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Using a data science approach to predict cocaine use frequency from depressive symptoms

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ABSTRACT

Background: Depressive symptoms may contribute to cocaine use. However, tests of the relationship between depression and severity of cocaine use have produced mixed results, possibly due to heterogeneity in individual symptoms of depression. Our goal was to establish which symptoms of depression are most strongly related to frequency of cocaine use (one aspect of severity) in a large sample of current cocaine users. We utilized generalized additive modeling to provide data-driven exploration of the relationships between depressive symptoms and cocaine use, including examination of non-linearity. We hypothesized that symptoms related to anhedonia would demonstrate the strongest relationship to cocaine use.
Method: 772 individuals screened for cocaine use disorder treatment studies. To measure depressive symptoms, we used the items of the Beck Depression Inventory, 2nd Edition. Cocaine use frequency was measured as proportion of self-reported days of cocaine use over the last 30 days using the Addiction Severity Index.
Results: Models identified 18 significant predictors of past-30-day cocaine use. The strongest predictors were Crying, Pessimism, Changes in Appetite, Indecisiveness, and Loss of Interest. Noteworthy effect sizes were found for specific response options on Suicidal Thoughts, Worthlessness, Agitation, Concentration Difficulty, Tiredness, and Self Dislike items.
Conclusions: The strongest predictors did not conform to previously hypothesized "subtypes" of depression. Non-linear relationships between items and use were typical, suggesting BDI-II items may not be monotonically increasing ordinal measures with respect to predicting cocaine use. Qualitative analysis of strongly predictive response options suggested emotional volatility and disregard for the future as important predictors of use.

1. Introduction

Cocaine is the third most abused illicit drug in the U.S. (Substance Abuse and Mental Health Services Administration (SAMHSA, 2017), and accounts for significant health burdens worldwide (Degenhardt et al., 2014). Identifying modifiable factors associated with cocaine use is important to reducing its use. Depressive symptoms may contribute to cocaine use and make it more difficult for individuals to quit using cocaine (Poling et al., 2007; Rounsaville, 2004). However, tests of the relationship between depression and cocaine use have produced mixed results. Some studies indicate that depressive symptoms relate to greater severity of cocaine use (Leventhal et al., 2006), while others show little to no relationship (Ford et al., 2009). A meta-analysis of 53 studies found a small but significant relationship between depression and concurrent cocaine use (Conner et al., 2008). The mixed nature of these findings suggests nuances in the relationship between depression and cocaine use. These may include moderating factors, such as population characteristics, or differences in how depression has been defined and measured in different studies.

One important factor determining the relationship between depression and severity of cocaine use may be the type of depressive symptoms that are experienced. There is increasing recognition that

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depression is not homogenous: two individuals receiving a depression diagnosis may actually have no symptoms in common. One theoretically-based distinction with relevance to addiction is between negative mood (i.e., sadness) and anhedonia (i.e., lack of interest or pleasure in activities; Treadway and Zald, 2011). Pre-clinical data suggest these symptom dimensions depend on distinct neurobiological circuits, and clinically they have different implications for outcomes and treatment (Treadway and Zald, 2011; Vrieze et al., 2014). Several lines of evidence suggest anhedonia is particularly important to use of stimulants such as cocaine. In a large, population-based sample of adults with stimulant use disorder, anhedonia was uniquely associated with lifetime stimulant use and stimulant dependence, even after controlling for depressed mood (Leventhal et al., 2010). This relationship could be due to differential responses to cocaine, as anhedonia was also associated with more positive hedonic responses to cocaine in cocaine users, while depressed mood did not predict subjective responses to cocaine. This suggests individuals with anhedonia may experience enhanced addictive effects of cocaine, leading to greater use and poorer treatment outcomes (Wardle et al., 2017). Thus, a failure to distinguish between anhedonia and other symptoms of depression such as negative mood may contribute to the generally weak relationship between overall measures of depression and indicators of cocaine use.

Although the distinction between negative mood and anhedonia represents a theoretically-driven parsing of depression symptoms with apparent relevance to addiction, there have also been a number of data-driven attempts to identify depression dimensions or sub-types. This includes a prior investigation in individuals with cocaine use disorder, which utilized the Beck Depression Inventory, 2nd Edition (BDI-II; Beck et al., 1996; Conner et al., 2008) to identify three symptom dimensions: Cognitive, Affective and Somatic (Seignourel et al., 2008). Another analysis in patients with depression utilizing multiple depression measures, including the BDI-II, found eight factors: Depressed Mood, Tension, Negative Cognition, Impaired Sleep, Suicidal Thoughts, Reduced Appetite, Anhedonia and Amotivation (Ballard et al., 2018). There has also historically been a distinction between "Melancholic" and "Atypical" subtypes of depression, with "Atypical" presenting with more fatigue and anxiety (American Psychiatric Association (APA, 2000). Thus, there are multiple possible ways to parse depressive symptoms into groups or dimensions, and it is unclear which of these dimensions might best explain heterogeneity in the relationship between depressive symptoms and cocaine use.

Therefore, our goal was to use data-driven modeling to establish which symptoms of depression most strongly relate to frequency of cocaine use in the last 30 days in a sample of current cocaine users. We utilized frequency of use in the last 30 days as our primary outcome because it is a parsimonious measure of severity that shows stronger predictive ability for treatment outcomes compared to other measures such as years of use or the Addiction Severity Index drug composite score (Reiber et al., 2002). However, we secondarily examined Cocaine Dependence diagnosis and severity of diagnosis in supplemental analyses as additional indicators of severity, to test the generality of the identified predictors. To measure depressive symptoms, we used the items of the Beck Depression Inventory, 2nd Edition. The BDI-II includes items related to depressed mood (e.g., sadness and crying), somatic symptoms (e.g., sleep and appetite), cognitive symptoms (e.g., being unable to make decisions), and anhedonia, including items for loss of pleasure, loss of interest in activities, loss of energy, and loss of interest in sex that have previously been identified as composing an anhedonia sub-scale (Joiner et al., 2003; Pizzagalli et al., 2005). We utilized tools from the field of data science to build a model predicting the proportion of the last 30 days on which an individual used cocaine from individual items on the BDI-II. Data science blends features of computer science, machine learning, and statistics to provide efficient, data-driven exploration of the relationships between variables and optimized prediction of outcomes (Hastie et al., 2009). In particular, we chose Generalized Additive Modeling. The *generalized* nature of GAM allows estimation of non-Gaussian outcome distributions, such as the proportion outcome used here. The *additive* nature of GAM allows for nonlinear relationships between BDI-II items and cocaine use. For example, some theories posit that both very high and very low levels of reward sensitivity may contribute to addictive behaviors, suggesting a possible quadratic relationship between anhedonia items and addiction (Davis and Fox, 2008). Additive models use a machine learning algorithm to fit predictors using smoothing functions across the range of each predictor's possible values; in essence allowing non-linear data-driven functions to be estimated, rather than fitting a single straight line through predictor values (Hastie et al., 2009). Each item on the BDI-II is measured on a 4-point Likert-type scale—fitting these items as smoothed (nonlinear) predictors enables investigation of the shape of the relationship to cocaine use over each of the four points on that scale. Previous studies (i.e., those reported by the meta-analysis in Conner et al., 2008) have examined the relationship between cocaine use and depression using total scale scores, rather than item-level data; such total scale scores may mask nonlinear contributions of individual items. Our hypothesis was that items previously identified as part of the BDI-II Anhedonia sub-scale would be the most strongly related to frequency of current cocaine use; however, our approach allowed extraction of the optimal combination of items for predicting cocaine use.

2. Materials and methods

2.1. Overall design

All data were obtained from electronic records of participants enrolled in an evaluation protocol at The University of Texas Health Science Center at Houston Center for Neurobehavioral Research on Addiction from August 2006 to January 2017. All participants signed an informed consent that was approved by the Committee for the Protection of Human Subjects at The University of Texas Health Science Center at Houston. Participants took part in a two- to three-day evaluation conducted over 7–10 days, in which they were screened for eligibility to participate in research studies of pharmacological and/or psychological interventions for the treatment of cocaine use disorder. The screening consisted of a battery of questionnaires including the BDI-II, a physical examination, laboratory measures, and an interview with a trained licensed professional counselor. Participants were recruited through local print advertisements, online postings, and referrals from other health institutions, friends, or family in the greater Houston area. The analyzed sample consisted of N = 772 unique participants that completed the baseline measures prior to any intervention and self-reported a minimum of one day of cocaine use of the past 30 days.

2.2. Measurements

Depression symptoms were measured using the 21-item BDI-II, which was administered within a battery of computerized self-report questionnaires. Cocaine use frequency was determined from the Addiction Severity Index (ASI). The ASI is a semi-structured interview that assesses seven problem areas (drug use, alcohol use, legal status, medical status, employment and support, family and social status, and psychiatric status) in individuals with current (last 30 days) and past (lifetime) substance use history, and was completed by the trained licensed professional counselor as part of the interview portion of the screening protocol (McLellan et al., 1980). This measure is where the proportion (0–1) of self-reported days of cocaine use over the last 30 days was captured. Supplemental analyses examined dichotomous presence vs. absence of cocaine use disorder based on Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (SCID-IV; First et al., 1996) as well as categorical mild/moderate/severe ratings of severity of cocaine dependence completed as a part of the SCID-IV for the n = 551 individuals with a diagnosis of cocaine dependence.

2.3. Data analytic strategy

The machine learning algorithm generalized additive modeling (GAM; Hastie and Tibshirani, 1986) in R (function gam() from the R package mgcv v. 1.8–22; Wood, 2017) was used to explore the strength and shapes of the relationships between each of the 21 items on the BDI-II with the proportion of days cocaine was used out of the past 30. The proportion of cocaine use days in the last 30 days was modeled using the binomial distribution. Of note, we repeated this analysis of cocaine use frequency in a subsample of patients (N = 267) who submitted at least one biochemically verified positive urine during intake, indicating they had definite cocaine use during the period queried. Results from this subsample were highly similar to the primary findings reported here, and will not be discussed in detail, but are available in Supplementary Material (Model S1). Secondarily, we modeled in supplemental analyses the dichotomous variables of DSM-IV diagnosis of Cocaine Dependence (yes/no) and categorical variable of severity of this diagnosis (mild/moderate/severe) to examine the generality of the predictors identified for frequency of use (see Supplementary Material 1, Models S2 and S3 for details). Automated selection features of the R package mgcv implementation of GAM enhanced the investigation of the nonlinear relationship structure. These selection features (a) established the optimal degree of smoothness for each item and (b) allowed the removal of an item through additional penalization of each model term. The mgcv implementation of GAM offers two major types of automated smoothing: restricted maximum likelihood (REML) and global cross-validation (GCV). REML, the default option in the software, has demonstrated fewer complications due to overfitting (Wood, 2011). Thus, it was utilized here. However, of note, re-analysis using the GCV method produced no inferential differences from the manuscript, with resulting plots being nearly identical.

The model obtained via GAM was also fit using generalized linear modeling (GLM) for comparison purposes. Several statistics examining fit and performance were obtained: (1) Akaike Information Criteria (AIC; Akaike, 1973), a measure of goodness-of-fit with a penalty for model complexity, (2) root mean squared error (RMSE), a measure of the deviation between predicted and observed values, and (3) area under the receiver operator characteristic curve (AUROC), a measure of classification performance in outcomes fit by a binomial distribution. Better fit is demonstrated by lower values of AIC and better performance is measured via lower RMSE and higher values of AUROC.

3. Results

3.1. Sample demographics

The sample was primarily male (75%) and African-American (69%) with a mean age of 44.1 (SD = 8.9) and a mean education level of 12. 5 years (SD = 1.9). Participants reported a mean of 14.48 days of cocaine use in the past 30 (SD = 9.3) and a mean BDI-II total score of 15.17 (SD = 10.9). BDI-II total score cutoff values indicated depression category representation of 48% minimum, 19% mild, 21% moderate, and 12% severe.

3.2. Generalized additive modeling

Generalized additive modeling explored the relationships between cocaine use frequency and the 21 items on the BDI-II. Model penalization reduced the effect of the Sadness item to 0, leaving 20 items. Estimated degrees of freedom (*edf*), Chi-square, and approximated *p*-values for each item are provided in Table 1. While these *p*-values are approximations (GAM has no value directly equivalent to traditional p-values; see Wood, 2013 for a discussion), results indicated that 17 of the 21 items contributed substantively to the model estimation. The chi-square value of each predictor provided an index of the relative contribution of each predictor to the overall model. Lacking an established heuristic, as a measure of convenience we define the strongest predictors as those with at least 25% of the highest chi-square value. The items with the strongest overall contribution to the model were crying, pessimism, changes in appetite, indecisiveness, and loss of interest. GAM diagnostics found no evidence for violation of assumptions (including normality of residuals, homogeneity of variance, and independence of residuals). For the purpose of comparison, generalized linear modeling was used to fit cocaine use frequency to the 20 items retained by the GAM. Metrics for comparison including AIC, RMSE, and AUC all demonstrated superior fit and predictive performance of the GAM (AIC = 11971.4, RMSE = 0.290, AUC = 0.619) over the GLM (AIC = 12643.5, RMSE = 0.302, AUC = 0.567).

Table 1
GAM results – estimated degrees of freedom, chi square value, and approximated significance for Beck Depression Inventory-II items, ordered by chi square value.

Item #	Item name	Estimated *df*	Chi Square	*p* Value	Shape
10	Crying	2.95	204.86	< 0.001	Cubic
2	Pessimism	2.68	114.78	< 0.001	Quadratic
18	Changes in Appetite	2.87	87.33	< 0.001	Cubic
13	Indecisiveness	2.9	68.3	< 0.001	Cubic
12	Loss of Interest	2.95	61.34	< 0.001	Cubic
16	Changes in Sleeping Pattern	2.72	47.84	< 0.001	Quadratic
21	Loss of Interest in Sex	2.22	46.54	< 0.001	Quadratic
14	Worthlessness	2.84	43.47	< 0.001	Quadratic
5	Guilty Feelings	2.84	40.21	< 0.001	Cubic
8	Self Criticalness	2.29	39.68	< 0.001	Quadratic
11	Agitation	2.91	38.9	< 0.001	Cubic
20	Tiredness	2.87	35.57	< 0.001	Cubic
19	Concentration Difficulty	2.77	24.65	< 0.001	Cubic
9	Suicidal Thoughts	2.18	22.01	< 0.001	Quadratic
3	Past Failure	2.72	21.8	< 0.001	Cubic
7	Self Dislike	2.81	18.65	< 0.001	Cubic
15	Loss of Energy	0.95	17.44	< 0.001	Linear
6	Punishment Feelings	1.89	11.33	0.002	Quadratic
4	Loss of Pleasure	1.03	2.22	0.112	Quadratic
17	Irritability	0.64	0.84	0.261	Linear
1	Sadness	0	0	0.967	N/A

GAM produced partial effects plots to describe the strength of the relationship between each predictor and the outcome (y-axis) across different values of the predictor (x-axis). As there are only four response options for each item (0 through 3), there may be a maximum of two bends in any line fit through those response options. Thus, the relationships may be linear (no bends), quadratic (one bend), or cubic (two bends). We determined the shape of the relationship through visual inspection. Ten items demonstrated a cubic relationship, eight demonstrated a quadratic relationship, and two were linear. The shape of each relationship is indicated in Table 1.

To further examine the relationships between the BDI-II items and cocaine use, odds ratios were obtained to describe the relationship between each response option for each item and cocaine use frequency. Odds ratios in the present context of a proportion outcome are interpreted such that a given one-unit increase on a BDI-II item (e.g., from 0 to 1, 1 to 2, etc.), is associated with a corresponding odds of having an additional cocaine use day. Unlike in GLM, odds ratios in GAM are not constant throughout the range of predictor values; instead, they are calculated for each potential distinct segment of a line fit through four response options on a given item (i.e., from option 0 to 1, option 1 to 2, and option 2 to 3) while holding the other predictors constant (Schratz, 2017). The odds ratios are reported in Table 2.

We focused a more detailed analysis on the five strongest predictors

Table 2
GAM Odds Ratios.

Item	Segment	OR	2.50%	97.50%
Crying	1 to 2	2.302	2.155	2.459
SuicidalThoughts	2 to 3	2.240	1.775	2.828
Worthlessness	2 to 3	2.198	1.899	2.543
Pessimism	2 to 3	1.866	1.750	1.990
LossOfInterest	2 to 3	1.732	1.669	1.797
SuicidalThoughts	1 to 2	1.689	1.348	2.117
Pessimism	1 to 2	1.440	1.376	1.508
ChangesInAppetite	1 to 2	1.381	1.337	1.427
Indecisiveness	1 to 2	1.378	1.325	1.433
Agitation	1 to 2	1.309	1.240	1.382
Tiredness	1 to 2	1.212	1.150	1.277
LossOfInterestInSex	0 to 1	1.206	1.205	1.208
ChangesInSleepingPattern	0 to 1	1.188	1.165	1.212
PastFailure	0 to 1	1.178	1.144	1.213
ChangesInAppetite	0 to 1	1.176	1.160	1.192
GuiltyFeelings	2 to 3	1.170	1.094	1.250
LossOfInterest	0 to 1	1.124	1.106	1.143
ChangesInSleepingPattern	1 to 2	1.121	1.100	1.143
Indecisiveness	0 to 1	1.111	1.094	1.128
Worthlessness	1 to 2	1.106	1.066	1.147
SelfDislike	1 to 2	1.084	1.081	1.086
GuiltyFeelings	0 to 1	1.049	1.027	1.072
PastFailure	**2 to 3**	**1.046**	**0.973**	**1.124**
ConcentrationDifficulty	1 to 2	1.046	1.000	1.093
PunishmentFeelings	2 to 3	1.045	1.037	1.053
LossOfPleasure	0 to 1	1.038	1.028	1.048
Worthlessness	0 to 1	1.022	1.016	1.028
LossOfPleasure	1 to 2	1.015	1.003	1.028
LossOfPleasure	**2 to 3**	**1.006**	**0.978**	**1.036**
Irritability	**0 to 1**	**1.000**	**0.996**	**1.005**
Sadness	**0 to 1**	**1.000**	**1.000**	**1.000**
Sadness	**1 to 2**	**1.000**	**1.000**	**1.000**
Sadness	**2 to 3**	**1.000**	**1.000**	**1.000**
SelfCriticalness	**0 to 1**	**0.993**	**0.976**	**1.010**
Irritability	**2 to 3**	**0.989**	**0.977**	**1.001**
Agitation	0 to 1	0.989	0.983	0.994
PunishmentFeelings	1 to 2	0.981	0.966	0.995
Irritability	1 to 2	0.978	0.966	0.991
SuicidalThoughts	0 to 1	0.936	0.915	0.957
PunishmentFeelings	0 to 1	0.898	0.897	0.898
PastFailure	1 to 2	0.896	0.882	0.910
Pessimism	0 to 1	0.887	0.877	0.897
LossOfEnergy	1 to 2	0.885	0.870	0.900
LossOfEnergy	2 to 3	0.885	0.853	0.919
LossOfEnergy	0 to 1	0.885	0.874	0.896
SelfDislike	0 to 1	0.882	0.872	0.891
LossOfInterestInSex	1 to 2	0.876	0.851	0.903
ConcentrationDifficulty	0 to 1	0.871	0.863	0.878
Tiredness	0 to 1	0.851	0.838	0.863
SelfCriticalness	2 to 3	0.846	0.821	0.871
Crying	2 to 3	0.845	0.803	0.889
SelfCriticalness	1 to 2	0.844	0.828	0.861
Crying	0 to 1	0.790	0.779	0.800
GuiltyFeelings	1 to 2	0.781	0.769	0.794
ChangesInSleepingPattern	2 to 3	0.757	0.749	0.765
LossOfInterestInSex	2 to 3	0.738	0.711	0.765
LossOfInterest	1 to 2	0.732	0.701	0.764
SelfDislike	2 to 3	0.715	0.630	0.812
ChangesInAppetite	2 to 3	0.709	0.677	0.743
Tiredness	2 to 3	0.709	0.650	0.774
ConcentrationDifficulty	2 to 3	0.701	0.626	0.786
Agitation	2 to 3	0.596	0.578	0.614
Indecisiveness	2 to 3	0.569	0.509	0.635

*__Bold Font__ – Confidence Interval includes 1.0.

in the GAM by chi-square value: Crying, Pessimism, Changes in Appetite, Indecisiveness, and Loss of Interest. The partial effects plots for these items may be found in Fig. 1 (parts A through E, respectively). However, additional attention was also granted to the strongest local (i.e., between two response options) effects occurring for items other than the five defined above. These high-magnitude local effects merit further consideration as their contribution may have been dampened by low-magnitude effects across the rest of the response options for that item, causing that item not to be represented in the overall strongest predictors of cocaine use. Partial effects plots for these items, including Suicidal Thoughts, Worthlessness, Agitation, Tiredness, Self-Dislike, and Concentration Difficulty, may be found in Fig. 2 (parts A through F). Below we discuss the relationship of the strongest predictors and the noteworthy local effects to cocaine use in more detail.

3.3. *Strongest overall predictors*

The strongest predictor in the overall model was Crying (Fig. 1A), and consistent with this the strongest individual positive odds ratio was found for the Crying item (O.R. = 2.30 [2.16, 2.46]). The relationship of Crying to cocaine use was cubic, such that it increased over the center two options but decreased at both tails, with the largest effect occurring between response options 1 ("I feel sad much of the time") and 2 ("I feel sad all the time"). This particular one-unit increase indicated an expected increase in the odds of cocaine use by a factor of 2.3. The Pessimism item (Fig. 1B) was the second strongest overall predictor, and demonstrated a quadratic relationship with cocaine use, such that a small decrease in use was observed between 0 and 1 response options, but the dominant trend from options 1 to 3 was for more severe cocaine use (average O.R. = 1.66). The third strongest overall predictor, Changes in Appetite (Fig. 1C), demonstrated an unusual quadratic pattern with both noteworthy positive and negative effects: an increase between options 1 to 2 (O.R. = 1.38 [1.34, 1.43]) and a decrease between options 2 and 3 (O.R. = 0.71 [0.68, 0.74]), both among the strongest individual odds ratios detected. This suggests response option 3 for Changes in Appetite "I have no appetite at all OR I crave food all the time" may not describe change in appetite in the same way that the other response options do (e.g., option 1: "My appetite is somewhat less than usual or somewhat more than usual"). The Indecisiveness item (Fig. 1D) was the fourth strongest overall predictor and also demonstrated this type of relationship, with a modest increase in cocaine use from option 1 to 2 (O.R. = 1.38 [1.33, 1.43]), from "I find it more difficult to make decisions than usual" to "I have much greater difficulty making decisions than usual," respectively, but a sharp decrease from option 2 to option 3 (O.R. = 0.57 [0.51, 0.64]), "I have trouble making any decisions." The Loss of Interest item (Fig. 1E) was the fifth strongest predictor of cocaine use frequency. The shape of the relationship was distinctly cubic, whereby the strength of the relationship increased from response option 0 to 1 (O.R. = 1.12 [1.11, 1.14]), then decreased to response option 2 (O.R. = 0.73 [0.70, 0.76]), and again increased (O.R. = 1.73 [1.67, 1.80]) to its strongest effect at option 3, "It's hard to get interested in anything." Endorsing option 3 was positively related to higher frequency, while endorsing the next-lower option "I have lost most of my interest in other people or things" was negatively related to frequency. This nonlinearity may lie in wording: the highest option relates to difficulty generating interest, as opposed to outright losing interest as in the highest option.

3.4. *Additional strong local effects*

Other strong local effects within items (Fig. 2) bear further mention here. While these effects were not reflected among the strongest overall predictors of cocaine use, these response options had disproportionately large effect sizes relative to many of the effects found across predictors. In particular, additional strong positive effects, both for between the two highest options, were discovered for Suicidal Thoughts (O.R. = 2.24 [1.76, 2.83]) and Worthlessness (O.R. = 2.20 [1.90, 2.54]). Additional strong negative effects were found between the two highest response options for Agitation (O.R. = 0.60 [0.58, 0.61]), Tiredness (O.R. = 0.71 [0.65, 0.77]), Self-Dislike (O.R. = 0.72 [0.63, 0.81]), and Concentration Difficulty (O.R. = 0.70 [0.63, 0.79]).

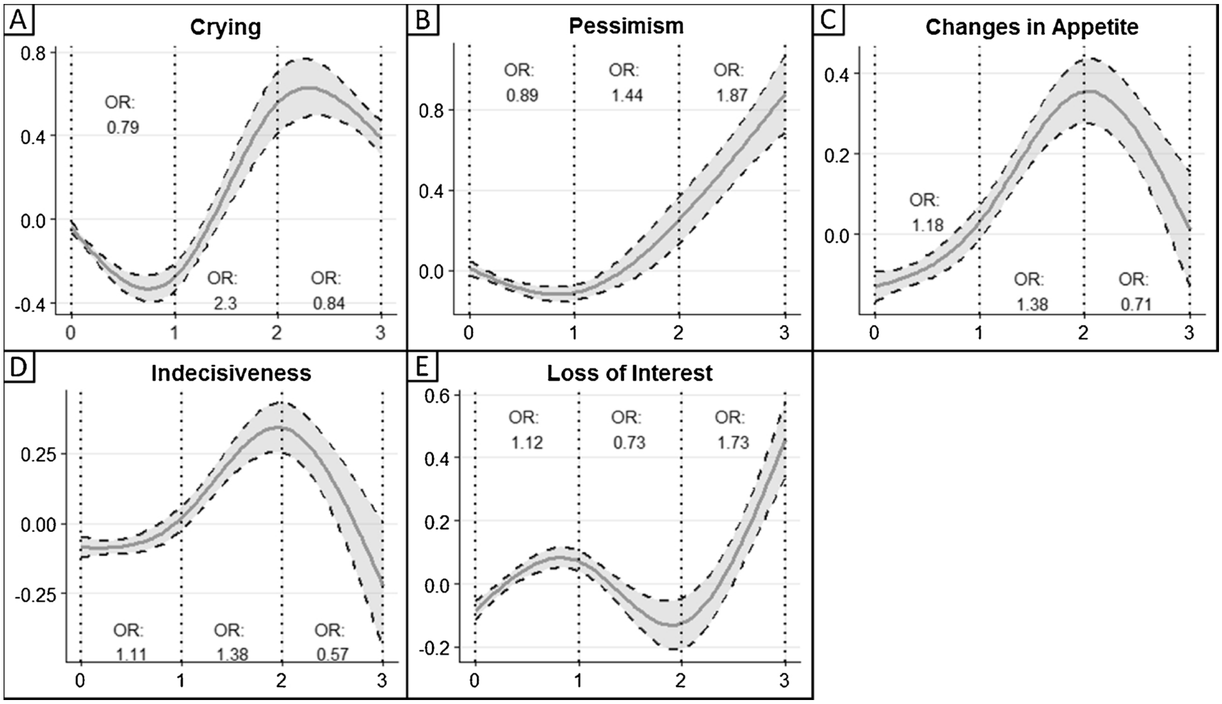

Fig. 1. Strongest Overall Predictors of Cocaine Use. Estimated partial effects of the strongest overall BDI-II items predicting cocaine use **frequency**. Partial effects plots describe the strength of the relationship between item and **frequency** (*y*-axis) across different values of the item (*x*-axis). The fitted line is surrounded by 95% Bayesian credible intervals. Odds ratios for the segments between each two response options are provided within the dotted lines.

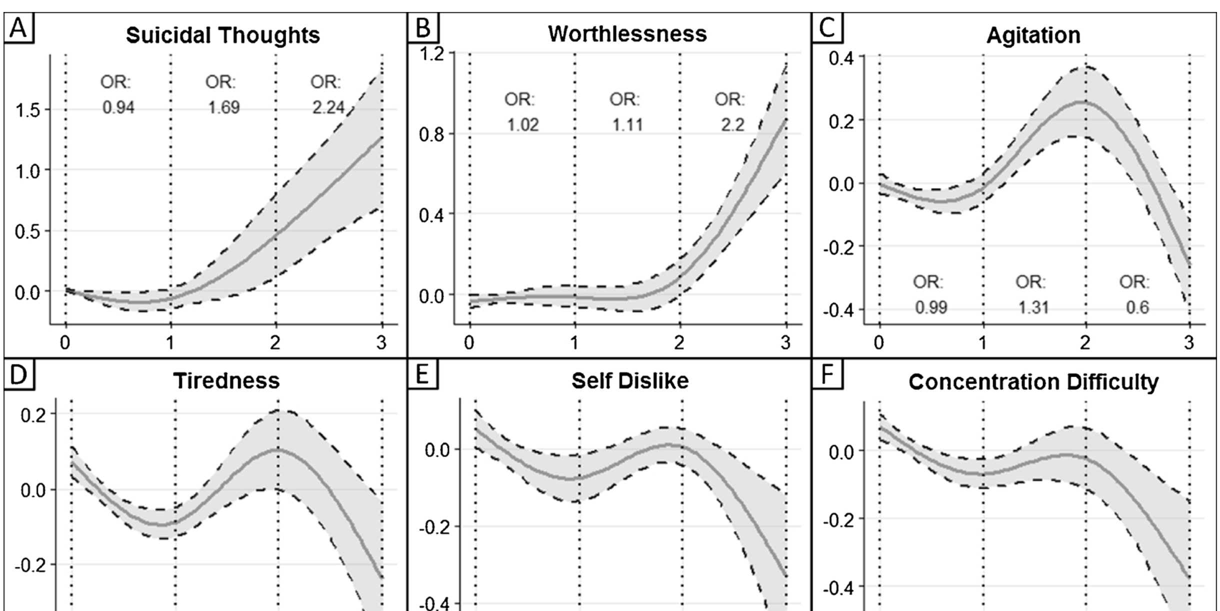

Fig. 2. Additional Strong Local Effects Predicting Cocaine Use. Additional estimated partial effects of BDI-II items predicting cocaine use **frequency**. These items were chosen for having strong local effects that may have been dampened by weak effects elsewhere in the prediction space of the item.

3.5. Supplemental analyses of cocaine dependence diagnosis and severity

Results of these analyses will not be discussed in depth here but are available in Supplementary Material (Models S2 and S3). In general, these models were more conservative, removing 12 predictors each, and did not find some of the more complex (quadratic, cubic) nonlinear relationships as the primary analysis. However, it should be noted that each model supported better fit for the GAM than a corresponding GLM fit to the same outcome, suggesting non-linearity continued to contribute importantly to prediction. Not all predictors identified in the primary model continued to be strong, but of note, crying, self-criticalness, worthlessness, and changes in appetite were generally retained as strong predictors in these other models, suggesting partial convergence.

4. Discussion

4.1. Significance

The present analyses explored the strength and shape of the relationships between cocaine use **frequency** and depressive symptoms. The set of strongest predictors did not conform to a previously hypothesized depression "subtype", as they consisted of Crying, Pessimism, Changes in Appetite, Indecisiveness, and Loss of Interest. Relevant to our hypothesis, although the anhedonia item "Loss of Interest" was a strong predictor of use, the selected top items also included some generally thought of as representing negative mood (e.g., "Crying") and excluded the other anhedonia scale items. The presence of Loss of Interest but absence of other anhedonia scale items could indicate key differences among the anhedonia items on the BDI-II. One possibility is that they differentially represent "pleasure" vs. "motivation," two reward-related functions thought to have separable neural substrates (Berridge et al., 2009). However, this is difficult to conclude based on single items, particularly when little is known about the relationship between these items and underlying reward-related functions. Primarily, this again points out that no previously hypothesized subtypes or subscales captured the most important symptoms for predicting cocaine use frequency.

We also found broad evidence for the importance of nonlinear effects over and above strictly linear effects. These stronger quadratic and cubic effects suggest the response options on the BDI-II deviate from the purported monotonically increasing ordinal scale of the instrument. For example, for the Crying item, we saw a strong positive linear trend between the second and third response options that reversed at the tails. The strongest effect of Crying, related to more severe cocaine use, was found at response option two, "I cry over every little thing." Endorsing the highest response option (three) "I feel like crying, but I can't" may not constitute an increase in magnitude of the construct "crying" as a symptom of depression. These nonlinear relationships have practical consequences for using individual items from this instrument to indicate strength of specific symptoms: higher order response options do not necessarily mean higher level effects. Note that this does not necessarily change the use of summary scores, including total scores and clinical cut-off values, as these have well-demonstrated utility (Dozois et al., 1998). Rather, care should be taken in extrapolating higher BDI-II scores on individual items as necessarily indicating higher levels of a symptom. Future efforts in the use or further development of the BDI-II should investigate nonlinearity across response options.

Interpretation beyond the strongest items focused on the strongest "local" effects for specific response options. Such effects were found in items related to Crying ("I cry over every little thing"), Suicidal Thoughts ("I would kill myself if I had the chance"), Worthlessness ("I feel utterly worthless"), and Pessimism ("I feel my future is hopeless and will only get worse") and Loss of Interest ("I have lost most of my interest in other people or things"). Qualitatively, these strongest individual response options describe emotional volatility and a disregard for the future, particularly in comparison to less-predictive items such as Sadness or Irritability. Interventions designed to target cocaine use may benefit from particular focus on depressive symptoms related to emotional volatility and a foreshortened or constricted perception of the future and world.

4.2. Limitations

Although use of a standard, short depression scale along with reliance on self-reported drug use allowed efficient collection of a large sample and improved ability to model complex effects, this approach also presents some limitations. First, the BDI-II items may not adequately cover all relevant symptoms of depression. Indeed, one previous analysis of multiple depression scales including the BDI-II suggested a higher number of sub-factors than analyses restricted to the BDI-II (Ballard et al., 2018). Inclusion of scales purposely designed to capture anhedonia, or even specific facets of anhedonia such as pleasure vs. motivation (e.g., the Temporal Experience of Pleasure Sacle; Gard et al., 2006) might provide greater clarity about the contribution of this construct. Second, our primary measure of cocaine use severity consisted of self-report of frequency of use in the past 30 days. This measure and timeframe are commonly used to capture use frequency, generally yield greater accuracy than longer periods (e.g., 90 days; McLellan et al., 1992), and have better predictive validity for the clinically important outcome of treatment success than some other measures of severity (Reiber et al., 2002). However, it can only be considered a one-dimensional "snapshot" of severity. Further, although information was collected by a trained interviewer in a situation in which participants had no systematic reason to downplay or exaggerate cocaine use, biochemical verification would be preferable. This is particularly the case as depression might systematically influence reporting of prior drug use through biases in recall (Rotteveel and Phaf, 2007). To partially address these issues, we conducted several supplemental follow-up analyses. First, we repeated our analysis of use frequency in a subsample of patients who submitted at least one biochemically verified positive urine during intake, indicating they had definite cocaine use during the period queried. Results from this subsample were highly similar to the primary findings reported here; however, this still does not fully address the issue with reliance on self-report for the primary outcome. Second, GAM was used in two models to explore the relationships between the BDI-II items in subsamples with available data on the structured clinical interview for DSM-IV (SCID-IV; First et al., 1996) measuring (a) dichotomous cocaine dependence (yes vs. no) and (b) categorical cocaine use severity (mild vs. moderate vs. severe), to explore convergence between our model and these other measures of severity. These models were more conservative, removing 12 predictors each, and did not find as many nonlinear relationships as the primary results reported in this manuscript. This may be because dichotomous cocaine dependence or categorical severity is an extreme coarsening of the same concept tapped by the primary frequency outcome; alternatively, the dichotomous and categorical outcomes may be too different qualitatively from frequency to be directly comparable to the primary outcome. However, it should be noted that each model supported better fit for the GAM than a corresponding GLM fit to the same outcome, continuing to emphasize the importance of non-linearity. Further, some evidence for convergent validity was supported by certain predictors (crying, self-criticalness, worthlessness, and changes in appetite) being retained by each model.

The type of applied data science research using machine learning algorithms undertaken here may also be limited by issues related to overfitting and generalizability. The GAM algorithm utilized by the present study utilized internal mechanisms to minimize overfitting (here, restricted maximum likelihood). However, the ultimate standard of generalizability would be to fit the algorithm to new data. Future research using the BDI-II should test for nonlinear relationships between individual depression items and outcomes using GAM, including the cocaine use outcomes examined here for purposes of replication.

Additionally, the study was cross-sectional, so the direction of influence between cocaine use frequency and depressive symptoms is not clear. Although our interest is in identifying potentially modifiable factors influencing drug use, depressive symptoms could also represent an outcome of more severe use, in the form of withdrawal. The withdrawal syndrome for cocaine features anhedonia and depressive symptoms, so it may have been the case that individuals with more severe use were also more likely to be experiencing withdrawal during the time period reported on by the BDI-II. A separate measure of withdrawal severity/frequency should be included in future research to address this question. There may even be reciprocal causation between cocaine use and depression such that they are related in a self-reinforcing feedback loop. We are not able to disentangle the direction of these effects here. Finally, our sample was a convenience sample of individuals self-referring for treatment, and men and African-Americans were over-represented compared to the general cocaine-using population (Substance Abuse and Mental Health Services Administration (SAMHSA, 2017). Expression of depressive symptoms differs between males and females (Altemus et al., 2014), so examination of sex differences may be particularly important in future work, as specific items may be more or less predictive in the context of different overall reporting patterns.

4.3. Conclusions

This study demonstrates substantial heterogeneity in the extent to which individual symptoms of depression relate to cocaine use frequency, suggesting that the constellation of symptoms associated with depression has a complex relationship with cocaine use. The findings support the use of data science techniques like generalized additive modeling to examine predictors of cocaine use; traditional linear models provided significantly worse fits for the data and would have obscured important non-linear relationships. Further, although aspects of anhedonia (specifically loss of interest in other activities) predicted cocaine use frequency, the items selected did not neatly conform to prior theories about sub-types or scales of depression. This was contrary to our hypothesis that anhedonia scale items would be the most predictive. We tentatively identified a pattern predicting cocaine use in the symptoms related to extreme emotional volatility and a constricted world-view that disregards the future, but this should be considered preliminary, and in need of replication and confirmation. Future research should examine the extent to which these same items predict or covary with treatment outcomes, covary with other measures of anhedonia and mood dysregulation, and ultimately whether treatment targeting these symptoms is more effective than addressing depression generally. Ultimately, the goal is to use data-driven approaches to both identify and efficiently target treatment to the most important modifiable factors associated with cocaine use.

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Contributors

RS, CEG, and MCW conceptualized the study. RS determined the analytic strategy and performed all analyses. MCW provided oversight and direction of the project. RS, JV, and MCW wrote the manuscript. All authors revised and made significant contributions to the manuscript. All authors have approved the final version of the manuscript.

Conflict of interest

No conflict declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2018.10.029.

References

Akaike, H., 1973. Information Theory and an Extension of the Maximum Likelihood Principle. Springer Science and Business Media, New York.
Altemus, M., Sarvaiya, N., Neill Epperson, C., 2014. Sex differences in anxiety and depression clinical perspectives. Front. Neuroendocrinol. 35, 320–330. https://doi.org/10.1016/j.yfrne.2014.05.004.
American Psychiatric Association (APA), 2000. Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision. American Psychiatric Association, Washington, D.C.
Ballard, E.D., Yarrington, J.S., Farmer, C.A., Lener, M.S., Kadriu, B., Lally, N., Williams, D., Machado-Vieira, R., Niciu, M.J., Park, L., Zarate, C.A., 2018. Parsing the heterogeneity of depression: an exploratory factor analysis across commonly used depression rating scales. J. Affect. Disord. 231, 51–57. https://doi.org/10.1016/J.JAD.2018.01.027.
Beck, A.T., Steer, R.A., Brown, G.K., 1996. Manual for the Beck Depression Inventory-II, 2nd ed. Psychological Corporation, San Antonio, TX.
Berridge, K.C., Robinson, T.E., Aldridge, J.W., 2009. Dissecting components of reward: "Liking", "wanting", and learning. Curr. Opin. Pharmacol. 9, 65–73. https://doi.org/10.1016/j.coph.2008.12.014.
Conner, K.R., Pinquart, M., Holbrook, A.P., 2008. Meta-analysis of depression and substance use and impairment among cocaine users. Drug Alcohol Depend. 98, 13–23. https://doi.org/10.1016/j.drugalcdep.2008.05.005.
Davis, C., Fox, J., 2008. Sensitivity to reward and body mass index (BMI): evidence for a non-linear relationship. Appetite 50, 43–49. https://doi.org/10.1016/j.appet.2007.05.007.
Degenhardt, L., Baxter, A.J., Lee, Y.Y., Hall, W., Sara, G.E., Johns, N., Flaxman, A., Whiteford, H.A., Vos, T., 2014. The global epidemiology and burden of psychostimulant dependence: Findings from the Global Burden of Disease Study 2010. Drug Alcohol Depend. 137, 36–47. https://doi.org/10.1016/j.drugalcdep.2013.12.025.
Dozois, D.J.A., Dobson, K.S., Ahnberg, J.L., 1998. A psychometric evaluation of the beck depression Inventory-II. Psychol. Assess. 10, 83–89. https://doi.org/10.1037/1040-3590.10.2.83.
First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B., 1996. Strutured Clinical Interview for DSM-IV Axis I Disorders. Biometrics Research Department, New York.
Ford, J.D., Gelernter, J., DeVoe, J.S., Zhang, W., Weiss, R.D., Brady, K., Farrer, L., Kranzler, H.R., 2009. Association of psychiatric and substance use disorder comorbidity with cocaine dependence severity and treatment utilization in cocaine-dependent individuals. Drug Alcohol Depend. 99, 193–203. https://doi.org/10.1016/j.drugalcdep.2008.07.004.
Gard, D.E., Gard, M.G., Kring, A.M., John, O.P., 2006. Anticipatory and consummatory components of the experience of pleasure: a scale development study. J. Res. Pers. 40, 1086–1102. https://doi.org/10.1016/j.jrp.2005.11.001.
Hastie, T., Tibshirani, R., 1986. Generalized additive models. Stat. Sci. 1, 297–310.
Hastie, T., Tibshirani, R., Friedman, J., 2009. The Elements of Statistical Learning: Data Mining, Inference, and Prediction, second edition. Springer, New York.
Joiner, T.E., Brown, J.S., Metalsky, G.I., 2003. A test of the tripartite model's prediction of anhedonia's specificity to depression: patients with major depression versus patients with schizophrenia. Psychiatry Res. 119, 243–250. https://doi.org/10.1016/S0165-1781(03)00131-8.
Leventhal, A.M., Brightman, M., Ameringer, K.J., Greenberg, J., Mickens, L., Ray, L.A., Sun, P., Sussman, S., 2010. Anhedonia associated with stimulant use and dependence in a population-based sample of American adults. Exp. Clin. Psychopharmacol. 18, 562–569. https://doi.org/10.1037/a0021964.
Leventhal, A.M., Mooney, M.E., DeLaune, K.A., Schmitz, J.M., 2006. Using addiction severity profiles to differentiate cocaine-dependent patients with and without comorbid major depression. Am. J. Addict. 15, 362–369. https://doi.org/10.1080/10550490600860148.
McLellan, A.T., Kushner, H., Metzger, D., Peters, R., Smith, I., Grissom, G., Pettinati, H., Argeriou, M., 1992. The fifth edition of the addiction severity index. J. Subst. Abuse Treat. 9, 199–213. https://doi.org/10.1016/0740-5472(92)90062-S.
McLellan, A.T., Luborsky, L., Woody, G.E., O'Brien, C.P., 1980. An improved diagnostic evaluation instrument for substance abuse patients: the Addiction Severity Index. J. Nerv. Ment. Dis. 168, 26–33.
Pizzagalli, D.A., Jahn, A.L., O'Shea, J.P., 2005. Toward an objective characterization of an anhedonic phenotype: a signal-detection approach. Biol. Psychiatry 57, 319–327. https://doi.org/10.1016/j.biopsych.2004.11.026.
Poling, J., Kosten, T.R., Sofuoglu, M., 2007. Treatment outcome predictors for cocaine dependence. Am. J. Drug Alcohol Abuse 33, 191–206. https://doi.org/10.1080/00952990701199416.
Reiber, C., Ramirez, A., Parent, D., Rawson, R.A., 2002. Predicting treatment success at multiple timepoints in diverse patient populations of cocaine-dependent individuals. Drug Alcohol Depend. 68, 35–48. https://doi.org/10.1016/S0376-8716(02)00103-5.
Rotteveel, M., Phaf, R.H., 2007. Mere exposure in reverse: mood and motion modulate memory bias. Cogn. Emot. 21, 1323–1346.
Rounsaville, B.J., 2004. Treatment of cocaine dependence and depression. Biol. Psychiatry 56, 803–809. https://doi.org/10.1016/j.biopsych.2004.05.009.
Schratz, P., 2017. R Package "oddsratio": Odds Ratio Calculation for GAM(M)s and GLM(M)s, Version 1.0.2.
Seignourel, P.J., Green, C., Schmitz, J.M., 2008. Factor structure and diagnostic efficiency of the BDI-II in treatment-seeking substance users. Drug Alcohol Depend. 93, 271–278. https://doi.org/10.1016/j.drugalcdep.2007.10.016.
Substance Abuse and Mental Health Services Administration (SAMHSA), 2017. Key Substance Use and Mental Health Indicators in the United States: Results From the 2016 National Survey on Drug Use and Health (HHS Publication No. SMA 17-5044,

NSDUH Series H-52). Substance Abuse and Mental Health Services Administration, Rockville, MD, USA.
Treadway, M.T., Zald, D.H., 2011. Reconsidering anhedonia in depression: lessons from translational neuroscience. Neurosci. Biobehav. Rev. 35, 537–555. https://doi.org/10.1016/j.neubiorev.2010.06.006.
Vrieze, E., Demyttenaere, K., Bruffaerts, R., Hermans, D., Pizzagalli, D.A., Sienaert, P., Hompes, T., de Boer, P., Schmidt, M., Claes, S., 2014. Dimensions in major depressive disorder and their relevance for treatment outcome. J. Affect. Disord. 155, 35–41. https://doi.org/10.1016/j.jad.2013.10.020.
Wardle, M.C., Vincent, J.N., Suchting, R., Green, C.E., Lane, S.D., Schmitz, J.M., 2017. Anhedonia is associated with poorer outcomes in contingency management for cocaine use disorder. J. Subst. Abuse Treat. 72, 32–39. https://doi.org/10.1016/j.jsat.2016.08.020.
Wood, S.N., 2017. Generalized Additive Models: an Introduction With R, 2nd edition. Chapman and Hall/CRC, Boca Raton, FL.
Wood, S.N., 2013. On p-values for smooth components of an extended generalized additive model. Biometrika 100, 221–228.
Wood, S.N., 2011. Fast stable restricted maximum likelihood and marginal likelihood estimation of semiparametric generalized linear models. J. R. Stat. Soc. Ser. B 73, 3–36.