

Supplementary Material

Title: Machine learning identifies substance-specific behavioral markers for opiate and stimulant dependence

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1. Neurocognitive Measures of Impulsivity

1.1. Impulsive Choice

1.1.1. Delayed Reward Discounting Task (DRDT)

Delayed reward discounting was assessed with the Monetary-Choice Questionnaire (MCQ) (Kirby et al., 1999). The MCQ consists of a set of 27 choices between smaller immediate rewards (S) available today and larger delayed rewards (L) of small, medium, and large magnitude available at delays ranging from 7 to 186 days (Kirby et al., 1999). Participants were given a 1-in-6 chance to receive an actual reward upon task completion, which consisted of $1/10^{\text{th}}$ of the value of one of their previous choices. Discount rate parameters were estimated from participants' patterns of choices across the nine questions in each of the three magnitude categories (Kirby et al., 1999). The discount rate was determined by k , a hyperbolic discount parameter that indexes how rapidly the participants' valuation of the reward declines as the delay interval increases. We estimated the value of k that would yield indifference between S and L for each of the 27 questions using the following equation: $V = A/(1 + kD)$, where V is the present value of reward A available at delay D , and k is the discount rate parameter used as an index of impulsivity

1.1.2. Iowa Gambling Task (IGT)

The IGT (Bechara et al., 2001; 2000) is a simulated gambling task, which measures decision-making under uncertainty and requires trial-and-error learning. Participants are required to select among four decks of cards such that they maximize their long-term gains. Participants are instructed to make choices to optimize their long-term gain. In the IGT ABCD version, Decks C and D are advantageous with regard to

their long-term positive gain but their immediate gains are small. Decks A and B are disadvantageous with regard to their long-term negative gain but their immediate gains are large. We used the total net score of choices as the performance index on the task (IGT-ABCD), which is calculated by subtracting the number of choices from disadvantageous decks (A+B) from those from advantageous (C+D). The IGT EFGH version reversed the signs of gains and losses of the IGT-ABCD: Advantageous decks yield high immediate punishments but large positive long-term gains and disadvantageous decks yield small immediate punishments but large negative long-term losses. We used a total net score of choices as the performance on the EFGH version (IGT-EFGH), again calculated by the number of choices from advantageous decks minus those from disadvantageous decks.

1.1.3. Balloon Analog Risk Task (BART)

In the BART (Lejuez et al., 2002), participants are instructed to incrementally inflate a balloon by clicking a button. Each button click (or pump) adds money that can be cashed out unless the balloon explodes. Thus, each pump can increase potential reward but confers greater risk. We used the adjusted number of pumps as an index of impulsivity, which is the average number of pumps (or button clicks) on unexploded balloons, which has been associated with greater risk-taking behavior (Lejuez et al., 2002).

1.1.4. Cambridge Gambling Task (CGT)

The CGT (Rogers et al., 1999) assesses risky decision-making, which, in contrast to the IGT, does not involve learning as all relevant information about risk is provided to participants. The CGT has two stages on each trial. In the selection stage, participants are

presented with ten boxes, some of which are blue and some red. The ratios of red:blue boxes vary from 1:9 to 9:1 in pseudorandom order. Participants earn points based on correct performance. A yellow token is hidden in one of the ten boxes and participants are asked to guess whether the yellow token is in a blue or red box. After making the selection, in the gambling stage, participants place a bet (i.e., decide what portion of their current total game points they would like to gamble) on their choice. The available bets range from 5% to 95% of their points appearing in sequence in ascending or descending order. The outcome measures of the CGT are risk taking, risk adjustment (betting more when odds are better and less when odds are poorer), quality of decision-making (the tendency to bet on the more likely outcome), deliberation time, and delay aversion (betting larger amounts earlier when wagers are presented in ascending order).

1.2. Impulsive Action

1.2.1. Stop Signal Task (SST)

The SST (Dougherty et al., 2005) (a.k.a. the GoStop Impulsivity paradigm) assesses participants' capacity to inhibit an already initiated motor response. Participants are required to attend to a series of randomly-generated 5-digit numbers presented in rapid succession and to press a button on *go* trials (when two consecutive numbers are the same). On some trials, the matching 5-digit number changes from black to red at 50- to 350-msec intervals after appearing on the screen. On these *stop* trials participants are required to withhold from responding to the target number. The duration that the matching number remains black before it turns red varies between 4 stop signal intervals: 50-msec, 150-msec, 250-msec, or 350-msec. At each interval, we calculated the average

response inhibition ratio, which is the number of commission errors on stop trials (i.e., pressing a button on stop trials) divided by the number of correct detections on go trials.

1.2.2. Immediate Memory Task (IMT)

The IMT (Dougherty et al., 2002) is a modified continuous performance task designed to impose more complex demands on impulse control and working memory. Similar to the SST, participants are presented with a series of 5-digit numbers (e.g., 59213) presented in rapid sequence and separated by a 0.5 second intervals. Participants are instructed to press a response button when two consecutive numbers are identical (target trials), or to withhold a response when the two numbers are different (catch trials). We used discriminability (d') and response bias (b) derived from signal detection theory, as well as commission error rate (i.e., rates of pressing a button on catch trials) and omission error rate (i.e., rates of not pressing a button on target trials) as predictors.

1.2.3. Go/No-go Task (GNGT)

In the GNGT (Lane et al., 2007), two visual stimuli are presented simultaneously side by side near the center of a computer screen. Participants are instructed to press a button when the two stimuli are identical or to withhold responding when they are different. Similar to the analysis of the IMT, we used discriminability (d'), response bias (b), commission error rate, and omission error rate in the analyses.

2. Machine learning: Penalized logistic regression analysis

For identifying predictors of heroin- and amphetamine-dependence, we used 5-fold cross validation (CV) across all samples ($N=222$), in which we used the same data as the training set and the test set, consistent with the procedure we used in another study

(Ahn et al., under review). The goal was to identify the most robust predictors and their effect sizes across all samples because otherwise the profile of survived predictors might depend on the choice of training/test divisions. Alternatively, data could be divided into independent training and test sets, then we can identify beta coefficients of survived predictors in the training set using 5-fold CV within the training set, repeat the procedure 1,000 times, and average the beta coefficients over all 1,000 repetitions. Note that both approaches will yield essentially the same beta coefficients.

Note that the elastic net has a mixing (α) parameter that needs to be estimated with CV. We estimated α over its 100 grids ($\alpha = 0.01, 0.02, 0.03, \dots, 1.00$), searching for the α value that minimizes the average binomial deviance. We computed the average binomial deviance after 1,000 repetitions at each α value (Ahn et al., 2014a). For α estimation, we also used 5-fold CV across all samples ($N=222$) because the goal was to estimate the most representative α value across all samples. Again, we can alternatively use a randomly selected training set only for the estimation of α and repeat the procedure multiple times. However, the estimated α value will be essentially identical in either way.

Figure S5 illustrates how α values were estimated for classifying individuals with heroin- and amphetamine-dependence (for **Figures 1-3**). The estimated mixing parameter was much lower for HD classification than for AD classification, which suggests that the solutions will be more parsimonious (i.e., more variables will shrink to zero) for AD. We used the area under the curve (AUC) of the receiver operating characteristic (ROC) curve as an index of model performance. For the elastic net analysis, we used the *glmnet* package (Hastie, 2010). The pROC package (Robin et al., 2011) was used for generating a ROC curve and computing the AUC. Note that we computed each individual's

“response” or fitted probabilities (e.g., 0: Without HD, 1: With HD) in each of 1,000 iterations. Then we computed the mean fitted probabilities out of the 1,000 iterations in each individual, then used the mean response and actual group information to generate a ROC curve (Castellanos-Ryan and Conrod, 2011; Cyders et al., 2009; Smith et al., 2007).

Elastic-net analyses using mono-substance dependent (pure) users

In **Figures S1-4**, we applied the same machine learning procedure described earlier to classify past pure heroin dependent individuals (HDIs, n=44), pure amphetamine dependent individuals (ADIs, n=39), and polysubstance dependent individuals (PDIs, n=58) against drug-naïve healthy control individuals (HCIs, n=81). We used the mixing (α) parameter values estimated from **Figure S5** (n=222, $\alpha=0.15$ and 0.98 for classifying heroin and amphetamine dependence, respectively). For classifying PDIs, we had to estimate α using HCIs and PDIs (total n=81+58=139) and the procedure reported earlier. The estimated α value for classifying PDIs was 0.97).

3. Elastic Net Results Using Mono-Substance Dependent (Pure) Users

We performed direct classifications of pure HDIs (N=44), pure ADIs (N=39), and PDIs (N=58) against drug-naïve HCIs (N=81) using identical machine learning procedures reported in the main text. **Figures S1, S2, and S3** show the receiver-operating characteristic (ROC) curve and its mean area under the curve (AUC) for the classification of pure HDIs, pure ADIs, and PDIs, respectively. Overall, AUCs were similar to those reported in **Figures 1 and 2**: For the classification of HDIs (**Figure S1**), AUCs were 0.978 for the training set and 0.884 for the test set. The mean AUCs across 1,000 repetitions were 0.968 and 0.878 for training and test sets. For the classification of ADIs

(**Figure S2**), AUCs were 0.844 for the training set and 0.746 for the test set. The mean AUCs across 1,000 repetitions were 0.856 and 0.766 for training and test sets. **Figure S3** shows the ROC curve for the classification of PDIs. Elastic net performed especially well and the AUCs were 0.928 and 0.939 for the training and test sets. The mean AUCs across 1,000 repetitions were 0.956 and 0.906 for training and test sets.

Figure S4 shows the multivariate classifiers for pure HDIs, pure ADIs, and PDIs (the order of variables is identical to that in **Figure 1**). Out of 24 variables classifying pure HDIs in **Figure S4**, 19 (79%) variables also classified HD in **Figure 1**, based on a mixed group of pure and polysubstance using HDIs. Likewise, 4 out of 5 (80%) variables classifying pure ADIs in **Figure S4** also classified a mixed group of ADIs in **Figure 1**. Overall, although some differences were noted, most of the important findings remain the same with the pure groups. For example, the antisocial /lifestyle factor of psychopathy (PCL:SV Factor 2) was the strongest classifier of heroin dependence. As in the mixed group analyses, higher delay discounting on the DRDT was specific to amphetamine dependence, as was higher sensation seeking (SSS Experience-Seeking and SSS Disinhibition). Finally, polysubstance dependent individuals were characterized by lower discriminability on the GNGT and higher scores on UPPS Urgency, SSS Experience Seeking, SSS Thrill/Adventure-Seeking, nicotine dependence, and ADHD.

4. Classification accuracy without the age variable

The groups differed significantly on age: HDIs were significantly older than all other groups including ADIs. This might reflect the timeline of heroin and amphetamine influx in Bulgaria (Kreek et al., 2005), but could also reflect more cumulative residual

effects of longer drug use history in HDIs or potentially arbitrary effects. Thus, we computed prediction accuracy for the (out-of-sample) test sets without the age variable in **Figure S6** (c.f., **Figures 2-3**).

5. Cross-cultural validity of the instruments

All assessment instruments were translated into Bulgarian by the senior author who is a native Bulgarian speaker and has been conducting research studies in Bulgaria since 2003; and back translated into English by the Bulgarian members of her research team who included both psychiatrists and psychologists. The majority of the measures have been used in previous studies in Bulgaria (Ahn et al., 2014b; Segala et al., 2015; Vassileva et al., 2011; 2007; 2014) and the Bulgarian versions of the instruments that have been explored in greater detail show adequate psychometric properties and similar factors structure as the English versions (Popov et al., 2015; Wilson et al., 2014)

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Figure S1

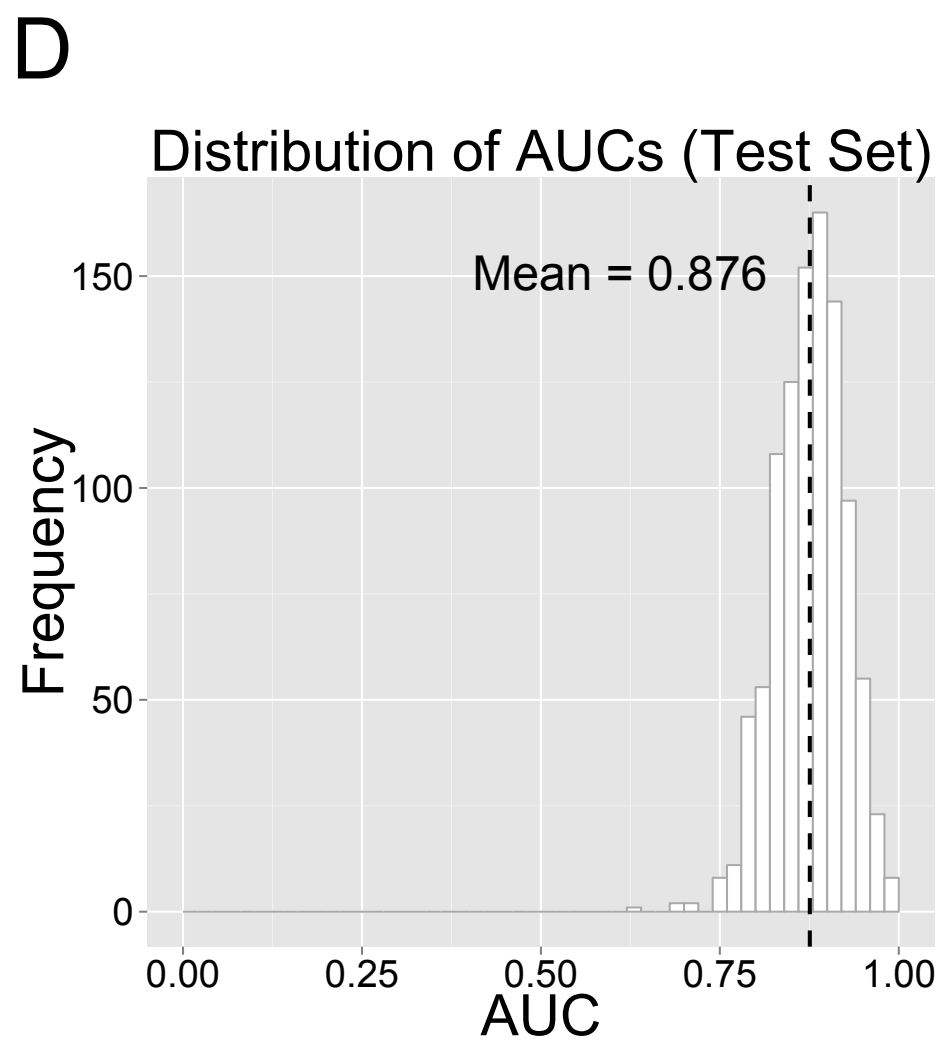
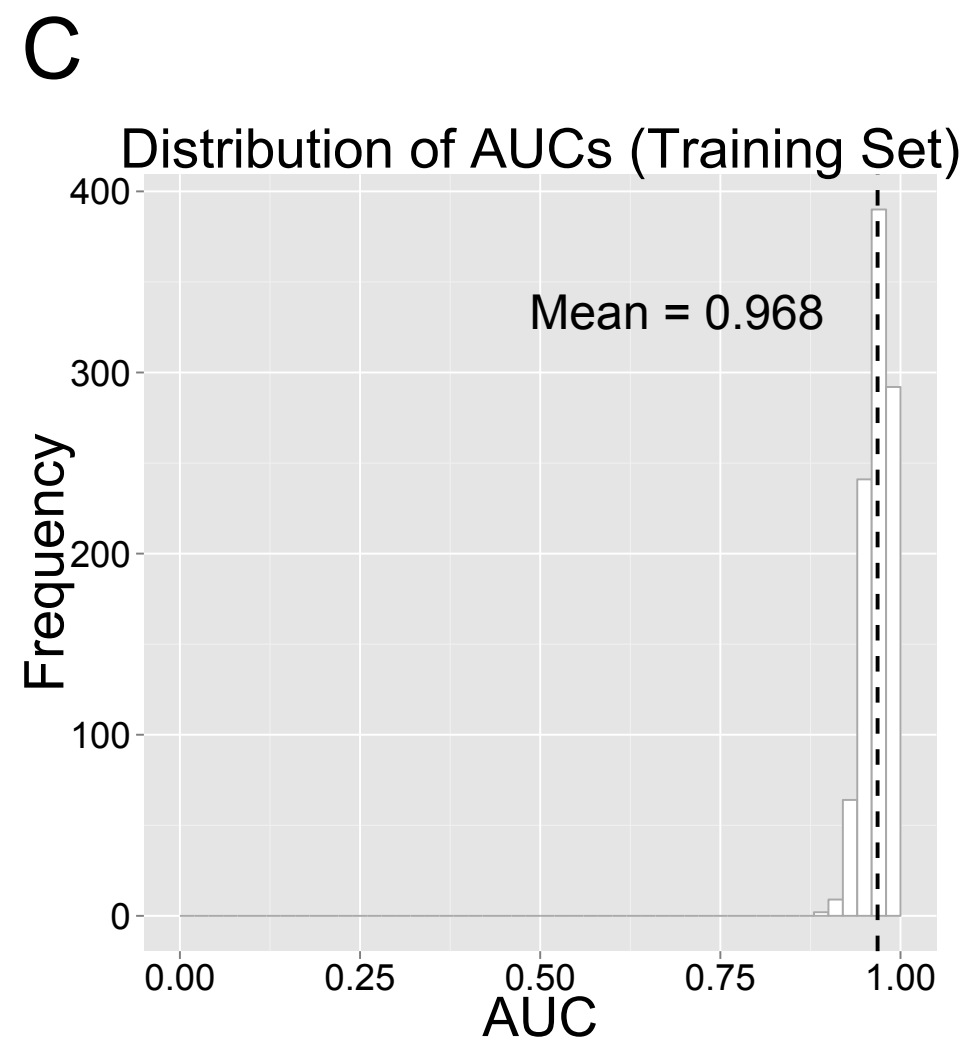
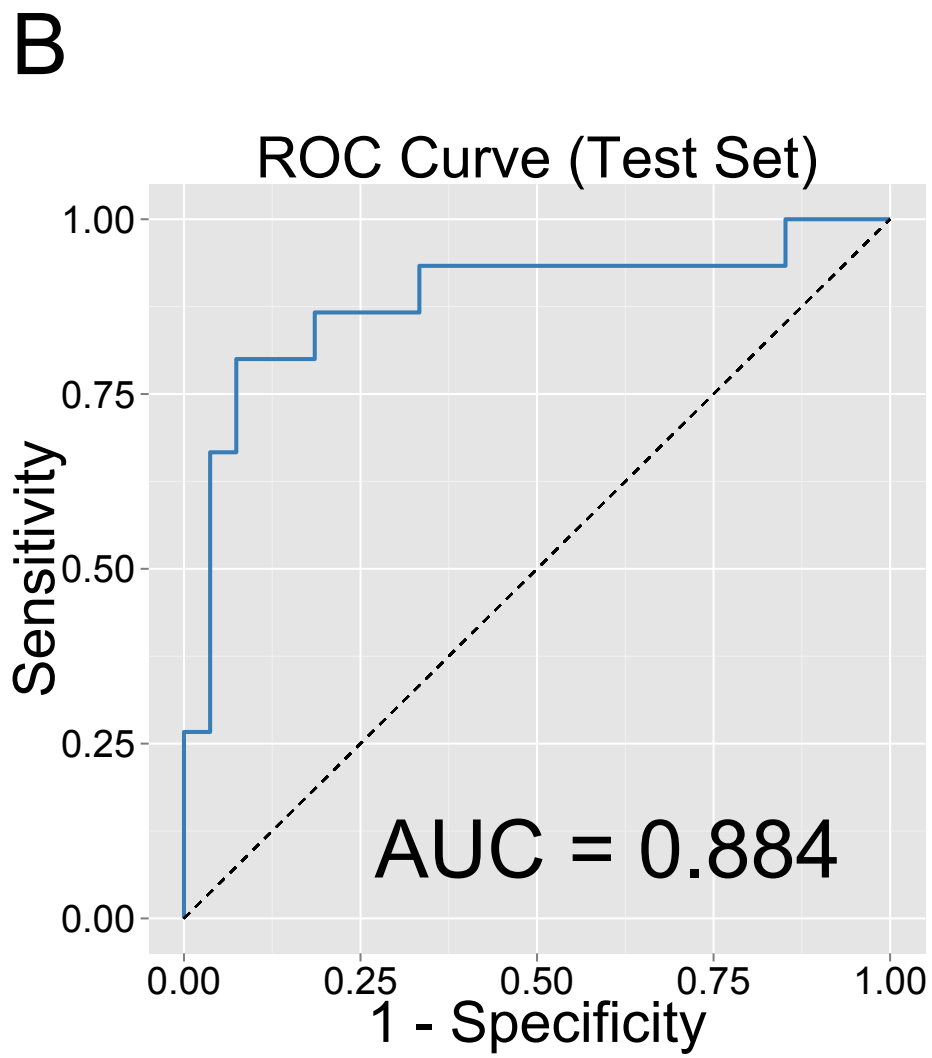
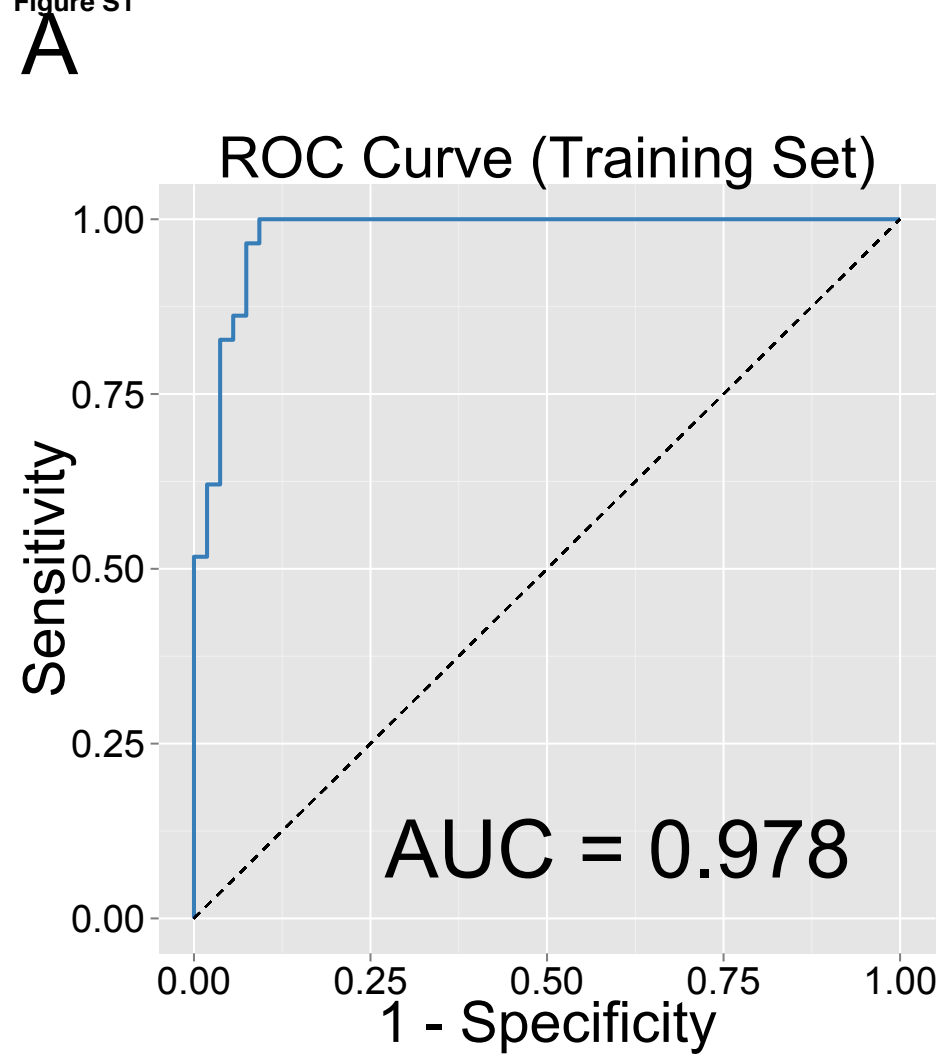


Figure S2

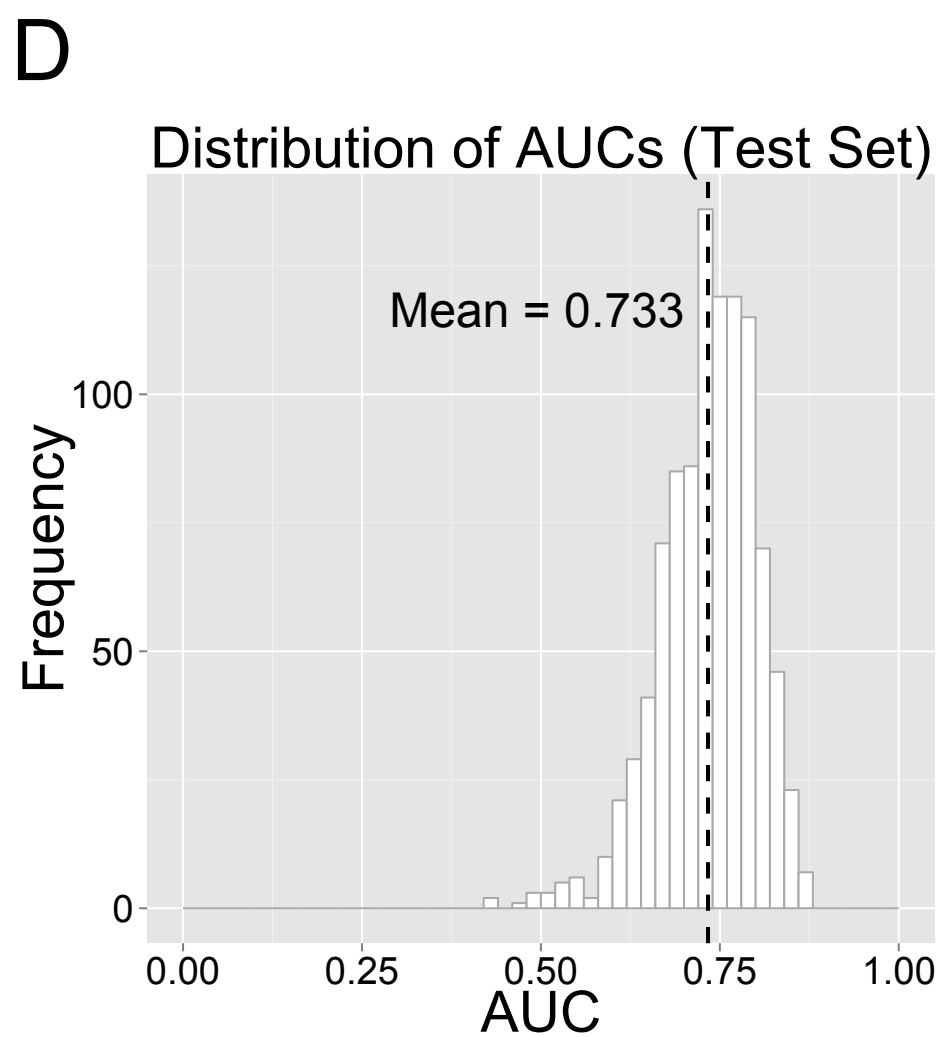
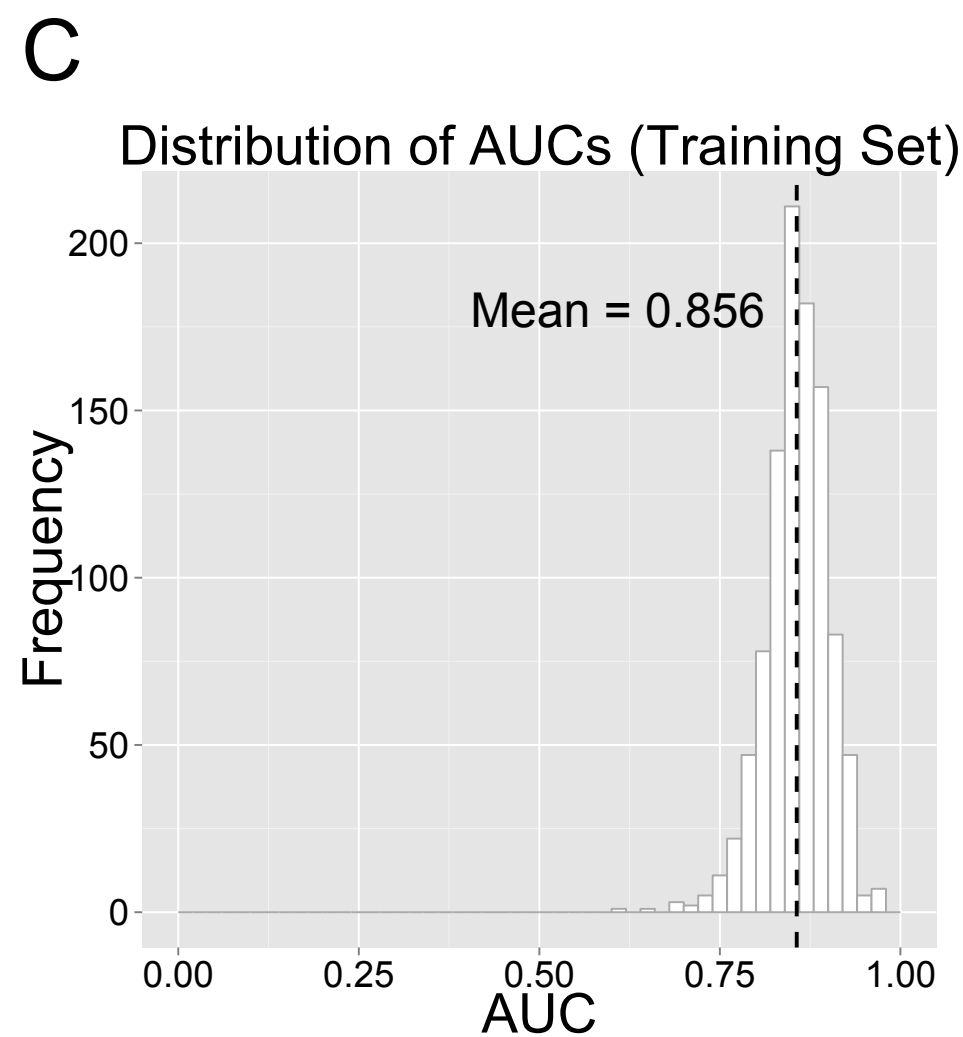
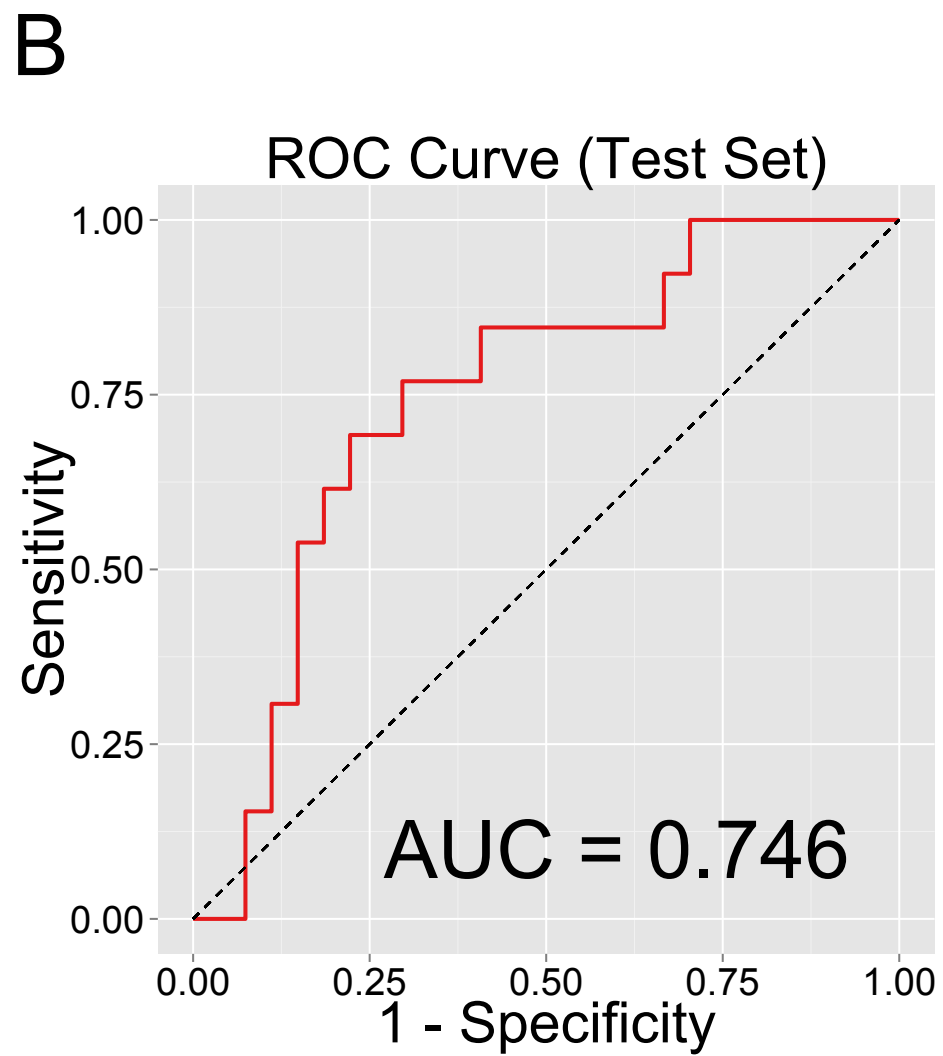
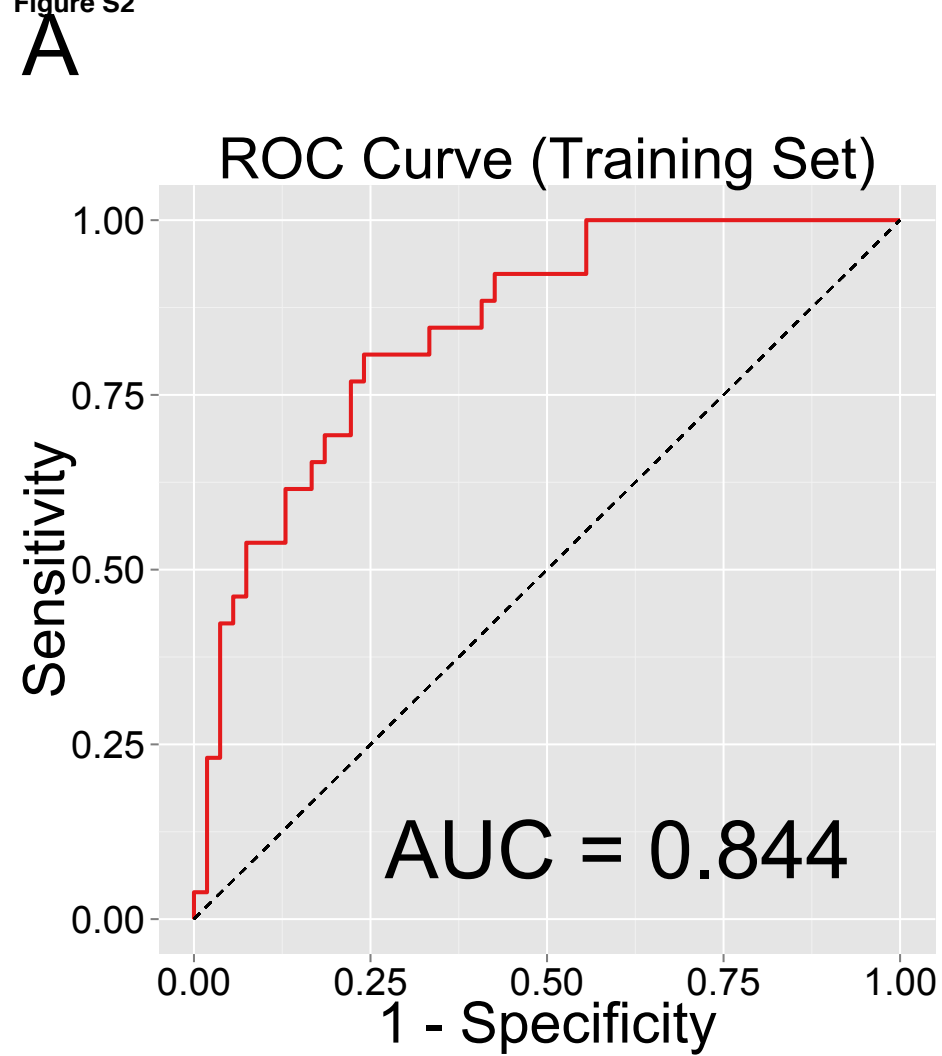


Figure S3

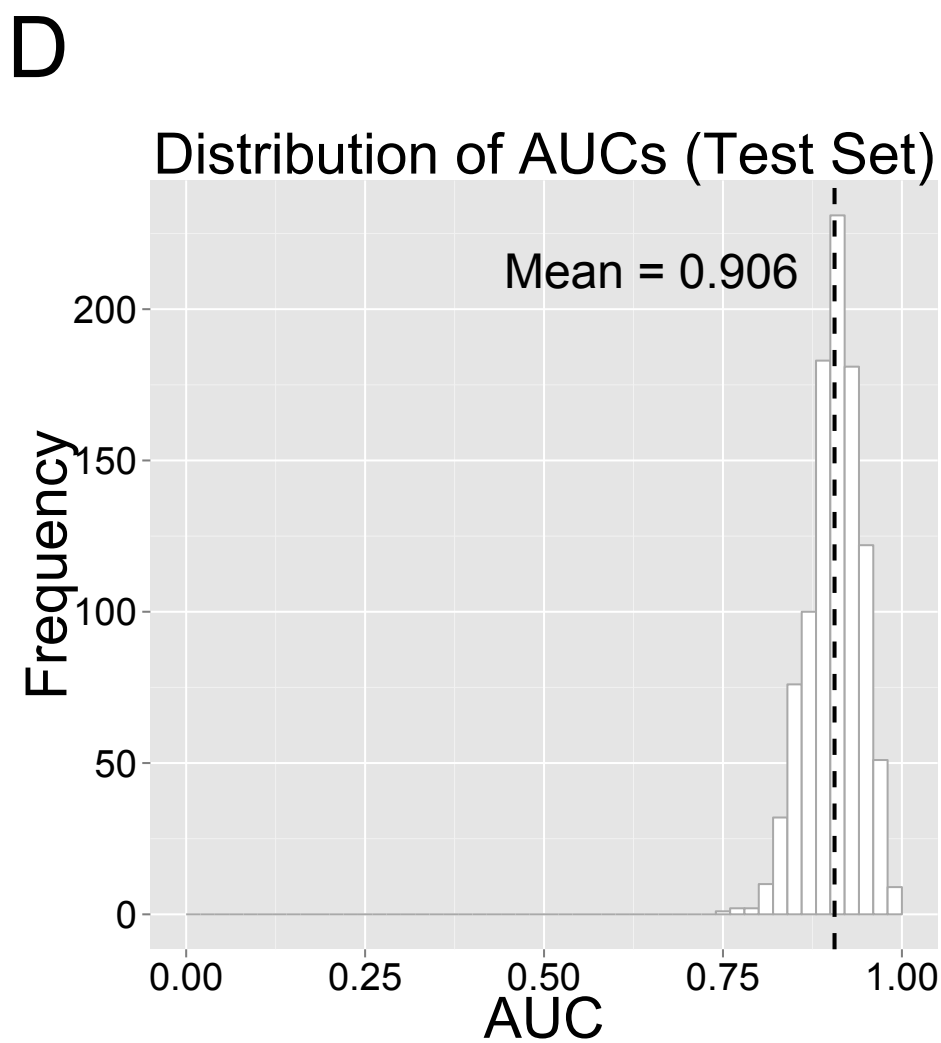
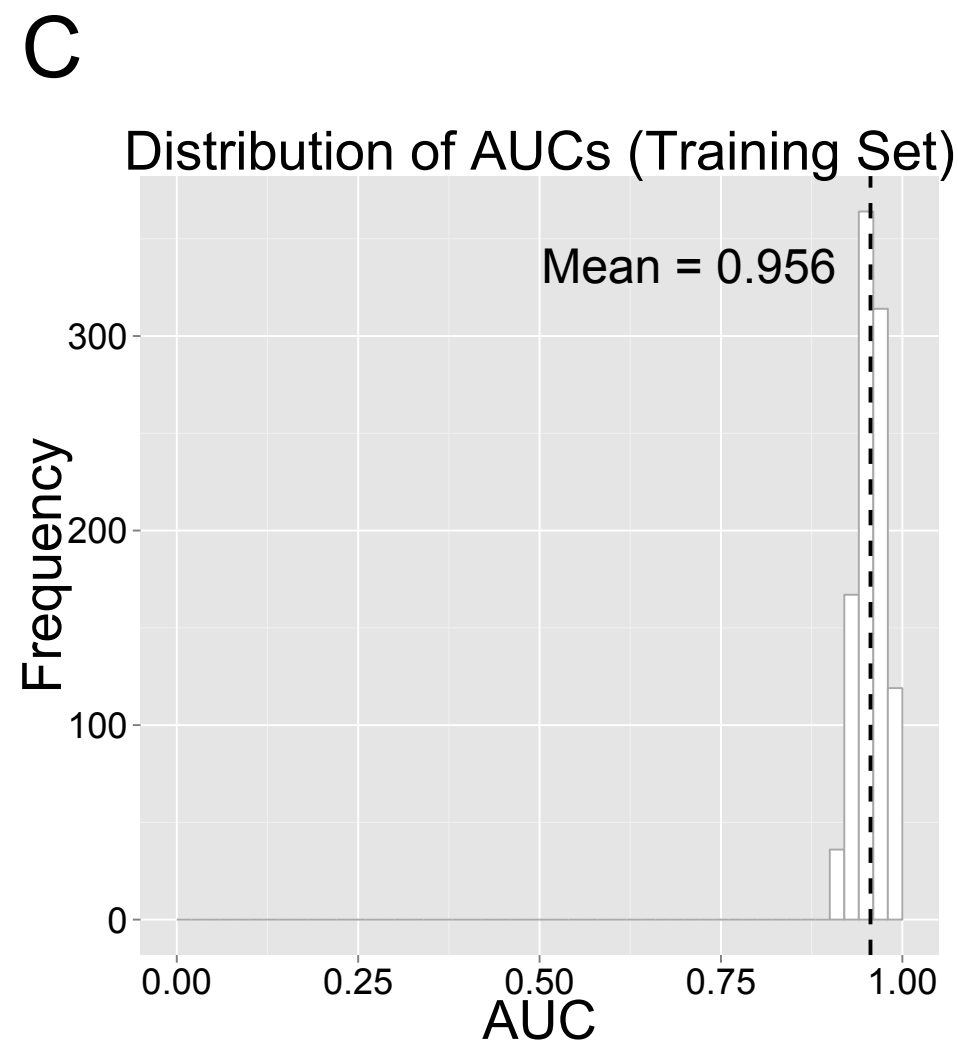
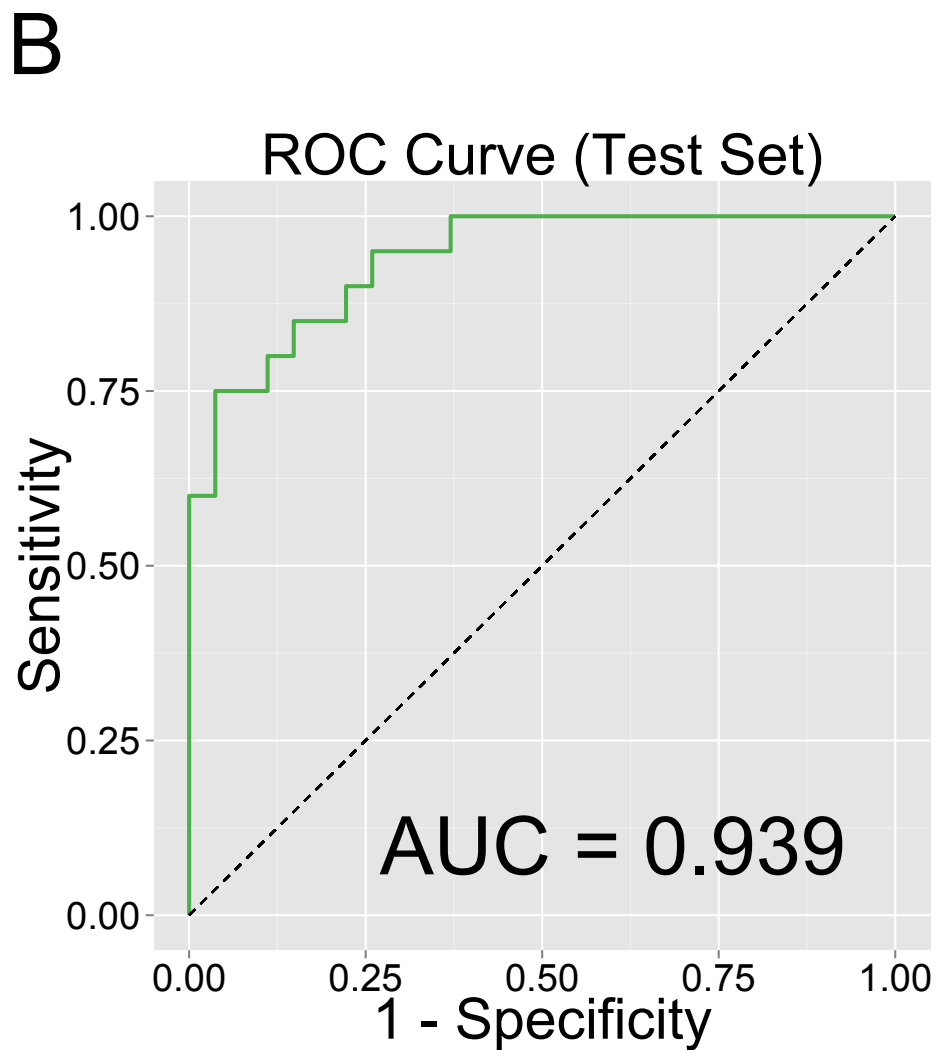
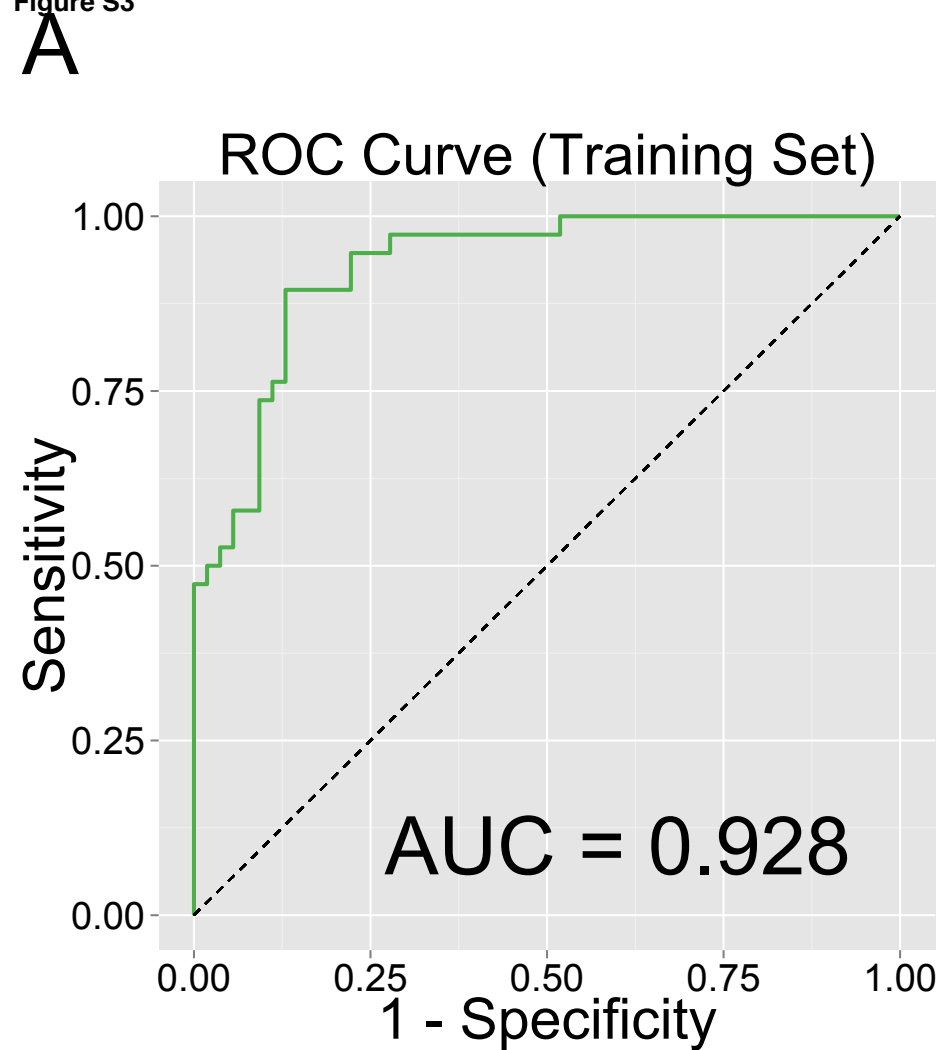


Figure S4

Predicting Heroin/Amphetamine/Poly DSM-IV dependence

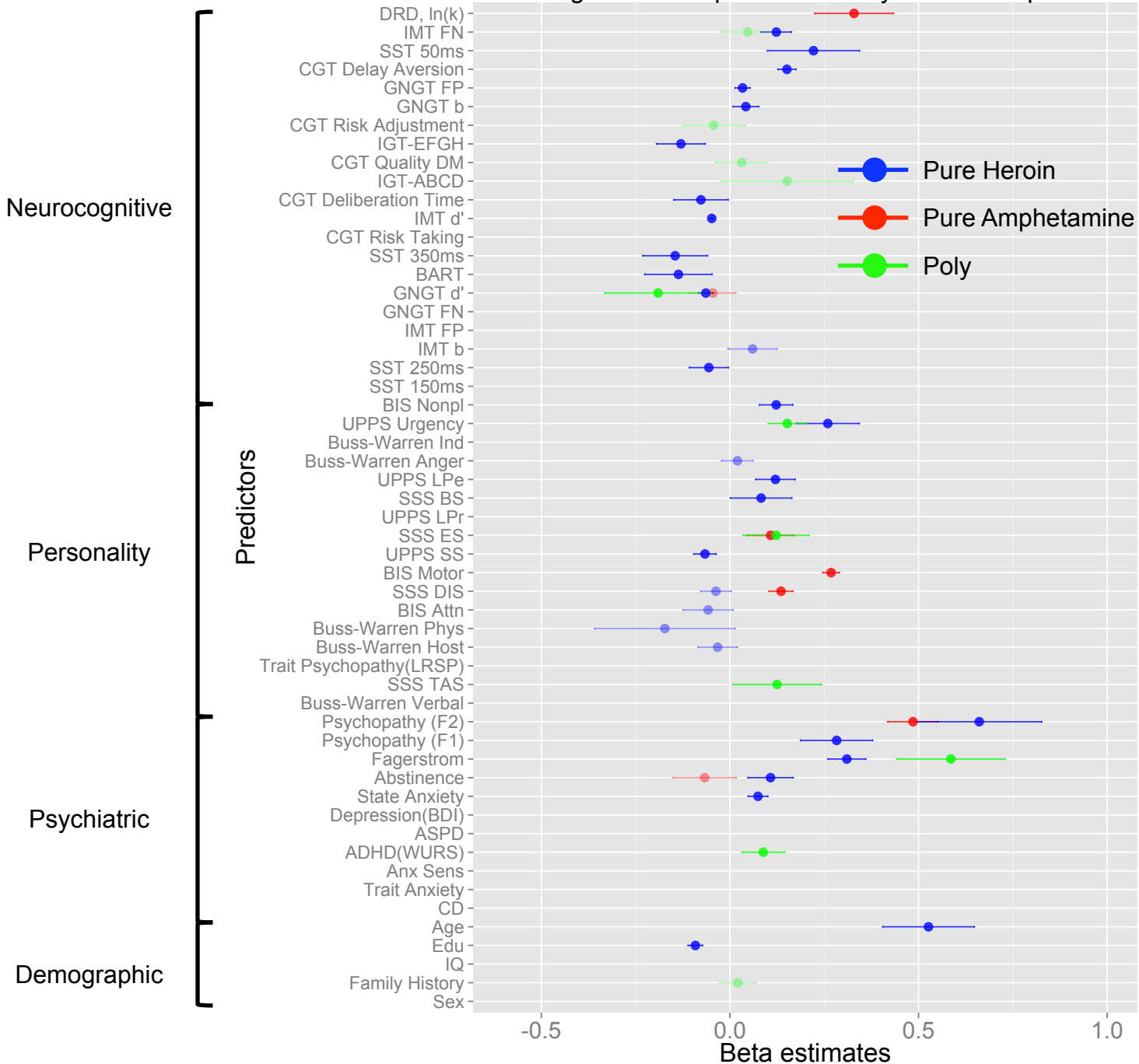


Figure S5

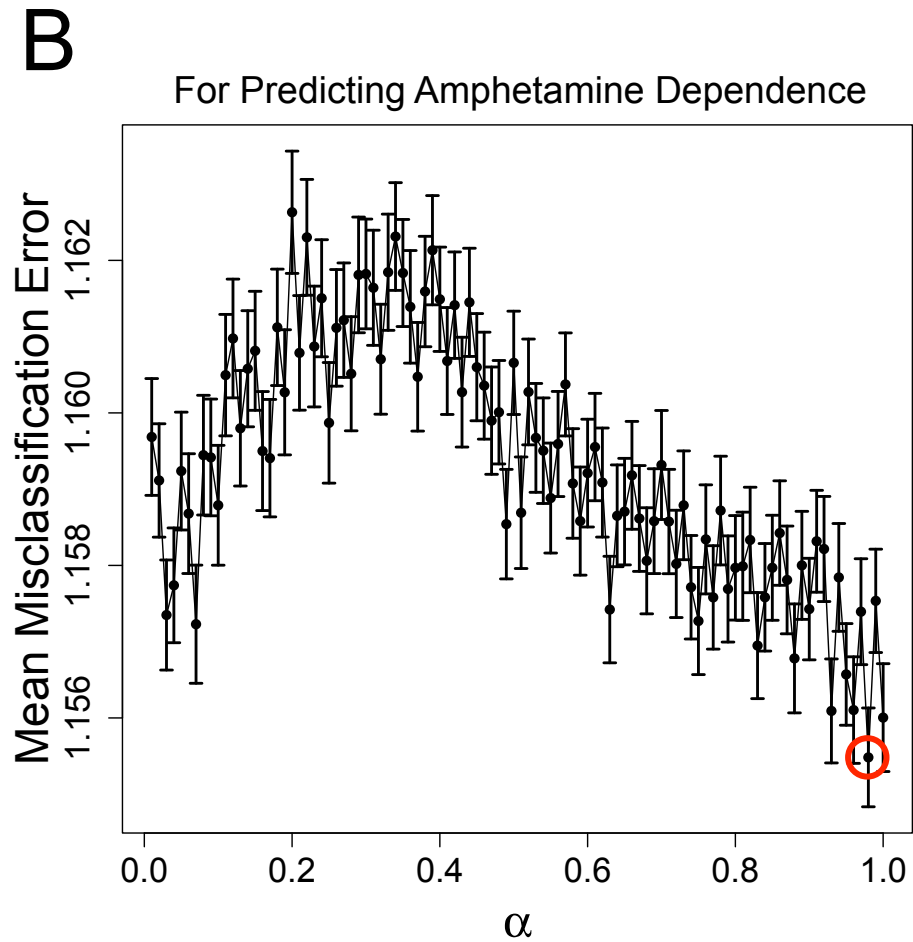
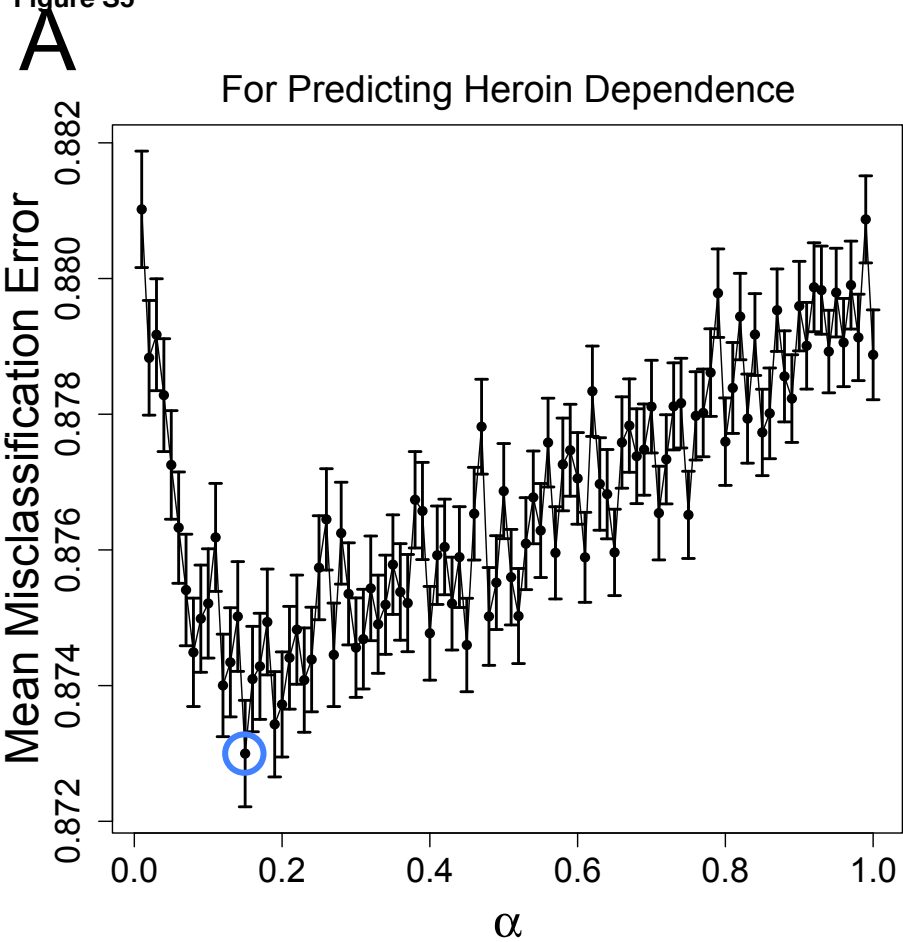


Figure S6

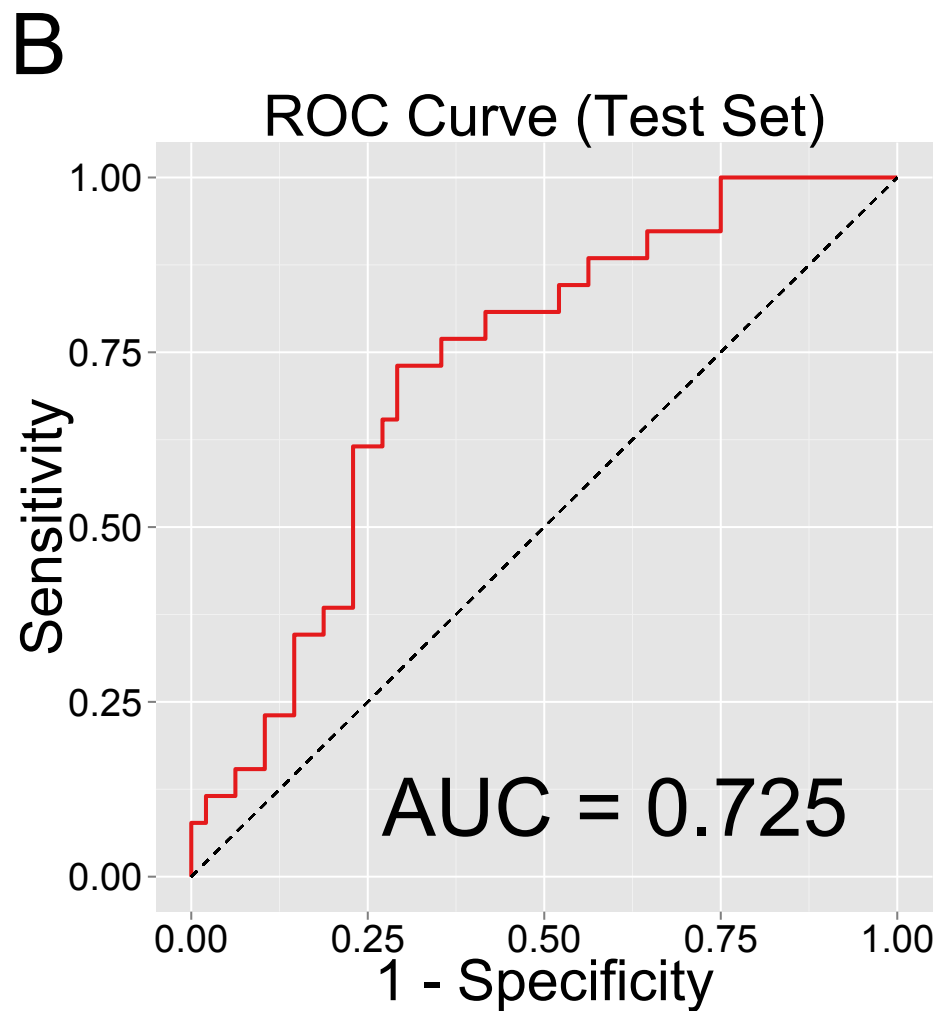
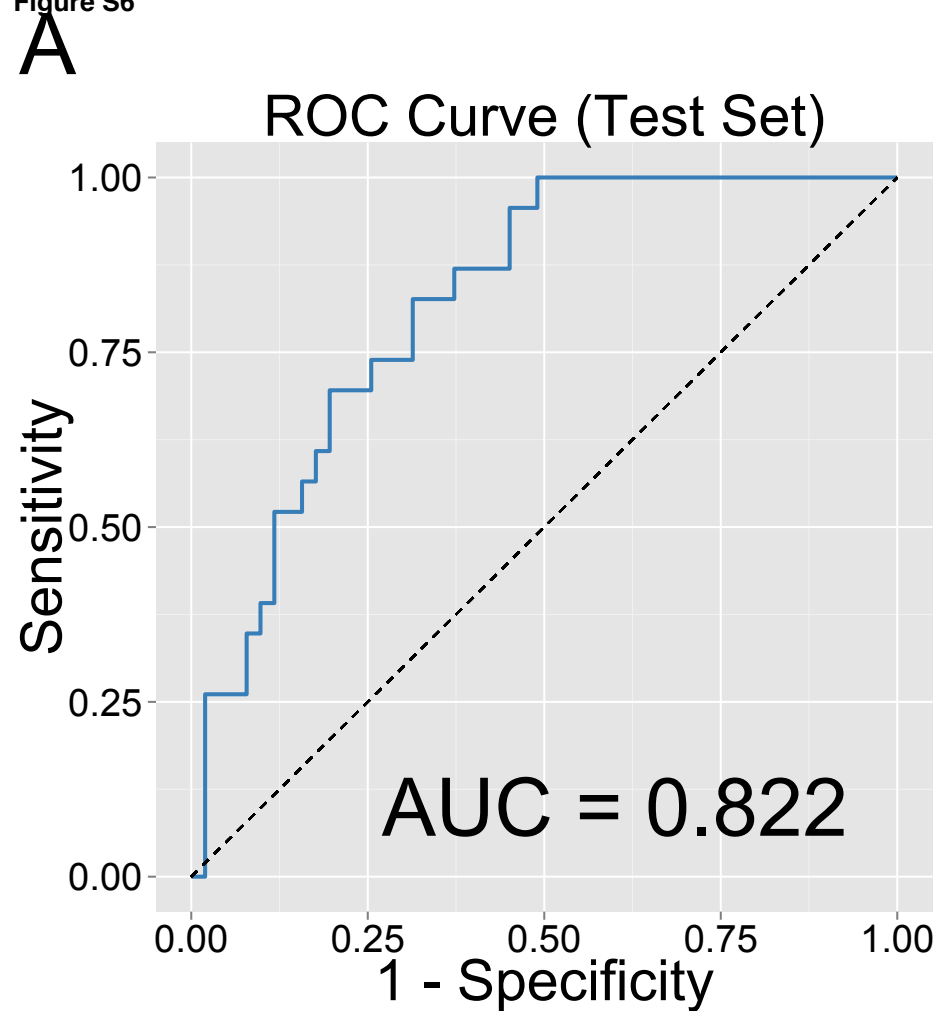


Table S1. Characteristics of participants classified by their heroin dependence (HD) status.

	Without HD (N=152)		With HD (N=70)		Test statistic	Sig.
	Mean	SD	Mean	SD		
Demographic						
Age	24.00	4.38	28.96	4.53	-7.66	3.80E-12
Gender (%Male)	73.03		80.00		0.91	n.s.
Education (yrs)	13.41	2.24	12.71	2.19	2.17	0.032
IQ	109.75	12.59	102.79	12.72	3.80	2.18E-04
# of relatives with alcohol/drug problems	0.55	0.78	0.73	0.87	-1.50	n.s.
Psychiatric						
History of Conduct Disorder (%)	72.61		48.57		10.89	9.68E-04
History of ASPD (%)	19.75		54.29		25.32	4.85E-07
Yrs of Heroin use	0.03	0.27	7.57	3.53	-17.74	2.74E-27
Yrs of Amphetamine use	2.18	2.97	0.73	1.99	4.17	4.82E-05
Yrs of Alcohol use	8.58	4.59	10.78	5.60	-2.72	0.008
DSM-IV Past dependence						
Alcohol (%)	4.46		8.57		2.16	n.s.
Sedatives (%)	0.64		4.29		2.26	n.s.
Cannabis (%)	15.92		32.86		5.42	0.020
Stimulants (%)	43.95		12.86		15.90	6.70E-05
Opiants (%)	0.00		100.00		216.40	2.20E-16
Cocaine (%)	1.27		2.86		0.13	n.s.
Hallucinogens (%)	0.00		5.71		5.88	0.150
Length of Abstinence (yrs)	0.79	1.75	1.49	2.00	-2.49	0.014
Fagerstrom Test of nicotine dependence	2.32	2.66	4.51	2.74	-5.59	1.26E-07
Psychopathy Checklist (PCL:SV) Factor 1	2.78	2.41	5.19	2.65	-6.48	2.02E-09
Psychopathy Checklist (PCL:SV) Factor 2	4.14	3.16	7.61	2.71	-8.39	2.90E-14
Wender Utah Rating Scale (WURS) for ADHD	24.56	13.23	32.73	15.78	-3.77	2.64E-04
Depression (BDI-II)	6.14	5.55	9.60	7.17	-3.57	5.35E-04
State Anxiety	32.41	7.22	36.87	8.35	-3.86	1.87E-04
Trait Anxiety	37.68	9.14	42.17	9.55	-3.30	1.26E-03
Anxiety Sensitivity	16.30	8.01	19.23	9.61	-2.22	0.028
Personality						
Levenson's Self-Report Psychopathy Scale	37.17	8.32	38.14	8.75	-0.78	n.s.
BIS Nonplanning	23.45	5.06	25.97	4.54	-3.71	2.94E-04
BIS Motor	22.85	4.57	23.54	5.42	-0.93	n.s.
BIS Attention	15.62	3.73	15.89	3.67	-0.50	n.s.
Buss-Warren Physical	17.36	6.16	19.87	6.64	-2.68	0.008
Buss-Warren Verbal	15.09	3.58	15.31	3.35	-0.45	n.s.
Buss-Warren Anger	15.82	3.75	17.43	4.18	-2.76	0.007
Buss-Warren Hostility	16.36	5.64	17.40	5.07	-1.37	n.s.
Buss-Warren Indirect	13.89	4.24	16.03	4.50	-3.35	0.001
UPPS Urgency	23.80	6.37	28.19	6.69	-4.61	9.62E-06
UPPS Lack of Premeditation	25.11	5.75	26.66	6.07	-1.79	0.075
UPPS Lack of Perseverance	19.80	5.14	21.50	4.95	-2.35	0.020
UPPS Sensation Seeking	28.59	7.35	28.01	7.87	0.51	n.s.
SSS: Disinhibition	5.09	2.52	5.06	2.60	0.09	n.s.
SSS: Boredom Susceptibility	3.66	2.03	3.83	2.15	-0.56	n.s.
SSS: Thrill and Adventure Seeking	6.64	2.90	6.36	2.82	0.68	n.s.
SSS: Experience Seeking	5.91	1.96	5.61	1.96	1.04	n.s.
Neurobehavioral						
IGT: ABCD	4.83	27.19	-1.26	24.17	1.67	0.096
IGT: EFGH	16.68	39.44	15.07	31.18	0.38	n.s.
SST %inhibition, 50ms	92.40	9.92	91.57	12.02	0.50	n.s.
SST %inhibition, 150ms	75.76	18.16	74.21	17.95	0.59	n.s.
SST %inhibition, 250ms	51.45	21.17	49.29	21.57	0.70	n.s.
SST %inhibition, 350ms	31.28	17.88	28.29	18.37	1.14	n.s.
IMT d'	1.17	0.50	1.04	0.51	1.77	0.079
IMT b	0.81	0.30	0.82	0.35	-0.26	n.s.
IMT Commission Error (%)	37.27	12.97	39.01	14.20	-0.87	n.s.
IMT Omission Error (%)	22.90	12.73	26.09	15.76	-1.48	n.s.
Delay discounting rate (log(k))	-2.90	1.11	-2.88	0.95	-0.16	n.s.
BART pumps	40.74	12.26	39.53	13.90	0.62	n.s.
Go/Nogo False Positives	15.86	7.95	17.11	9.83	-0.93	n.s.
Go/Nogo False Negatives	16.79	16.55	18.56	16.13	-0.75	n.s.
Go/Nogo d'	2.17	0.73	2.06	0.85	0.91	n.s.
Go/Nogo b	0.53	0.41	0.60	0.57	-0.96	n.s.
CGT Delay Aversion	0.32	0.19	0.39	0.22	-2.29	0.024
CGT Decision Time (msec)	2397.13	671.37	2299.61	759.89	0.92	n.s.
CGT Quality Decision Making	0.88	0.12	0.85	0.16	1.26	n.s.
CGT Risk Aversion	0.92	0.83	0.89	0.84	0.26	n.s.
CGT Risk Taking	0.63	0.13	0.61	0.12	0.98	n.s.

Note: ASPD = Antisocial Personality Disorder; BDI = Beck Depression Inventory; BIS = Barratt Impulsiveness Scale; SSS = Sensation-Seeking Scale; IGT = Iowa Gambling Task; SST = Stop Signal Task; IMT = Immediate Memory Task; CGT = Cambridge Gambling Task; n.s = non-significant (p > 0.10).

Table S2. Characteristics of participants classified by their amphetamine dependence (AD) status.

	Without AD (N=143)		With AD (N=79)		Test statistic	Sig.
	Mean	SD	Mean	SD		
Demographic						
Age	26.47	5.16	23.92	4.21	3.97	1.00E-04
Gender (%Male)	75.52		74.68		0.00	n.s.
Education (yrs)	13.33	2.31	12.94	2.12	1.28	n.s.
IQ	106.97	13.27	108.62	12.55	-0.92	n.s.
# of relatives with alcohol/drug problems	0.52	0.81	0.75	0.79	-1.98	0.049
Psychiatric						
History of Conduct Disorder (%)	27.27		49.37		9.95	0.002
History of ASPD (%)	24.48		41.77		6.37	0.012
Yrs of Heroin use	3.27	4.48	0.81	2.33	5.35	2.19E-07
Yrs of Amphetamine use	0.46	1.93	3.98	2.63	-10.21	4.71E-18
Yrs of Alcohol use	9.58	5.30	8.58	4.34	1.47	n.s.
DSM-IV Past dependence						
Alcohol (%)	2.10		12.66		9.39	2.00E-03
Sedatives (%)	2.10		1.27		0.00	n.s.
Cannabis (%)	10.49		41.77		50.61	1.12E-12
Stimulants (%)	0.00		100.00		192.84	2.20E-16
Opiates (%)	42.67		11.39		21.17	4.20E-06
Cocaine (%)	1.40		2.53		0.00	n.s.
Hallucinogens (%)	0.00		5.06		4.97	0.028
Length of Abstinence (yrs)	1.32	2.21	0.46	0.62	4.33	2.46E-05
Fagerstrom Test of nicotine dependence	2.76	2.90	3.48	2.76	-1.84	0.067
Psychopathy Checklist (PCL:SV) Factor 1	3.31	2.70	3.95	2.72	-1.69	0.094
Psychopathy Checklist (PCL:SV) Factor 2	4.64	3.49	6.33	3.03	-3.77	2.22E-04
Wender Utah Rating Scale (WURS) for ADHD	26.52	14.68	28.25	14.35	-0.86	n.s.
Depression (BDI-II)	6.96	6.13	7.73	6.62	-0.86	n.s.
State Anxiety	33.59	7.80	34.22	7.99	-0.56	n.s.
Trait Anxiety	38.29	9.11	40.57	10.01	-1.68	n.s.
Anxiety Sensitivity	16.36	8.12	18.78	9.33	-1.94	0.054
Personality						
Levenson's Self-Report Psychopathy Scale						
BIS Nonplanning	23.97	5.04	24.73	5.02	-1.08	n.s.
BIS Motor	22.37	4.80	24.33	4.71	-2.94	0.004
BIS Attention	15.18	3.47	16.65	3.95	-2.76	0.007
Buss-Warren Physical	17.39	6.45	19.52	6.15	-2.43	0.016
Buss-Warren Verbal	14.95	3.49	15.54	3.52	-1.21	n.s.
Buss-Warren Anger	16.05	4.07	16.82	3.71	-1.44	n.s.
Buss-Warren Hostility	15.83	5.00	18.24	5.97	-3.04	0.003
Buss-Warren Indirect	14.33	4.59	14.99	4.12	-1.10	n.s.
UPPS Urgency	24.57	6.96	26.28	6.31	-1.86	0.065
UPPS Lack of Premeditation	25.12	5.70	26.47	6.14	-1.61	n.s.
UPPS Lack of Perseverance	19.90	4.77	21.11	5.67	-1.61	n.s.
UPPS Sensation Seeking	27.73	7.51	29.63	7.39	-1.83	0.069
SSS: Disinhibition	4.55	2.56	6.05	2.20	-4.60	8.04E-06
SSS: Boredom	3.41	1.95	4.25	2.16	-2.87	0.005
Susceptibility						
SSS: Thrill and Adventure Seeking	6.26	2.99	7.08	2.58	-2.13	0.034
SSS: Experience Seeking	5.49	2.01	6.41	1.72	-3.57	4.59E-04
Neurobehavioral						
IGT: ABCD	2.97	26.02	2.81	27.18	0.04	n.s.
IGT: EFGH	17.99	35.63	12.89	39.30	0.96	n.s.
SST %inhibition, 50ms	92.90	9.78	90.76	11.90	1.37	n.s.
SST %inhibition, 150ms	75.98	17.62	73.99	18.90	0.77	n.s.
SST %inhibition, 250ms	51.50	20.32	49.43	22.97	0.67	n.s.
SST %inhibition, 350ms	29.16	18.24	32.47	17.61	-1.32	n.s.
IMT d'	1.14	0.51	1.10	0.51	0.62	n.s.
IMT b	0.81	0.32	0.81	0.31	-0.01	n.s.
IMT Commission Error (%)	37.36	13.59	38.65	12.97	-0.70	n.s.
IMT Omission Error (%)	24.00	14.06	23.75	13.40	0.13	n.s.
Delay discounting rate (log(k))	-3.01	1.09	-2.69	0.98	-2.28	0.024
BART pumps	40.14	11.90	40.75	14.31	-0.32	n.s.
Go/Nogo False Positives	15.37	8.40	17.86	8.74	-2.06	0.041
Go/Nogo False Negatives	17.68	17.56	16.75	14.16	0.43	n.s.
Go/Nogo d'	2.19	0.81	2.03	0.69	1.58	n.s.
Go/Nogo b	0.58	0.51	0.50	0.36	1.29	n.s.
CGT Delay Aversion	0.35	0.21	0.33	0.18	0.49	n.s.
CGT Decision Time (msec)	2299.56	702.55	2487.34	683.87	-1.94	0.054
CGT Quality Decision Making						
CGT Risk Aversion	0.86	0.15	0.87	0.11	-0.45	n.s.
CGT Risk Taking	0.97	0.86	0.81	0.77	1.45	n.s.
CGT Risk Taking	0.62	0.12	0.63	0.14	-0.43	n.s.

Note. ASPD = Antisocial Personality Disorder; BDI = Beck Depression Inventory; BIS = Barratt Impulsiveness Scale; SSS = Sensation-Seeking Scale; IGT = Iowa Gambling Task; SST = Stop Signal Task; IMT = Immediate Memory Task; CGT = Cambridge Gambling Task; n.s = non-significant ($p > 0.10$).