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Identifying cognitive deficits in cocaine dependence using standard tests and machine learning

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Abstract

There is a growing need to address the variability in detecting cognitive deficits with standard tests in cocaine dependence (CD). The aim of the current study was to identify cognitive deficits by means of Machine Learning (ML) algorithms: Generalized Linear Model (Glm), Random forest (Rf) and Elastic Net (GlmNet), to allow more effective categorization of CD and Non-dependent controls (NDC and to address common methodological problems. For our validation, we used two independent datasets, the first consisted of 87 participants (53 CD and 34 NDC) and the second of 40 participants (20 CD and 20 NDC). All participants were evaluated with neuropsychological tests that included 40 variables assessing cognitive domains. – Using results from the cognitive evaluation, the three ML algorithms were trained in the first dataset and tested on the second to classify participants into CD and NDC. While the three algorithms had a receiver operating curve (ROC) performance over 50%, the GlmNet was superior in both the training (ROC = 0.71) and testing datasets (ROC = 0.85) compared to Rf and Glm. Furthermore, GlmNet was capable of identifying the eight main predictors of group assignment (CD or NCD) from all the cognitive domains assessed. Specific variables from each cognitive test resulted in robust predictors for accurate classification of new cases, such as those from cognitive flexibility and inhibition domains. These findings provide evidence of the effectiveness of ML as an approach to highlight relevant sections of standard cognitive tests in CD, and for the identification of generalizable cognitive markers.

Introduction

Cocaine dependence (CD) is a substance use disorder (SUD) that affects 52.5 out of 100,000 citizens worldwide (Peacock et al., 2018) and the chronic use of this particular drug is associated with cognitive dysfunction. Some systematic reviews have explored the most affected domains in CD, most identify instance attention, memory and executive functions. However, these reviews also report that there is insufficient evidence to confirm the relationship between cocaine use and broad cognitive deficits (Frazer et al., 2018; Potvin et al., 2014; Spronk et al., 2013). The variability between studies is not yet explained, and may be multifactorial. Some factors that increase variability may be the heterogeneity of the population of interest (i.e. addicts), heterogeneity of the application of standard cognitive tests, and the sensitivity of the tests to find effects. Differences across standardized cognitive tests have mainly been investigated using control-case studies, where the task performance is compared between, for example, CD patients and non-dependent controls (NDC) (Frazer et al., 2018). Many studies have documented that patients with CD show altered executive functions performance in comparison to NDC's, commonly found in studies using tests such as: the Wisconsin Card Sorting Test (WCST) (Colzato et al., 2009; Simon et al., 2001; Woicik et al., 2011), the Go/No Go task (Fernández-Serrano et al., 2012), and the Backward Digit Span task (Simon et al., 2001).

Frazer et al. (2018) identified some methodological problems in past studies, such as the use of multiple cognitive measures, which influenced performance due to their exhaustive and onerous nature. When comparing CD and NDCs, researchers normally assume cognitive impairment by testing statistical significance within variables. However, this may result in the overstatement of findings, when there are typically a number of correlated variables belonging to the same domain. Consequently, the use of multiple tests of hypotheses on individual variable may confound results and increase false positive rates (Type I error) (Cupples et al., 1984). Hence, the main problems seem to be: 1) the lack of clarity as to which task subtest are adequately assessing the domains impaired in CDs, and 2) the inadequate statistical analysis employed in previous studies. We aim to address these problems by applying Machine Learning (ML), to translate complex pattern discovery methods into a clinical application (Bzdok and Meyer-Lindenberg, 2018; Dwyer et al., 2018).

ML is an efficient statistical method, which can make use of large quantities of available information, to generate valid predictions for future observations (Iniesta et

al., 2016; James et al., 2013). By using heterogeneous databases and/or having multiple predictors, ML constitutes a powerful alternative (or extension) to traditional multivariate methods, because it is capable of dealing with databases when the number of features exceeds the number of subjects, and in situations when multiple predictors are correlated between each other (Friedman et al., 2010). Due to its multivariate algorithmic nature, ML is able to: 1) localize markers that allow identification of valid and reproducible categories, 2) select among multiple variables those which may be correlated, and 3) avoid increases in false positive rate (Iniesta et al., 2016; Saeb et al., 2017). Based on an initial training of an independent dataset, the model “learns” from the input i.e. labels, and applies that learning to classify new data in an independent test dataset (James et al., 2013). “Traditional” prediction techniques based on the general linear model, such as multiple regression, might allow precise predictions. However, such models assume that predictors are independent, introducing a risk of overfitting that limits the generalization to new data (Kuhn and Johnson, 2013). Moreover, these traditional models do not consider performance in new data as an indicator of model validity. This is what renders ML more powerful.

Although the use of ML is beginning to emerge in health sciences, (see for instance, Saeb et al., 2017), applications to substance use disorders (SUDs) research is quite recent. Only three studies used the approach for SUD classification (Ahn et al., 2016; Ahn and Vassileva, 2016; Whelan et al., 2014), and only two focused on stimulant drug dependence. One of these was a cocaine study, using the method Elastic Net regression (Zou and Hastie, 2005), with the goal of localizing specific cognitive markers to correctly classify whether individuals were heroin or amphetamine dependents (Ahn and Vassileva, 2016). Their findings showed the Delay Reward Discounting Task as a unique predictor for amphetamine dependence, while other variables such as the Iowa Gambling Test (IGT) predicted heroin dependence. The second study, using the same algorithm to classify individuals with current cocaine dependence, applied predictors related to impulsivity dimensions, such as the IGT score and Barratt Impulsivity Scale (BIS) (Ahn et al., 2016). Their results showed that the general IGT score and BIS acted as significant predictors to classify cocaine dependents. These two studies represent important steps forward for the use of ML in classification and identification of generalizable predictors of SUDs. However, the limitation of Ahn et al. (2016) was the small sample size (cocaine dependent = 31, controls = 23), and the limitation for both studies was the lack of validation in an independent test set (Ahn and Vassileva, 2016), which is crucial to generalize the algorithm and main cognitive predictors.

The aim of the present study was to identify generalizable cognitive markers, using supervised classification ML, and validation of findings with an independent test set. Thus, our goals were: 1) to compare performance of different ML algorithms against a traditional GLM approximation, 2) to contrast the performance between two popular ML algorithms: Elastic net Regression and Random Forests, 3) to evaluate the use of two subsampling techniques to control category imbalance, 4) to examine the efficiency of the models in terms of three known metrics: area under the Receiver Operating Characteristic Curve (ROC), sensitivity and specificity, and 5) to validate the models in an independent dataset.

Methods

Participants

Two independent datasets were acquired for the current study. The training set consisted of a subsample of 87 participants (out of 160), from a large study of addiction at our institute (Garza-Villarreal et al., 2017). The subset was comprised of 34 non-dependent controls (NDC) (5 female) and 53 cocaine dependent patients (CD) (5 female). NDCs were matched by age (± 2 years), sex and handedness to the CDs, and education was matched as closely as possible. All participants in the training set were recruited at the National Institute of Psychiatry “Ramón de la Fuente Muñiz” in Mexico City (INPRF). The independent test set consisted on 40 participants, 20 CDs (0 females) from a registered clinical trial (Gonzalez-Olvera and Garza-Villarreal, 2017) also recruited at the INPRF and 20 NDCs randomly selected from a sample of 152 university students from a private institution (0 females), the Anahuac University (further details in Table 1). Participants all completed the same cognitive tests.

In the training set, CDs were diagnosed by a psychiatrist based on DSM-IV criteria for SUD. Those participants with dependence other than cocaine were excluded (First et al., 1997). NDCs were evaluated with the SCL-90 (Derogatis and Cleary, 1977) and the Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1997) (Inclusion and exclusion criteria are shown in Supplementary Table 1). Demographic characteristics are detailed in Table 1. The subsample for the training set was chosen by selecting participants without any missing data from the cognitive tests. In the test set, CDs were diagnosed in the same manner, while the NDCs were not evaluated with the SCL-90 and the MINI. The study was approved by the local ethics committee and carried out according to the Declaration of Helsinki. All participants were given a full explanation of what their participation entailed, and their verbal and written consent was obtained.

[Table 1 Should appear here]

Participants were given an array of tests to measure several cognitive domains in two different modalities: computer-based using the Psychology Experiment Building Language (PEBL) version 2.0 (Mueller and Piper, 2014), and paper-based. The tests administered via PEBL were: 1) the Berg's Card Sorting Test (BCST) (Berg, 1948), 2) Flanker Task (Eriksen and Eriksen, 1974), 3) Go No-go task (Gomez et al., 2007), 4) Tower of London (ToLo) (Krikorian et al., 1994), 5) Iowa Gambling Task (IGT) (Bechara et al., 1994), and 6) Reading the Mind in the Eyes Test (RMET) (Baron-Cohen et al., 2001). The Digit Span Backward and Letter-Numbers Sequencing (Wechsler, 2008) were paper-based tests. The approximate duration for the cognitive tests was 45 minutes, and they were administered in a silent room without distractors by trained psychologists and psychology students. Supplementary Table 2 contains predictors used in this study and we explain each test in the following section.

Domain - Cognitive Flexibility

Berg's Card Sorting Test (BCST)

The computer version consists of a 128-card deck displayed on a screen, one at the time. The participant must discover the rule (shape, color or quantity) by trial and error, to match the given card with key cards shown at the top of the screen. After ten cards have been successfully matched, the set is completed and the sorting rule changes. This process continues until the participant sorts all 128 cards or completes successfully 9 sets (Berg et al., 1995; Greve et al., 2005).

Domain – Inhibition

Flanker Task

This cognitive task was designed to measure the impact of “noise” in the identification of stimuli by Reaction Time (RT) and inhibitory processes (Eriksen and Eriksen, 1974; Sanders and Lamers, 2002). The screen displays a rapid changing row of arrows, where the participants are instructed to respond to the middle arrow (stimuli target) ignoring the other arrows (distracting flankers).

Go / No go Task

On the Go / no-go task, participants have to respond as quickly and accurately as possible to signal stimulus (go signal) and withhold the response when a no-go signal is presented. This particular task measures the ability to cancel a response after it has started, known as response inhibition (Gomez et al., 2007; Wright et al., 2014).

Domain - Working Memory*Letter-Number Sequencing*

The participant is required to remember and repeat out loud a series of letters and numbers, starting with the numbers followed by the letters, in ascending and alphabetical order (Wechsler, 2008).

Digit Span Backward

The participant is asked to repeat in reverse order a list of numbers (Wechsler, 2008). Difficulty increases every two-item block; the task stops if an entire block is not completed successfully.

Domain - Decision Making*Iowa Gambling Task (IGT)*

This task intends to simulate a real-time decision-making process. Participants start with a \$2,000 and the objective is to maximize profits over the course of 100 trials by selecting cards from one of four decks, previously determined as advantageous or disadvantageous, unknown to the participant (Bechara et al., 1994; Buelow and Suhr, 2009).

Domain - Planning*Tower of London (ToLo)*

This test consists of a top board, which shows a goal model that the participant must reproduce on the bottom board, with as few movements as possible and managing just one of the three available tokens at the time (Krikorian et al., 1994; Unterrainer et al., 2004).

Domain- Theory of Mind*Reading the Mind in the Eyes Test (RMET)*

The revised version was administered, which includes 36 photographs of greyscale eyes (male and female), representing a complex mental state. The participant is required to identify what the person is thinking or feeling from one of four options, just one is deemed as correct (Baron-Cohen et al., 2001).

Machine Learning Analysis

We used an exhaustive cross-validation procedure not previously used in similar studies (k-fold cross-validation with repetitions), and the generation of control models

with sub-sampling methods to assess the algorithms' prediction performance when groups (CD and NDC) are unbalanced in terms of sample size (Kuhn and Johnson, 2013). The present study statistically compares the area under the ROC curve using a stringent method of adjusting the significance level (all data and R scripts are available at <https://osf.io/m7h3x/>).

Data Preprocessing

Standardization of the predictors was performed, subtracting the mean of each predictor from each data point, and dividing by its standard deviation.

Classification algorithms

We trained three algorithms: the generalized linear model (Glm), the random forest (Rf) (Breiman, 2001), and the generalized linear model with elastic net penalty (GlmNet) (Zou and Hastie, 2005). In all three cases, the sample was the same (53 CD and 34 NDC) and each model was fitted and evaluated under comparable conditions.

Generalized linear model (Glm)

Glm is an extension of the general linear model that includes different probability functions, which are useful for modeling response variables whose error distribution is not normal. We used a binomial error distribution, because we are addressing a classification problem (CD or NDC). The Glm is based on the additive combination of predictors used to indicate the group to which the cases belong (Iniesta et al., 2016).

Random forest

Rf consists of a set of decision trees comprised of nodes and branches. Breinman's (2001) algorithm was used for model training, which to reduce the heterogeneity in training data assigned to each branch. Such an algorithm identifies the rule that is capable of dividing the data into two branches with the least amount of heterogeneity, then subdivides each branch using the same criteria. It continues until there are no rules to subdivide the data and reduces impurity. Using the rules derived from this training of the model, the algorithm is able to "learn" what values accompany each class. However, instead of using only one decision tree, Rf uses an assembly of decision trees with different random subsamples selected from the complete data set, and different subgroups of predictor variables selected at each split. Later, trees are added and the value of the most popular result is selected.

Elastic Net Generalized linear model (GlmNet)

GlmNet can deal with a large number of predictors compared to the number of observations. It includes the Ridge penalty (L2) and the Least Absolute Shrinkage and Selection Operator (LASSO) penalty (L1), which allow the selection of variables and dimensionality reduction by means of shrinkage predictors coefficients, as well as reduction of correlated coefficients by their average (Friedman et al., 2010). The best GlmNet model, selected by cross-validation includes two adjustment parameters: alpha indicates whether the best model is more like Ridge or LASSO regression, while lambda parameter controls how much the smallest coefficients are penalized. The best GlmNet model had a value of $\alpha = 1$ and $\lambda = 0.042$, which indicates that GlmNet was totally LASSO and the regularization of the smallest coefficients was very low.

Subsampling methods

Two additional models were trained and validated for each model of interest, to evaluate if participant number imbalances affect any of the prediction metrics. Additional models were assisted by two sub-sampling procedures: up and down. Subsampling up consists of randomly sampling with replacement the minority class, in order to make it the same size as the majority class. Subsampling down randomly selects from the whole dataset two subsets (one for each class) of the same size as the least prevalent class. Therefore, in the end, 9 models were fitted: 1) three models of interest (Glm, Rf, GlmNet) by 2) three subsampling methods (no subsampling, subsampling up and subsampling down) (Kuhn and Johnson, 2013).

Cross-Validation (training set)

The presence or absence of a diagnosis (CD or NCD) was used as the dependent variable (or response). In all of the models, cognitive test scores and the age of each individual were used as independent variables (or features). Thus, the final database consisted of 41 variables, one of which was the class (CD or NCD) and the others served as predictors. Models were fitted using the programming language R 3.4.3 (R Core Team, 2017) and the Caret package (Kuhn, 2008), which allows the implementation and evaluation of various models in a flexible manner. Each model was trained using the repeated k-fold cross-validation method with 10 groups (10 folds) and 10 repetitions (Kuhn and Johnson, 2013), which means that the total dataset was randomly stratified into 10 approximately identical groups. Subsequently, nine of these groups were used to train the model and the rest to validate how well the model

learned to classify subjects to the original groups. In the second iteration, another combination of the nine original groups was selected to train the model for the second time; the remaining group, which is a different group from the iteration number 1, is again used to validate predictions of the model. The previous step is reproduced until the 10 original groups have been part of the training process and each group has been used to validate the model once. Finally, the cross-validation of 10 k-folds and 10 repetitions indicates that all described steps (stratification, training and validation) are carried out 10 times in such a way that each individual had 10 predictions, resulting in 870 predictions for each model. Throughout the k-fold loop, the best models were selected in terms of the highest ROC scores.

Validation (test set)

We tested our trained algorithm using the independent test set and we carried out a performance assessment with the best algorithms derived from the cross-validation step in the training.

Algorithm Performance Metrics

The effectiveness of the classification of each model was evaluated using these metrics: 1) area under the Receiver Operating Characteristic curve (ROC), 2) sensitivity and 3) specificity. ROC curve is used to evaluate the accuracy of a continuous measure in the classification of a binary result (Kuhn and Johnson, 2013). An area under the ROC curve of 1 indicates perfect performance of the classifier. If the area under the curve is equal to or less than 0.5, it indicates a performance equal to, or worse than a random classification respectively. Sensitivity is the percentage of cases in which an algorithm correctly classified a CD participant and specificity refers to the percentage of cases in which the algorithm correctly classified an NDC. Higher scores were considered better indicators of classifier performance.

Models comparison

To determine the differences in performance of each model, a bootstrap random sample (randomized sample with replacement) of 100 cases was obtained from the 870 predictions with which the cross-validation was performed. Subsequently, differences in the three metrics (ROC, Sensitivity and Specificity) between each possible combination of models were estimated. When bootstrap sampling is undertaken, the resulting performance observations are independent and identically distributed (iid) (Eugster and Leisch, 2011; Hothorn et al., 2005). For this reason, they

can be analyzed using standard inferential statistical methods. For this purpose, we used a one sample t-test, applying a Bonferroni correction for multiple comparisons, to estimate if the population differences were different from zero.

Results

Table 2 and Figure 1 show descriptive summaries of a random sample of 100 cases that represent the 870 predictions of the cross-validation process. The model that obtained the largest mean of areas under ROC curve (best model) was the GlmNet, followed by its variants with subsampling methods “up” and “down”. Models with the lowest ROC were Glm and Rf-Down. Similar results are shown for Sensitivity: the GlmNet model performed best. However, here the Glm-Down had the worst performance. Finally, when assessing specificity, the GlmNet model performed worst, similarly to Rf, while Rf-Down performed better.

[Table 2 and Figure 1 Should appear here]

ROC

Table 3 shows the estimates of differences in ROC for training dataset, using a corrected significance level. The ROC for the GlmNet was significantly different than that of Rf-Up, Rf-Down, Glm, Glm-Up, Glm-Down, showing evidence of the GlmNet superiority with respect to these models. However, this was not the case with respect to subsampling GlmNet models (“up” and “down”), nor Rf. Rf was only better than Rf-Down, and none of its two sub-sampling variants achieved differences other than zero. Finally, Glm was not superior to any of the other models, nor with any of its subsampling variants (see Figure 2A).

[Table 3 and Figure 2 Should appear here]

Sensitivity

GlmNet was significantly different from zero in its comparison with all other models except Rf (Supplementary Table 3 shows estimates of differences in Sensitivity).

Specificity

GlmNet performed significantly worse than all of the other models and differences were statistically significant in comparison with all models for the training dataset (Supplementary Table 4 shows estimates of differences between models in Specificity). Nevertheless in the testing dataset GlmNet performance was the highest (See Table 2).

Independent test set performance

According to the performance assessment on the independent dataset, ROC scores were: GlmNet 0.850, Rf 0.715 and Glm 0.504 (See Figure 2B). These results are again consistent with performance on the previous training dataset (training and testing values for ROC score, sensitivity and specificity are depicted in Table 2).

Best model: GlmNet

GlmNet was superior on all metrics to the other models in performance of the testing dataset, whose most important variables and their estimated coefficients were: “experienced categories” from the cognitive flexibility domain, which was negatively associated with the probability of being in the CD group. Coefficients of logistic models can be divided by 4, to obtain an upper limit in the predicted difference, corresponding to a unit of difference in the predictor (Gelman and Hill, 2006). Therefore, a difference of 1 in the variable of experienced categories was associated with a reduction of 12.4% of the probability of being CD ($-0.495 / 4 = -0.124$). Increments of 1 in the “No-Go hits” variable of the inhibition domain were associated with a reduction of 8.1% in the probability of being in the CD group ($-0.324 / 4 = -0.081$). The cocaine dependent (CD) patients and non-dependent controls (NDC) “Letters and numbers” variable from the working memory domain, was associated with a reduction of 6.9% in the probability of being in the CD group ($-0.277 / 4 = -0.069$). The variable where increased scores were positively associated with the probability of being in the CD group was the total money variable from the IGT. Increases of 1 in that test were related to increases of 5.3% in the probability of being in the CD group ($0.213 / 4 = 0.053$) (Most variables and their estimated coefficients are in Supplementary Table 5).

Discussion

Using machine learning, we could accurately classify cocaine dependent (CD) patients and non-dependent controls (NDC) based on their cognitive test performance. Of the algorithms assessed, the GlmNet algorithm emerged as superior. We validated our model with independent test dataset, where the ROC score was superior in the

independent test set. This provides evidence of the generalizability of our model. Moreover, only eight variables from the different cognitive test contributed to the accurate cocaine dependence classification.

As measures by the ROC, the GlmNet algorithm outperformed the rest of the tested algorithms, and from the original 40 cognitive predictors. Only 8 of these predictors could consistently classify the groups. For the cognitive flexibility domain, a lower score on both “experienced categories” and “finished categories,” indicated a higher probability of belonging to the CD group. Case-control differences in these variables have been shown in other studies (Spronk et al., 2013), which suggest that CDs may not successfully adapt their behavior to changing contingencies or context. Therefore, they are more likely to persist with problematic behavior, which may be reflected in their higher “perseverative responses” scores. For the inhibition domain (Go/No-Go task), we found that low scores on the “hits-no go” variable were related to CD classification. Low scores on this variable are thought to reflect an impaired capacity to withhold a response and is a control deficit described in previous studies on the long-term effects of cocaine use (Frazer et al., 2018). We also found a small prediction effect for the “Flanker effect” variable, which may indicate that cognitive interference reduced participants’ reaction times (Franken et al., 2007).

For the working memory domain, results show that the Letter-Numbers test predicted CD status. Many studies have demonstrated that substance dependent individuals have poorer performance on tasks measuring working memory, not only due to a mnemonic impairment, but also because of difficulties in implementing strategies for storing and manipulating information (Van Der Plas et al., 2009). In our study, negative scores in the letter-number sequencing subtask differentiated the CD group from the NDC. For the theory of mind domain, we found that negative hits differentiated the groups, with a small effect. Preller et al. (2013) reported no significant differences for the RMET sum score between CDs and controls (Preller et al., 2013). However, Kuypers et al. (2015) found that cocaine use was associated with impairment in negative emotion recognition, with better recognition of happiness than anger, consistent with our findings (Kuypers et al., 2015). Finally, concerning the decision-making domain, a high “IGT total score” was an important predictor for the CD group status. This finding conflict with some studies that have described a poorer test execution of this group compared to controls using different tests (Hulka et al., 2015; Vadhan et al., 2009; Verdejo-garcia et al., 2007). Nonetheless, these studies noted that they had tested an unrepresentative sample, limiting generalizability (Verdejo-garcia et

al., 2007). Interestingly, Hulka et al. (2015), reported similar findings to ours in a longitudinal study, which considered drug use variables, such as dose and duration. Those who increased their cocaine consumption over one year tended to improve their performance on the task (the IGT “total score”), which was correlated with the IGT “total gain”. Likewise, our sample was composed of current cocaine users (not abstainers), which may explain the higher risk taking and therefore higher gains in the IGT.

Machine learning classification performance may differ depending on both the algorithm used and the data used (Kuhn and Johnson, 2013). For this reason, we wanted to compare several common algorithms to observe their performance with the same data and sample size. To the best of our knowledge, this is the first study that carries out a comparison between contemporary ML methods (GlmNet and Rf) and a traditional algorithm (Glm), with the purpose of classifying CD patients using variables from cognitive tests. GlmNet and Rf were superior to Glm in the ROC score. Even though GlmNet was not significantly better than Rf in the training set, it was a more reliable predictor in the testing set. These results are consistent with another study, carried out with simulations, where the Elastic Net was superior than Rf and a Two Sample t-test for selecting variables and predicting future data (Lu and Petkova, 2014). The only previous work using the GlmNet that specifically studied cocaine dependence (Ahn et al., 2016) had some limitations such as sample size and lack of validation in an independent test set. Thus, our study is an important extension of previous work. Finally, this is also the first study of its kind to use an independent test dataset for validation of the ML algorithm, an important methodological improvement in the field.

We had some limitations that should be considered. First, there was an imbalance in the number of CDs and NDCs in the sample employed for the training phase. Nonetheless we used an ‘up and down’ subsampling procedure to control the impact of the imbalance (??) on ROC scores (Kuhn and Johnson, 2013). We showed that the xxx were consistent for GlmNet. Some demographic differences need to be noted. For example, the training dataset was mainly comprised of males, while in the testing dataset, NDCs were male only and mainly bachelor students, and therefore are different in age and year of education. This subsample was not clinical evaluated to exclude further subclinical or psychiatric conditions, and tobacco use. Despite these limitations, the testing phase ROC scores were better than those of the training phase, and, specifically, the fraction of the NDC cases correctly classified (specificity), were higher than in the training dataset. This might be counterintuitive, and may result

from the demographic variables, which strongly impact cognitive functioning. However, we reiterate that this is an exploratory analysis, and that further replication is needed before suggesting these predictors as generalizable cognitive markers.

In conclusion, our study provides evidence of the effectiveness of ML techniques for the identification of potential cognitive markers, and for showing sections of standard cognitive tests, which appear disrupted in cocaine dependent patients.

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Figure legends

Figure 1. Distributions of the ROC, Sensitivity (Sens) and Specificity (Spec) scores for the three main models on training set. X axis is the algorithm performance (between 0-1) and Y represents the density of cases. The dashed line represents the mean of each distribution. It is a random sample of 100 scores obtained from the 870 predictions resulted from the cross-validation process.

Figure 2. A) Example of receiver operating characteristic (ROC) curves from training set, from which the area under the curve was obtained. If models perform at random, their "curves" would be in a line that divides the graph panel into two equal parts (therefore, their area under the curve would be 50% and their ROC score would be 0.5). ROC curves consistently above 0.5, are the models that perform best in classification. For this particular case, the GlmNet shows a better performance than the Rf. **B)** ROC curves of independent testing set, GlmNet shows a highest performance than Rf and Glm.

Table 1. Demographic characteristics of the training and testing datasets

Training Set				Testing Set		
	NDC	CD	Statistic	NDC	CD	Statistic
	(n = 34)	(n = 53)		(n = 152)	(n = 20)	
Age						
	31.6 ± 7.7	31.6 ± 7.4	t (85) = 0.05 p = 0.96	22.1 ± 1.55	34 ± 8.34	t (38) = 6.51 p < 0.001
Administration						
None	34 (100%)	-		34 (100%)	-	
Cocaine	-	18 (34%)		-	0 (0%)	
Crack	-	35 (66%)		-	20 (100%)	
Tobacco Use						
Years of consumption	6.73 ± 8.19	12.4 ± 5.72	t (72) = -3.54 p < 0.001	NA	16.11 ± 10.16	
Sex						
Male	29 (85.3%)	48 (90.6%)	X ² (1) = 0.17 p = 0.68	152 (100%)	16 (80%)	X ² (1) = 2.5 p = 0.11
Female	5 (14.7%)	5 (9.4%)		0 (0%)	4 (20%)	
Degree						
NA	-	-		4 (2.6%)	-	
Grade school	1 (2.9%)	6 (11.3%)	X ² (5) = 16.5 p = 0.006	7 (4.6%)	0 (0%)	X ² (5) = 7.44 p = 0.19
Middle school	6 (17.6%)	23 (43.4%)		6 (4%)	4 (20%)	
High school	10 (29.4%)	4 (7.5%)		6 (4%)	5 (25%)	
Trade school	4 (11.8%)	10 (18.9%)		0 (0%)	0 (0%)	

Bachelor	12 (35.3%)	10 (18.9%)	127 (83.6%)	8 (40%)
Graduate	1 (2.9%)	0 (0%)	2 (1.3%)	3 (15%)

Data are given as $N(\%)$ or mean (SD). Two sample t-test was performed for age, and χ^2 for categorical variables. The table shows participants demographic characteristics divided by the two independent samples, used for the training and the testing set. The subsamples of each set are separated by Non-dependent control subjects (NDC) and Cocaine Dependents (CD). The testing set section describes the original database from which a NDCs subsample of 20 subjects was hold out randomly to balance with CD group. Comparison in tobacco use was performed in 74 cases with complete information.

Table 2. Description of training and testing classification performance by models

Model	Training Set					
	ROC		Sensitivity		Specificity	
	Mean	SD	Mean	SD	Mean	SD
GlmNet	0.71	0.19	0.84	0.16	0.43	0.27
GlmNet-Up	0.70	0.19	0.69	0.21	0.59	0.27
GlmNet-Down	0.69	0.21	0.64	0.23	0.62	0.27
Rf	0.67	0.20	0.82	0.18	0.43	0.27
Rf-Up	0.64	0.21	0.74	0.2	0.52	0.27
Rf-Down	0.62	0.19	0.6	0.2	0.63	0.27
Glm	0.62	0.17	0.64	0.23	0.60	0.27
Glm-Up	0.62	0.17	0.65	0.22	0.60	0.26
Glm-Down	0.61	0.2	0.56	0.22	0.61	0.31

Model	Testing Set		
	ROC	Sensitivity	Specificity
Glm	0.504	0.490	0.400
Random forest	0.715	0.630	0.690
GlmNet	0.850	0.720	0.870

Training set: Means and standard deviations of a random sample of 100 metrics obtained from the 870 predictions of each model. Testing set: models' performance scores on the independent testing set. ROC, area under the curve of receiver operating characteristic curve; SD, standard deviation; GlmNet, generalized linear model elastic net; GlmNet-Up, generalized linear model elastic net - subsampling up; GlmNet-Down, generalized linear model elastic net - subsampling down; Rf, random forest; Rf-Up, random forest - subsampling up; Rf-Down, random forest - subsampling down; Glm, generalized linear model; Glm-Up, generalized linear model - subsampling up; Glm-Down, generalized linear model - subsampling down.

Table 3. Estimates of the differences between models and their significance level in ROC

Model	Glm Net	Glm Net-Up	Glm Net-Down	Rf	Rf-Up	Rf-Down	Glm	Glm-Up	Glm-Down
GlmNet		.016	.027	.037	.067	.093	.091	.090	.102
GlmNet-Up	1.000		.011	.022	.051	.077	.075	.074	.086
GlmNet-Down	.397	1.000		.010	.040	.066	.064	.063	.075
Rf	.548	1.000	1.000		.030	.055	.053	.053	.065
Rf-Up	.002**	.066	1.000	0.074		.025	.024	.023	.035

Rf-Dow n	<.001***	<.001***	.013*	<.001***	1.000		-0.002	-0.002	.009
Glm	<.001***	.004**	.132	.760	1.000	1.000		-0.001	.011
Glm-Up	<.001***	.005**	.125	.909	1.000	1.000	1.000		.012
Glm-Dow n	<.001***	.007**	.072	.530	1.000	1.000	1.000	1.000	

Table's Upper diagonal part show s the estimates of differences, while low er diagonal show s the p-values for estimates different from zero ($H_0 = 0$). Values in the upper diagonal part are differences betw een means of a random sample of 100 of the 870 predictions for each model. Low er diagonal show s levels of significance adjusted by the number of comparisons w ith Bonferroni method. '*' p < 0.05, '**' p < 0.01, '***' p < 0.001

Highlights

- Cognitive deficits in cocaine dependence are inconsistent
- Machine learning applied to cognitive tests may help find these deficits
- We found that the GlmNet algorithm had superior performance in categorizing the sample, in comparison to other algorithms.
- Eight variables from all cognitive domains were found as consistent predictors
- Those predictors were reproducible in an independent test set