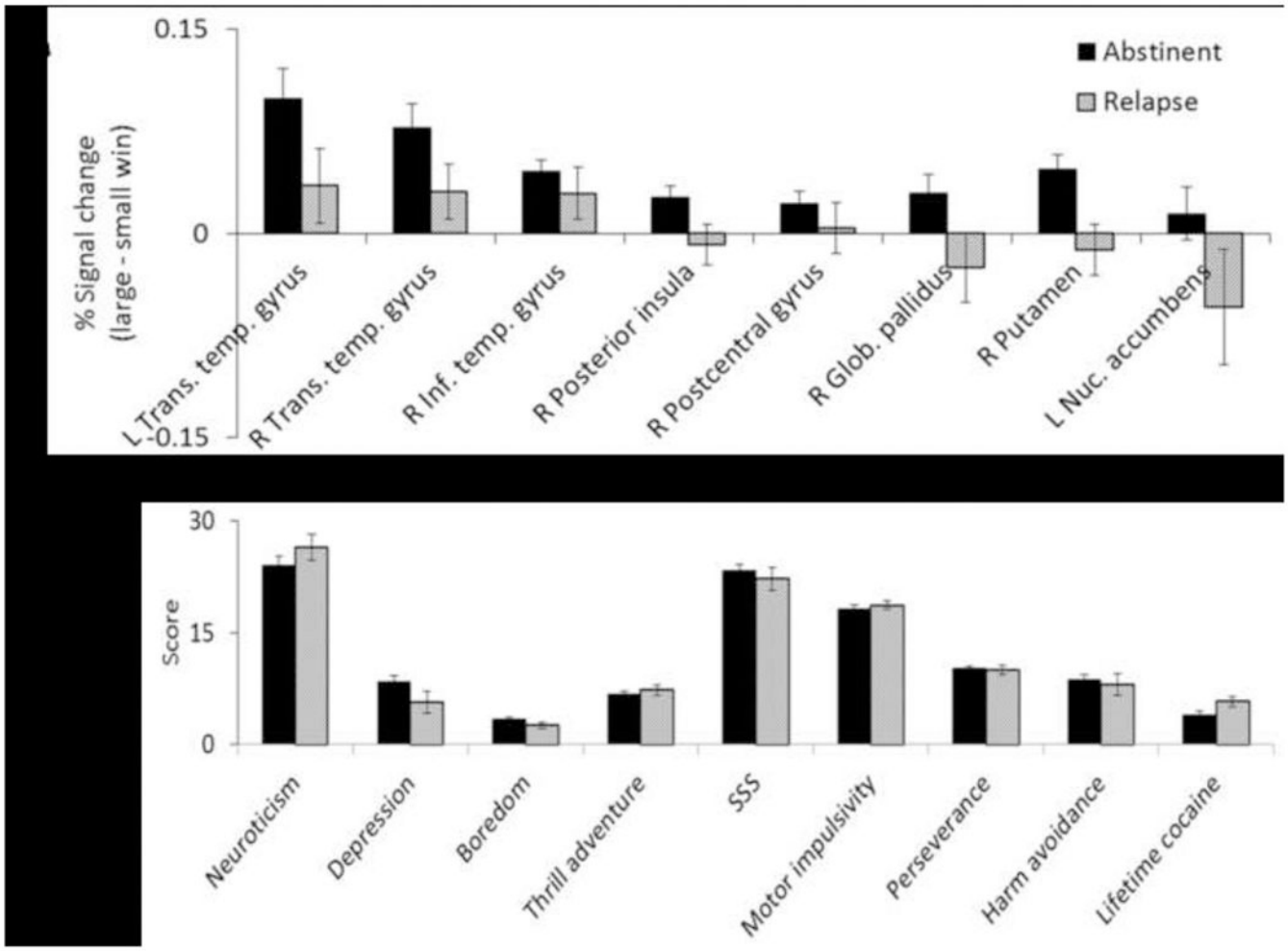

Figure 2.

Random Forest measures. These graphs show the central tendency and variance of the variables in the random forest models. Panel A shows that MD who remained abstinent showed greater activation during large, risky versus small, safe wins. MD who relapsed, in contrast, showed less differential activation when receiving large, risky versus small, safe wins. Panel B shows the values for the personality measures. Relapse and abstinent MD showed similar levels on these variables, but in combination the variables were useful in random forest modeling of relapse. This suggests that the random forest model may be able to detect higher order interactions not evident from the individual variables. Bars represent mean and error bars represent SEM.

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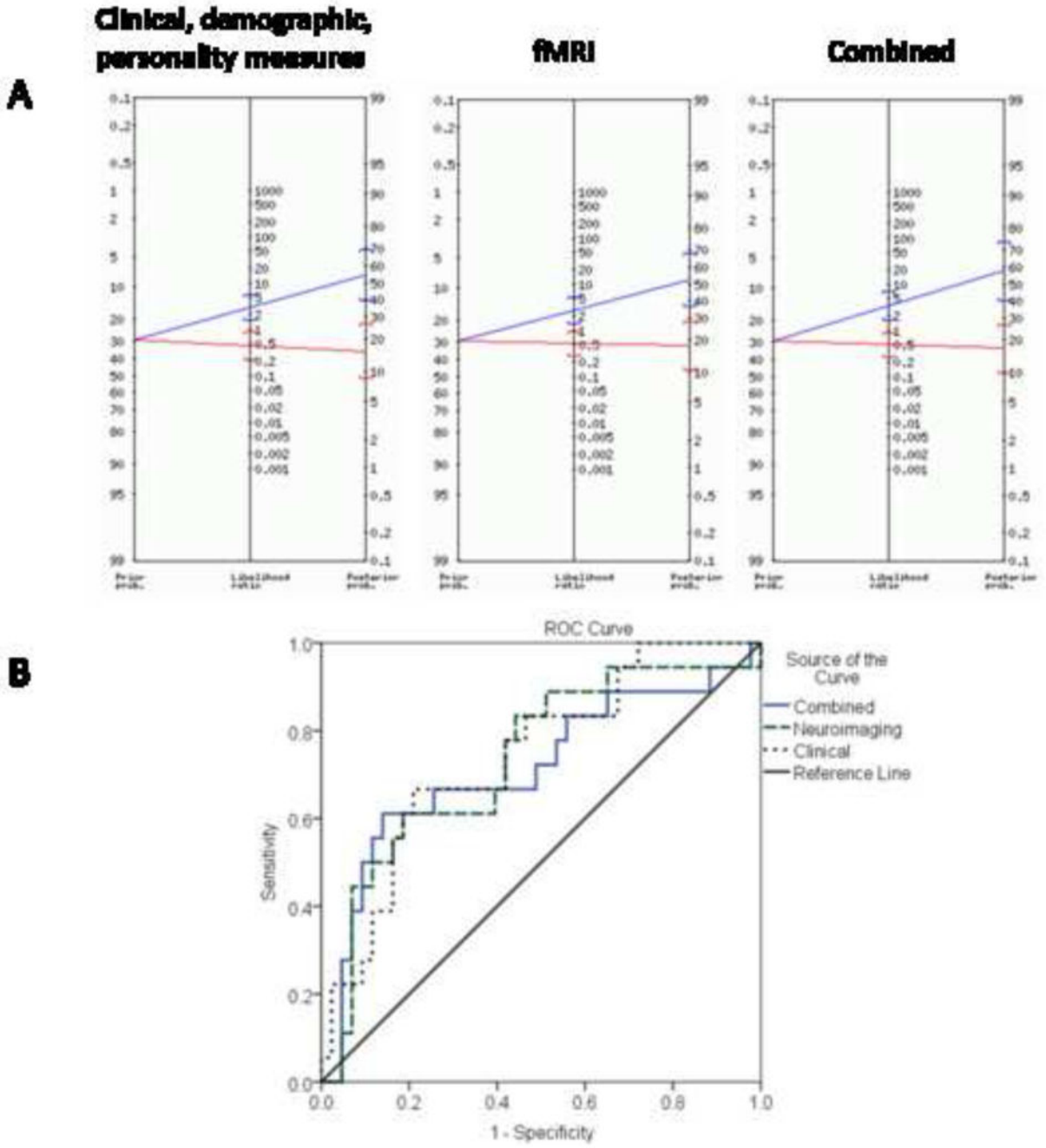

Figure 3.

Predictive value of models. In panel A, a Bayes nomogram is depicted for each random forest model. The left side of the nomogram shows the prior probability of relapse, or the proportion of the total sample that relapsed. The right side shows the posterior probability of relapse given a positive or a negative test result in the random forest model. The brackets around the central estimate represent the 95% confidence interval of the probability. When the 95% confidence intervals do not intersect, positive and negative tests are statistically significantly different. The middle line represents the likelihood ratio of a positive or

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negative test. All three models produced similar nomograms. In panel B, the receiver operating characteristic curves are depicted for each random forest model. All three models show significant improvement relative to the no-discrimination line.

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Table 1

Subject characteristics by group

Characteristic	Abstinent (n=43)	Relapsed (n=18)
Female (%)	10 (23)	4 (21)
Treated at VA (%) [a]	28 (65)	14 (78)
Lifetime alcohol dependence (%)	18 (37)	10 (53)
Lifetime marijuana dependence (%)	8 (17)	5 (26)
Lifetime cocaine dependence (%)	13 (27)	7 (37)
Current alcohol dependence (%)	8 (17)	6 (32)
Current marijuana dependence (%) [b]	2 (4)	4 (21)
Current cocaine dependence (%)	5 (10)	4 (21)
Age, years (mean, SD)	38.8 (11.1)	37.4 (9.2)
Education, years (mean, SD)	12.8 (1.7)	13.3 (1.5)
Verbal IQ (mean, SD) [c]	108.0 (10.2)	109.7 (7.3)
Alcohol, drinks/week (mean, SD) [d]	11.0 (17.6)	14.4 (33.0)
Nicotine, cigarettes/day (mean, SD) [d]	11.8 (9.3)	8.7 (9.2)
Methamphetamine age onset, (mean, SD) [e]	24.1 (9.4)	24.9 (9.1)
Time since last methamphetamine use before treatment, days (mean, SD) [e]	32.4 (18.8)	34.0 (19.7)
Methamphetamine estimated lifetime uses, (mean, SD)[e]	14624.5 (32414.1)	8841.6 (12353.1)
Cocaine estimated lifetime uses, (mean, SD)[e]	2551.4 (6116.9)	3942.9 (7250.8)
Marijuana estimated lifetime uses, (mean, SD)[e]	10882.5 (30375.4)	4743.5 (8851.2)

[a] The participants not recruited from the Veterans Affairs (VA) hospital were recruited from Scripps Green

[b] $p<.05$ for group difference, based on chi-squared analysis

[c] Assessed by the North American Adult Reading Test (Uttl, 2002)

[d] Recent patterns of use.

[e] Determined using the Semi Structured Assessment for the Genetics of Alcoholism (Hesselbrock, 1999)

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Table 2

Significant clusters identified using a linear mixed-effects model for the group-by-condition contrast.

Volume (μL)	*x*	*y*	*z*	Left/Right	Brain Region	Brodmann Area
11968	-9	33	0	L	Anterior Cingulate	32
5568	-1	-30	31	L	Cingulate Gyrus	31
4288	-30	9	11	L	Insula	13
3648	7	-62	33	R	Precuneus	7
2496	-14	-12	14	L	Thalamus	
2048	25	-1	4	R	Lentiform Nucleus	
1792	28	-1	-26	R	Parahippocampal Gyrus	28
1600	49	-1	22	R	Inferior Frontal Gyrus	9
1280	26	48	17	R	Superior Frontal Gyrus	10
1280	37	-59	37	R	Angular Gyrus	39
1216	-35	-56	41	L	Inferior Parietal Lobule	40
1152	39	-7	40	R	Precentral Gyrus	6
1088	19	-10	22	R	Caudate	
1088	-11	-74	35	L	Precuneus	7
1088	-13	-36	42	L	Cingulate Gyrus	31
960	-38	17	-31	L	Superior Temporal Gyrus	38
960	65	-31	-5	R	Middle Temporal Gyrus	21
960	8	-78	3	R	Lingual Gyrus	18
960	1	-88	16	R	Cuneus	18
896	9	-52	5	R	Posterior Cingulate	30
768	12	15	2	R	Caudate	
768	11	-69	21	R	Cuneus	18

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Table 3

Test characteristics of each model

Table 3 provides characteristics for each model. The clinical and personality model contains only variables describing temperament, drug use history and demographics (e.g. age). The fMRI model contains average activation from 72 discrete anatomical brain regions encompassing the entire brain (except cerebellum). The combined model includes all the predictors from the clinical and personality and fMRI models. Area under the curve (AUC) for the receiver operating characteristic plot is one of the best metrics of how good a predictive model is; .5 suggests the test offers no discriminative ability and closer to 1 suggests perfect discrimination. The positive likelihood ratio (LR) describes how likely a positive test for relapse indicates an actual relapse. The negative LR describes how likely a negative test for relapse indicates that a person will remain abstinent.

Model	Accuracy	Sensitivity	Specificity	AUC	Positive LR (95% CI)	Negative LR (95% CI)
Clinical and personality	74%	.67	.77	.74	2.87 (1.52, 5.40)	.43 (.22, .85)
fMRI	72%	.61	.77	.73	2.63 (1.36, 5.07)	.51 (0.28, 0.93)
Combined	75%	.61	.81	.71	3.28 (1.59, 6.79)	.48 (0.26, 0.87)