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Neural responses to negative outcomes predict success in community-based substance use treatment

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ABSTRACT

Background and aims Patterns of brain activation have demonstrated promise as prognostic indicators in substance dependent individuals (SDIs) but have not yet been explored in SDIs typical of community-based treatment settings. **Design** Prospective clinical outcome design, evaluating baseline functional magnetic resonance imaging data from the Balloon Analogue Risk Task (BART) as a predictor of 3-month substance use treatment outcomes. **Setting** Community-based substance use programs in Bloomington, Indiana, USA. **Participants** Twenty-three SDIs (17 male, aged 18–43 years) in an intensive outpatient or residential treatment program; abstinent 1–4 weeks at baseline. **Measurements** Event-related brain response, BART performance and self-report scores at treatment onset, substance use outcome measure (based on days of use). **Findings** Using voxel-level predictive modeling and leave-one-out cross-validation, an elevated response to unexpected negative feedback in bilateral amygdala and anterior hippocampus (Amyg/aHipp) at baseline successfully predicted greater substance use during the 3-month study interval ($P \leq 0.006$, cluster-corrected). This effect was robust to inclusion of significant non-brain-based covariates. A larger response to negative feedback in bilateral Amyg/aHipp was also associated with faster reward-seeking responses after negative feedback ($r_{(23)} = -0.544$, $P = 0.007$; $r_{(23)} = -0.588$, $P = 0.003$). A model including Amyg/aHipp activation, faster reward-seeking after negative feedback and significant self-report scores accounted for 45% of the variance in substance use outcomes in our sample. **Conclusions** An elevated response to unexpected negative feedback in bilateral amygdala and anterior hippocampus (Amyg/aHipp) appears to predict relapse to substance use in people attending community-based treatment.

Keywords Amygdala, Balloon Analogue Risk Task, fMRI, naturalistic samples, negative feedback, prediction, relapse, stress reactivity, substance use disorders, treatment outcome.

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INTRODUCTION

The majority of substance-dependent individuals (SDIs) resume use within 2 years of treatment [1,2] and as few as 4% achieve continuous abstinence [3]. Recovery from substance use disorders (SUDs) involves a complex interaction between intrinsic and extrinsic factors, including motivation, social environment and capacity for balanced decision-making—which vary across individuals and over time [4]. As demographic, psychosocial, clinical and cognitive–behavioral predictors have demonstrated limited utility [5], attention has turned increasingly to brain-based 'neuromarkers' of relapse risk [6].

Alterations in brain function underlie compulsive use (e.g. incentive sensitization of drug cues) and failures of self-control [7] and these may serve as prognostic indicators in SDIs. For example, aberrant activation (e.g. hyperactivation of reward and sensory processing areas) to substance-related [8–15] and non-substance-related reward cues [16–20] has been associated with earlier and/or more likely relapse, as has impaired control-related processing during risky [21] or probabilistic decision-making [18,19,22] and other control-demanding tasks [13,23–27].

In line with models of stress-induced relapse [28,29], relapse risk also increases with ventromedial prefrontal cortex/anterior cingulate cortex (vmPFC/ACC) hyperactivation during relaxation and hypoactivation during stress [30,31], as well as reduced functional connectivity between vmPFC/ACC and amygdala, which may reflect

impaired stress and affect regulation [32]. Risk-related structural abnormalities within prefrontal control areas [8,15,33–36] and the amygdala [8,15,33,34,37], are also consistent with this account.

Relapse-related neuromarkers have contributed to enthusiasm for neuroimaging to enhance clinical assessment and inform personalized treatment [6]. Several studies have demonstrated that brain-based measures outperform subjective self-reports and other traditional clinical indicators [12,13,21,25,26,31,32]. However, as was identified recently by Whelan & Garavan [38], many studies fail to correct for statistical optimism when assessing brain-based predictors and may not generalize. This may be particularly problematic in studies of substance use relapse, which have focused generally on a single SUD and excluded comorbid conditions, already limiting generalizability to real-world treatment settings.

SUDs co-occur commonly with internalizing psychopathology, which has also been associated with abnormal reward-processing and stress-reactivity [39,40]. Relapse prediction based on naturalistic samples (i.e. including comorbid SUD and internalizing disorders) may thus reflect transdiagnostic constructs relevant to chronicity. Dysfunction of negative valence systems underlying threat and stress-reactivity, for example, may increase vulnerability to internalizing disorders [40–42] and substance use compounds this effect [43]. However, SUDs and internalizing comorbidities may also act in opposition; for example, with the former decreasing and the latter increasing error signaling [44]. It is therefore possible that neural predictors from SUD samples without comorbidity will not effectively translate for clinical use.

The current study represents a first step toward addressing this issue by exploring neural predictors of relapse in a heterogeneous sample of SDIs, typical of community-based treatment settings. We used a Balloon Analogue Risk Task (BART) that concurrently measures several predictive domains (i.e. risky decision-making, reward/negative outcome processing), uses monetary incentives rather than substance-specific stimuli and has ecological validity [45]. Fast event-related imaging further allowed differentiation of decision-making and outcome evaluation phases of the BART [46]. Non-brain-based measures were also assessed, against which the predictive utility of brain-based measures could be evaluated. Despite including a mixed SUD sample with representative comorbidity, we hypothesized that previous findings of increased relapse risk with impaired error signaling in ACC [25] would replicate for negative outcomes in the BART and extend to risk-related signaling during decision-making. Due to our novel use of a community-based sample, we additionally conducted data-driven, exploratory analyses of corticolimbic circuitry to inform future work.

METHODS

Design

We utilized a prospective clinical outcome design. Neuroimaging, cognitive–behavioral and self-report measures were collected at the beginning of treatment and examined as candidate predictors of 3-month substance use outcomes.

Participants

Twenty-six SDIs were enrolled upon engagement with community-based treatment and assessed within 1–4 weeks of self-reported abstinence; a sample of 23 (aged 18–43 years) was followed for 3 months (see Table 1 for demographic and recruitment data). Participants received treatment-as-usual through one of two abstinence-oriented, community-based addiction treatment programs (one intensive outpatient and one residential program; see Supporting information for additional details) and were not receiving replacement pharmacotherapy. All met DSM-IV criteria for alcohol, drug or polysubstance dependence, without history of traumatic brain injury, neurocognitive disorders, bipolar or psychotic illness. An electronic breathalyzer and six-panel urine drug screen were conducted at baseline and 3-month follow-up; behavioral signs of intoxication were also evaluated. Assessments were conducted only if blood alcohol content was 0.000% by volume, urinalysis was negative for illicit substances and behavioral signs of intoxication were absent. Participants provided written informed consent; all methods were approved by the Indiana University Institutional Review Board.

Functional magnetic resonance imaging (fMRI) acquisition and BART procedure

Imaging data were acquired at baseline and 3-month follow-up using a 32-channel head coil-equipped, Siemens Magnetom Trio 3-Tesla MRI scanner; follow-up data are reported elsewhere [47]. Echo-planar gradient-echo $T2^*$-weighted sequences of 240 whole-brain volumes measured the functional blood-oxygen-level-dependent (BOLD) response during two 8-minute blocks of BART (see Fig. 1). Acquisition, task and pre-processing parameters were identical to previous work [46,48]; details provided in Supporting information. In brief, the BART involved button-press responses to either 'Inflate' a balloon—incrementally and quasi-exponentially increasing its size and value in parallel with the probability of explosion—or 'Redeem' it for its current value. Stimuli were presented using E-Prime (Psychology Software Tools, Pittsburgh, PA, USA); a projector was used for display within the scanner bore. Trials began with an image of a balloon. A red rectangle

Table 1 Summary of demographic, recruitment and clinical characteristics of study sample (n = 23).

Demographic variables[a]		*Mean (SD) or count*
Age		27 (6.5)
Male		17
Total years of education		13 (1.8)
Employment status	Employed full time	6
	Employed part time	6
	Unemployed	9
	Student	2
Recruitment information		*Count*
Treatment setting	Outpatient	14
	Residential	9
Referral source	Self	13
	Drug court	5
	Probation	5
Clinical variables		*Mean (SD) or count*
Times in previous treatment		2 (2.4)
Primary DSM-IV diagnosis	Alcohol dependence	13
	Sedative, hypnotic or anxiolytic dependence	1
	Cannabis dependence	1
	Amphetamine dependence	1
	Opioid dependence	3
	Polysubstance dependence	4
Additional psychiatric diagnoses	Major depressive disorder	4
	Dysthymic disorder	1
	Generalized anxiety disorder	4
	Post-traumatic stress disorder	1
	Anxiety disorder NOS	2
	Antisocial personality disorder	1
	None	7
Substance use outcomes		*Mean (SD)*
	Substance use metric	0.64 (0.12)
	% Days of use	12.8 (24.2)
	% Days use to intoxication	9.6 (16.0)

[a]The substance use metric (SUM) did not correlate with demographic factors, age ($r_{(23)} = -0.171$, $P = 0.435$) and years of education ($r_{(23)} = -0.332$, $P = 0.122$), and did not differ significantly with respect to sex ($t_{(22)} = 2.08$, $P = 0.222$) or employment status ($F_{(3,19)} = 0.67$, $P = 0.581$). SD = standard deviation; NOS = not otherwise specified.

was presented for 1.5–2.5 seconds, indicating to wait before responding and subsequently turning green, indicating to respond when ready. Participants responded with left or right index fingers (response-mapping counterbalanced across subjects).

Each balloon sequence began with a balloon worth $0.00. After each response, a jittered delay of 0–6 seconds preceded feedback ('Successful_Gamble', 'Explode', 'Confirmed_Gain') such that the BOLD response could be estimated separately for decision and outcome intervals. 'Inflate' responses could result in either (1) a 'Successful_Gamble', whereupon the display was updated with a larger balloon and increased wager value, initiating the next decision, or (2) 'Explode' feedback, indicating loss of the current wager. 'Redeem' responses always resulted in 'Confirmed_Gain' feedback and addition of the balloon value to block winnings (visible at bottom of screen). Participants completed an average of 95 decision trials and 16 balloon sequences per block.

Additional measures

The time-line follow-back procedure was administered at 1-, 2- and 3-month time-points to document drug and alcohol use during the study interval. Narrative details of use (e.g. subjective intoxication) were also acquired. Details of the time-line follow-back procedure, as well as psychodiagnostic, self-report and cognitive–behavioral assessments are provided in Supporting information.

fMRI analysis

Imaging data were analyzed using SPM5 and Matlab R2013a. BART BOLD responses were estimated using a

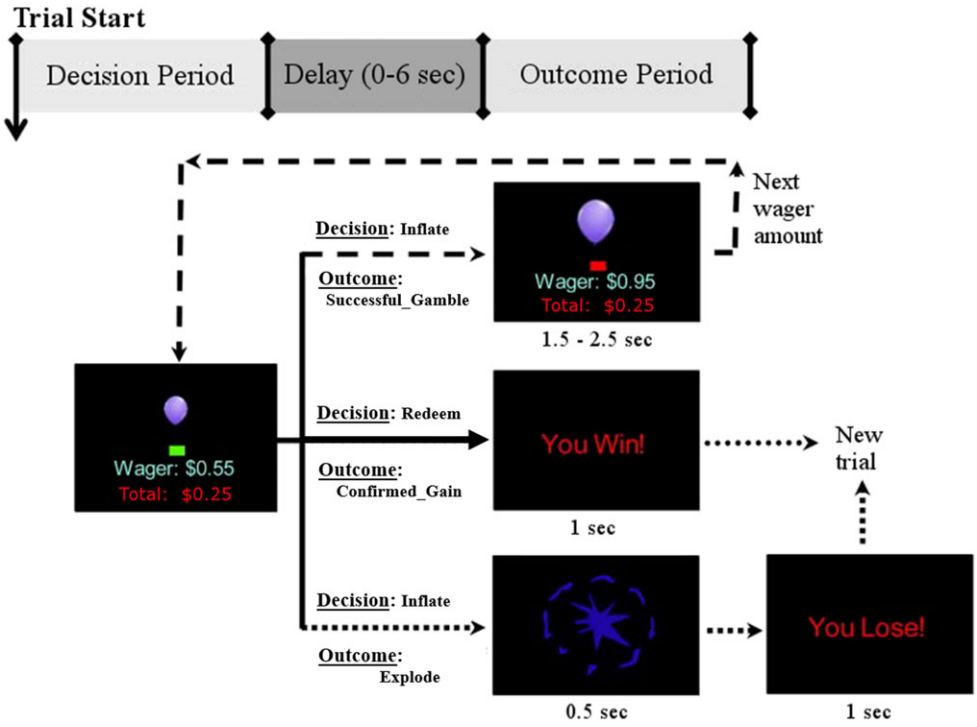

Figure 1 Schematic representation of the Balloon Analogue Risk Task (BART), reproduced with permission from Fukunaga *et al.* [46] [Colour figure can be viewed at wileyonlinelibrary.com]

general linear model with 20 regressors: six motion regressors, two constants, five main effect regressors ('Redeem', 'Inflate', 'Explode', 'Successful_Gamble', 'Confirmed_Gain'), five parametric modulators representing explosion probability for each event and 2 parametric modulators representing 'Redeem' and 'Inflate' response times (RTs). A canonical hemodynamic response function was used to model event-related signals during decision (i.e. RT) and outcome (i.e. feedback onset) intervals. Subject was included as a random effect at the second-level.

Contrasts isolated the effects associated with negative outcomes over uncertain ('Explode—Successful_Gamble') and certain gains ('Explode—Confirmed_Gain'), decisions to pursue uncertain gains ('Inflate—Redeem') and decisions to pursue certain gains ('Redeem—Inflate'), as well as regions in which trial-to-trial fluctuations in BOLD signal correlated with the probability of explosion [i.e. parametric modulators, designated by '*p(Explode)']. Using a cluster-forming threshold of $P < 0.001$, clusters of 30 or more voxels with a cluster-corrected P-value of < 0.05 were identified as regions of interest (ROIs). The cluster-extent threshold was determined using AFNI's 3dClustSim to provide a type I error rate of $\alpha = 0.005$. Two participants were excluded from the second-level 'Explode*p(Explode)' contrast, because low explosion frequency precluded unique specification in the first-level general linear model.

Whole-brain correlational analyses were conducted for each contrast to identify regions in which task-related activity was associated with substance use during the study interval. A substance use metric (SUM) was calculated from time-line follow-back data for each participant, representing incidents of drug and alcohol use during the study, weighted by presence/absence of intoxication[1]; a log-odds transformation was applied prior to analysis. This approach was chosen to more effectively capture variability in substance use outcomes within the study sample (see Supporting information). Next, voxel-level predictive modeling and leave-one-out cross-validation were used to identify ROIs predictive of substance use outcomes and compare performance of models based on brain- and/or non-brain-based predictors (see Supporting information for details). Briefly, linear regression was applied with cross-validation on a voxel × voxel basis. Clusters wherein constituent voxels yielded predicted SUM values for left-out participants that correlated strongly with actual SUM values were targeted for further investigation. Leave-one-out cross-validation was selected for optimism-correction because this approach has been recommended for small neuroimaging data sets [49] and used in similar work with a comparable sample size [16]. Predictive analysis of binary treatment outcomes was also conducted using receiver operating characteristic (ROC) curves and is described in Supporting information and Figure S1.

[1](Total days monitored/4) × [days alcohol used without intoxication + (2 × days alcohol used with intoxication) + days drugs used without intoxication + (2 × days drugs used with intoxication)].

Analysis of cognitive–behavioral and self-report measures

Pearson's correlations with the substance use outcome variable (i.e. SUM) were calculated for each measure. Paired *t*-tests and repeated-measures analysis of variance (ANOVA) were utilized for comparisons between conditions, as necessary. Statistics were computed in SPSS. Self-report and behavioral findings for cognitive–behavioral tasks other than BART are summarized in Supporting information and Table S1.

RESULTS

BART performance

BART performance is summarized in Table 2. Consistent with successful performance, average winnings were $16 per block, 'Confirmed_Gains' occurred more often than 'Explode' events and the average number of inflations prior to 'Redeem'/'Confirmed_Gain' events was higher than that for 'Explode' outcomes. The number of completed balloons, proportion of balloons ending in 'Confirmed_Gain' versus 'Explode' and number of inflations did not differ significantly between blocks. There were no significant effects of block or response type on RT. A higher number of inflations prior to 'Redeem' responses was associated with increased substance use during the study interval; this effect was significant at $P = 0.046$, two-tailed, ($r_{(23)} = 0.42$). Average RT did not correlate significantly with SUM ($r_{(23)} = -0.23$, $P = 0.291$).

Neural prediction of relapse risk

Basic event-related and parametric modulator contrasts are described in Supporting information and Tables S2a–c. Whole-brain correlational analyses between planned contrasts and SUM values are summarized in Table 3. Contrary to our hypotheses, an elevated response to negative feedback ('Explode—Confirmed_Gain') in the right supplementary motor area (SMA), left dorsal posterior cingulate and a region including right amygdala and anterior hippocampus (Amyg/aHipp) was associated with greater use, as was an increased BOLD response with increasing explosion probability in midline SMA during 'Inflate' events [i.e. Inflate*p(Explode)]. A similar effect was observed in the left angular gyrus and putamen for 'Successful_Gamble*p (Explode)' and in the right insula and left SMA for 'Explode*p(Explode)'. Greater 'Redeem—Inflate' activation in the left inferior frontal gyrus (IFG) was associated with less use.

Given our modest sample size, correlational findings may not have external validity (see [38]). To address this, leave-one-out cross-validation was used to test outcome prediction by event-related brain signals on a voxel × voxel basis. Only two contrasts ('Explode—Confirmed_Gain' and 'Explode—Successful_Gamble') revealed regions of 30 or more voxels in which predicted outcomes for left-out participants correlated strongly with actual SUM values ($r \geq 0.70$) and survived cluster-level correction. For both contrasts, peak model performance (indicated by the strongest correlation between actual and predicted values) was identified in bilateral Amyg/aHipp (see Table 3, Fig. 2). It is noted that the 'Explode—Successful_Gamble' right Amyg/aHipp cluster was 29 voxels, just below our conservative, a priori threshold.

To investigate further these significant clusters, spherical ROIs (radius = 1 voxel; volume = 7 voxels) were defined around voxels associated with peak model performance in bilateral Amyg/aHipp and leave-one-out cross-validation was repeated following addition of non-brain-based measures that correlated significantly with SUM (specifically, DOSPERT expected benefit scores), as well as a 'null' model including only non-brain-based covariates (NM1). Mean Akaike information criterion (AIC) values for each model and ROI are summarized in Table 4. Model comparison

Table 2 Summary of Balloon Analogue Risk Task (BART) behavioral performance measures ($n = 23$).

		Confirmed_Gain	*Explode*	*All*	*Confirmed_Gain versus Explode t-value* (*P-value*)
No. of balloons		21 (5.4)	11.7 (4)	32.7 (3.1)	4.78 (< 0.001)
Inflation count	Mean (SD)	6.3 (0.7)	5.2 (0.6)	5.9 (0.5)	9.77 (< 0.001)
	Range	2–10	2–9	2–10	NA
	Within-subject SD	1.0	1.3	1.3	NA
		Redeem	*Inflate*	*All*	*F-value* (*P-value*)
Response time (ms)	Mean (SD)	1018 (732)	1044 (445)	1037 (463)	NA
				Main effect: block	1.55 (0.226)
				Main effect: response type	0.08 (0.782)
				Block × response type interaction	1.90 (0.182)

SD = standard deviation; NA = not applicable.

Table 3 Regions of interest from whole-brain correlation analysis of substance use outcomes and leave-one-out cross-validation analysis.

Negative correlation: greater activation associated with less use			*Peak MNI coordinates*				
Contrast	*Region*	*Size*	*x*	*y*	*z*	*t-Value*	*P-value (cluster- corrected)*
Redeem—Inflate	L inferior frontal gyrus (BA 45/47)	105	–46	24	8	5.23	0.019
Explode—Successful_Gamble	NA	–	–	–	–	–	–
Explode—Confirmed_Gain	NA	–	–	–	–	–	–
Redeem*p(Explode)	NA	–	–	–	–	–	–
Inflate*p(Explode)	NA	–	–	–	–	–	–
Explode*p(Explode)	NA	–	–	–	–	–	–
Successful_Gamble*p(Explode)	NA	–	–	–	–	–	–
Confirmed_Gain*p(Explode)	NA	–	–	–	–	–	–
Positive correlation: greater activation associated with more use			*Peak MNI coordinates*				
Contrast	*Region*	*Size*	*x*	*y*	*z*	*t-Value*	*P–value (cluster-corrected)*
Redeem—Inflate	NA	–	–	–	–	–	–
Explode—Successful_Gamble	NA	–	–	–	–	–	–
Explode—Confirmed_Gain	R supplementary motor area (BA 6)	222	14	–26	62	5.55	< 0.001
	R amygdala/anterior hippocampus	341	34	–22	–16	5.54	< 0.001
	L dorsal posterior cingulate (subgyral)	148	–24	–30	46	5.37	0.001
Redeem*p(Explode)	NA	–	–	–	–	–	–
Inflate*p(Explode)	L/R supplementary motor area (BA 6)	132	–8	0	68	5.61	0.003
Explode*(Explode)	R insula (BA 13)	56	36	4	12	4.41	0.042
	L supplementary motor area (BA 6)	74	–12	–12	60	3.91	0.010
Successful_Gamble*(Explode)	L angular gyrus (BA 39)	149	–40	–82	30	5.90	0.001
	L putamen	83	–26	10	–4	3.78	0.028
Confirmed_Gain*p(Explode)	NA	–	–	–	–	–	–
Leave-one-out cross-validation analysis			*Peak MNI coordinates*				
		Size	*x*	*y*	*z*	*Mean r-value*[a]	*P-value (cluster–corrected)*
Explode—Successful_Gamble	L amygdala/anterior hippocampus	38	–34	–4	–22	0.77	< 0.001
	R amygdala/anterior hippocampus	29	34	–20	–16	0.78	0.006
Explode—Confirmed_Gain	L amygdala/anterior hippocampus	38	–34	–8	–26	0.80	< 0.001
	R amygdala/anterior hippocampus	33	38	–16	–16	0.80	0.002

[a]Reported *r*-values reflect the mean of voxel-level correlation coefficients for each cluster, representing the relationship between actual and predicted SUM values for the left-out participant. Correlation coefficients are provided as descriptive rather than inferential statistics and corresponding *P*-values are omitted. Reported *P*-values reflect whole-brain cluster-level correction to account for multiple comparisons. MNI = Montreal Neurological Institute; SUM = substance use metric; NA = not applicable.

was conducted separately for each ROI; multiple brain-based predictors were not included in the same model due to collinearity concerns. Left and right 'Explode—Successful_Gamble' ROIs and the right 'Explode—Confirmed_Gain' ROI passed the model comparison test, each demonstrating a reduction in AIC following addition of the voxel-based predictor. A second null model (NM2) added covariates with $P \leq 0.125$ (i.e. DOSPERT risk perception and Go/No-Go performance) and intuitive clinical indicators (i.e. craving scores, SUD symptom counts). Here, addition of the voxel-based predictor increased AIC (see Table 4), indicating that the brain-based measure was not supported with this expanded set of non-brain-based covariates.

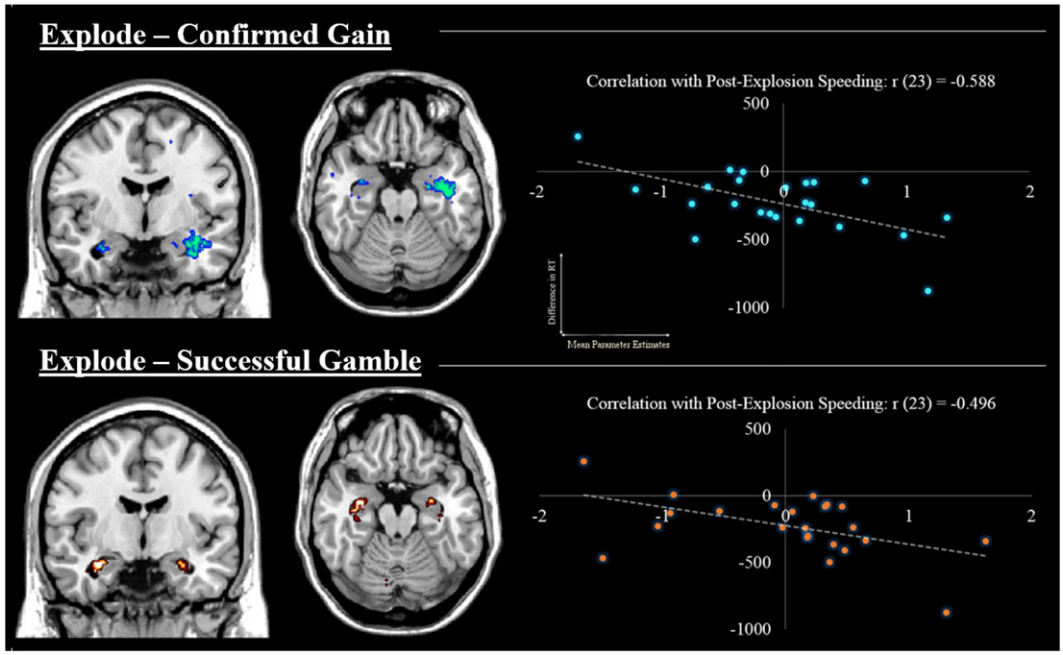

Figure 2 Correlation between the blood-oxygen-level-dependent (BOLD) response to negative feedback in predictive regions identified through leave-one-out cross-validation analysis and the post-explosion speeding effect. Regions of interest (ROIs) identified in the leave-one-out cross-validation analysis for both contrasts include voxels in left and right amygdala and anterior hippocampus. Scatterplots depict mean BOLD response within spherical ROIs (radius = 1 voxel) defined around the maximally predictive voxel for each contrast (38, −16, −16 for 'Explode—Confirmed_Gain' and −34, −4, −22 for 'Explode—Successful_Gamble') versus post-explosion speeding (i.e. Post-Explosion RT—Post-Confirmed_Gain RT). Mean BOLD responses in left and right Amyg/aHipp ROIs for the 'Explode—Confirmed_Gain' contrast correlated significantly with post-explosion speeding ($r_{(23)} = -0.544$, $P = 0.007$ and $r_{(23)} = -0.588$, $P = 0.003$, respectively), indicating that a stronger response to negative feedback was associated with a greater reduction in post-explosion response time (RT). The left ROI for the 'Explode—Successful_Gamble' contrast also correlated significantly with post-explosion speeding ($r_{(23)} = -0.496$, $P = 0.016$) but the right ROI did not ($r_{(23)} = -0.345$, $P = 0.107$) [Colour figure can be viewed at wileyonlinelibrary.com]

Behavioral correlates of predictive activation

Although not predicted in our original hypotheses, identification of Amyg/aHipp-based predictive signals may be consistent with the amygdala's putative role in stress-induced reinstatement of drug-seeking [28]. If unexpected negative feedback (i.e. stress) increased reward-seeking in the current paradigm, it may be evident in faster inflation responses following 'Explode' versus 'Confirmed_Gain' events. To explore this possibility, the difference in initial inflation RT between post-Explode and post-Confirmed_Gain events was calculated for each participant ([mean = −229 ms, standard deviation (SD) = 225] and correlated significantly with SUM, such that greater post-explosion speeding corresponded with increased use ($r_{(23)} = -0.537$, $P = 0.008$). In addition, a significant negative correlation between BOLD signal change and post-explosion speeding (i.e. greater activation during 'Explode' events associated with faster post-explosion RTs) was identified in three of four Amyg/aHipp ROIs (see Fig. 2).

Leave-one-out cross-validation was again repeated with post-explosion speeding added as a significant non-brain-based covariate (NM3). Resulting AICs were lower for the null model in all four ROIs (see Table 3) but approached zero for both ROIs in right Amyg/aHipp, suggesting that improved model performance with addition of the voxel-based predictor was nearly sufficient to justify increased model complexity. For right Amyg/aHipp ROIs, the full model accounted for 45.2 and 45% of variance in substance use outcomes for 'Explode—Confirmed_Gain' and 'Explode—Successful_Gamble' contrasts, respectively. Equations for these models are provided in Supporting information.

DISCUSSION

This study extends previous findings that brain-based measures outperform non-brain-based measures (e.g. clinical indicators, self-reports, etc.) in predicting substance use treatment outcomes by demonstrating this effect in a mixed sample of SDIs, generally representative of community-based treatment settings with respect to psychiatric and substance use comorbidities. While our initial hypotheses were not supported, voxel × voxel predictive modeling specifically revealed a bilateral effect in Amyg/aHipp for negative feedback contrasts, wherein an elevated Amyg/aHipp response was associated with increased use during early recovery. This effect

Table 4 Summary of predictive model performance in peak regions of interest (ROIs) identified through leave-one-out cross-validation analysis (n = 23).

					Null model		*Voxel only model*			*Voxel model with covariates*		
							Voxel model r-value[a]					
Voxel model comparison	*Contrast*	*Peak MNI coordinates*			*AIC*	R^2	*Peak voxel*	*ROI Mean*	*Mean* R^2	*Mean AIC*	*Mean AIC Diff*[b]	*Mean* R^c
NM1: model with significant covariates	Explode—Confirmed_Gain	−34	−8	−26	44.09	0.141	0.93	0.81	0.116	46.78	−2.69	0.113
	Explode—Confirmed_Gain	38	−16	−16	44.09	0.141	0.96	0.80	0.226	42.13	1.96	0.306
	Explode—Successful_Gamble	−34	−4	−22	44.09	0.141	0.92	0.75	0.287	40.59	3.50	0.370
	Explode—Successful_Gamble	34	−20	−16	44.09	0.141	0.88	0.64	0.368	41.11	2.98	0.349
NM2: model with significant and trending covariates + clinical indices	Explode—Confirmed_Gain	−34	−8	−26	52.04	0.144	0.93	0.81	0.116	58.50	−6.46	−0.042
	Explode—Confirmed_Gain	38	−16	−16	52.04	0.144	0.96	0.80	0.226	56.73	−4.69	0.032
	Explode—Successful_Gamble	−34	−4	−22	52.04	0.144	0.92	0.75	0.287	54.63	−2.59	0.119
	Explode—Successful_Gamble	34	−20	−16	52.04	0.144	0.88	0.64	0.368	53.57	−1.53	0.163
NM3: model with significant covariates + post-explosion speeding	Explode—Confirmed_Gain	−34	−8	−26	40.10	0.390	0.93	0.81	0.116	43.68	−3.58	0.325
	Explode—Confirmed_Gain	38	−16	−16	40.10	0.390	0.96	0.80	0.226	40.63	−0.53	0.452
	Explode—Successful_Gamble	−34	−4	−22	40.10	0.390	0.92	0.75	0.287	41.21	−1.11	0.427
	Explode—Successful_Gamble	34	−20	−16	40.10	0.390	0.88	0.64	0.368	40.67	−0.57	0.450

[a]Reported r-values represent the correlation between actual and predicted SUM values for the left-out participant. [b]A positive mean AIC diff indicates that the addition of a voxel-based predictor was preferred despite constraints to limit model complexity. [c]$R^2 = 1 - (SSE_{Residual}/SSE_{Total})$, where $SSE_{Residual}$ reflects the sum of squared differences between actual and predicted values for each left-out participant and SSE_{Total} reflects the sum of squared differences between actual values for each left-out participant and the average of all actual values. Given our leave-one-out cross validation approach, a reduced (or negative) R^2 for the full model reflects overfitting on the basis of training data, which can worsen performance on the independent test set. MNI = Montreal Neurological Institute; SUM = substance use metric; AIC = Akaike information criterion; SSE = sum of squared errors of prediction.

corresponded with faster inflation responses following negative feedback, possibly reflecting increased reward-seeking in response to negative affect, as predicted by models of stress-induced relapse.

Importantly, the consistency of observations between 'Explode—Confirmed_Gain' and 'Explode—Successful_Gamble' contrasts suggests that the identified effect is associated with negative feedback processing and is not a consequence of differing feedback certainty in 'Explode' versus 'Confirmed_Gain' conditions. However, our findings require replication, and effects of uncertainty versus negative valence should be examined directly in future work. Taken together, a predictive model including right Amyg/aHipp response to negative feedback (from either contrast), the behavioral post-explosion speeding effect and DOSPERT expected benefits scores accounted for approximately 45% of variance in substance use outcomes in our sample. These results support the utility of multi-modal predictive models (including neural, behavioral and self-report measures) to assess relapse vulnerability in community-based treatment settings.

Consistent with our findings, abnormality of the amygdala and hippocampus has been reported widely in SDIs. Reduced amygdalar and hippocampal volumes have been noted in SDIs [33,34,37], and smaller amygdalae have been associated with increased craving and relapse severity [34,37]. Hyperactivation of the amygdala and hippocampus in SDIs has also been observed in response to stress [31] and substance-related cues [31,50] and increased resting cerebral blood flow to posterior hippocampus has been associated with greater relapse risk [51,52]. Amygdala activation has similarly been associated with poorer treatment outcomes [17], as well as increased cue-induced craving [50,53–57]. Importantly, the amygdala is integral to the aversive experience of monetary loss [58], as well as negative affect more generally [59], suggesting that a stronger experience of negative outcomes may contribute to greater substance use in the current study.

The amygdala has been implicated similarly in animal models of stress-induced relapse [28,29] and in the 'frustration effect', wherein response speed increases following reward omission [60,61]. With respect to the latter, a similar effect (i.e. increased inflation speed following explosions) was correlated significantly with both substance use outcomes and activation of Amyg/aHipp ROIs in the current study. Behaviorally, this phenomenon is similar to 'loss-chasing' in pathological gamblers [62,63], which has also been linked to amygdala in animal models [64]. Gambling disorder was not assessed herein, but is commonly comorbid with SUDs and may share similar neurobiological substrates [65].

Amygdala has been implicated further in individual differences in risky reward-seeking by the triadic model of motivated behavior [66], wherein different neurodevelopmental trajectories of the striatal approach system, amygdala-based avoidance system and prefrontal control system underlie cognitive–behavioral changes during adolescence. In line with predictions of this model, problematic alcohol use has been associated with a striatal–amygdalar imbalance, precipitating alcohol use disorder when relative amygdalar hyperactivity is potentiated by stress [67]. Consistent with current findings, stress has also been shown to increase functional connectivity between the amygdala and dorsal striatum which may drive a shift towards faster, more impulsive responding [68]. However, while a greater dorsal striatal 'Successful_Gamble*p(Explode)' signal correlated positively with substance use in the current study, neither ventral nor dorsal striatal ROIs were identified by voxel-wise predictive modeling.

Taken together, the current results add to converging evidence in support of amygdala-based models of stress-induced relapse. Susceptibility to stress-induced relapse is state-dependent, making it challenging to characterize through conventional psychometric approaches. A reliable brain-based predictor of stress-induced relapse would have a significant translational impact, but has not been described previously for a naturalistic sample wherein vulnerability to relapse is shaped, in part, by psychiatric comorbidity. Recent evidence suggests that amygdala reactivity predicts a fundamental vulnerability to life stress that may predispose individuals to internalizing disorders [40], as well as SUDs. In effect, previous exclusion of comorbid presentations may have precluded identification of amygdala-based neuroprognostic indicators. However, by extension, the current findings may not generalize to those with unimorbid SUDs.

Importantly, neural predictors may also inform development of novel interventions and individualized treatment approaches [5,69,70]. Antagonism of corticotropin-releasing factor (CRF) may dampen the stress response in the hypothalamic–pituitary–adrenal axis and amygdala and has been shown to attenuate stress-induced relapse in rats [71]. Evidence-based cognitive–behavioral interventions may also prevent relapse by altering neural pathways associated with stress responsivity and negative affect [72]. In addition, interventions that up-regulate dorsolateral prefrontal cortex (dlPFC) function (e.g. cognitive reappraisal [73], repetitive transcranial magnetic stimulation (rTMS) [74] and transcranial direct current stimulation [75]) may improve regulation of amygdala reactivity [76]. Indeed, rTMS over left dlPFC has been shown to reduce subjective craving and improve control of compulsive substance use [77].

To our knowledge, this is the first study to utilize cross-validation of voxel-wise predictive modeling with a continuous substance use outcome variable. This method uniquely identified ROIs in bilateral Amyg/aHipp

associated with negative feedback. By comparison, whole-brain correlation analyses identified several additional predictive clusters and only a single ROI in right Amyg/aHipp for 'Explode—Confirmed_Gain'. Small volume correction for bilateral amygdala and hippocampus was sufficient to identify clusters approaching cluster-corrected significance in left Amyg/aHipp for both 'Explode—Confirmed_Gain' ($x = -34$, $y = -20$, $z = -18$; cluster size: 18; $t_{(21)} = 4.30$, $P = 0.057$) and 'Explode—Successful_Gamble' ($x = -32$, $y = -4$, $z = -20$; cluster size: 26; $t_{(21)} = 4.50$, $P = 0.046$) contrasts. However, this bilateral effect would have been overlooked if analyses were limited to whole-brain correlations.

The current study has several limitations. Our modest sample size precluded systematic investigation of sex differences [78–80] which may exist in neuropredictive signals [25]. In addition, while we made efforts to identify generalizable predictive signals (e.g. monetary incentives rather than substance-related cues, leave-one-out cross-validation), we were unable to explore SUD subgroups or specific comorbidities. Moreover, we did not have a matched healthy control group, so we cannot conclude that predictive signals localized to Amyg/aHipp are elevated relative to individuals without SUDs, although this view is supported by existing evidence [31,50].

The current study represents the first effort to identify neuropredictive indicators of relapse risk in a naturalistic sample of SDIs, typical of community-based treatment. We identified ROIs in bilateral Amyg/aHipp as significantly predictive of substance use outcomes, even when controlling for significant non-brain-based covariates. In addition, a novel behavioral correlate of relapse risk—faster reward-seeking responses after negative feedback—was also identified. Results of the current study may have translational relevance to the development of multi-modal assessment tools and targeted interventions for individuals at the highest risk of relapse.

Declaration of interests

None.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Appendix S1 Supplementary Methods, Results and Discussion.

Figure S1 Location of right corticomedial amygdala (cmAmyg) ROI and corresponding ROC curves for abstinence versus use and abstinence/lapse versus relapse classification criteria. Predictive regions identified for both 'Explode – Confirmed_Gain' and 'Explode – Successful_Gamble' contrasts included the right cmAmyg. For the 'Explode – Confirmed_Gain' contrast, the right cmAmyg demonstrated "excellent" test quality for both classification methods (with AUCs of 0.946 and 0.939 for abstinence versus use and abstinence/lapse versus relapse, respectively). BOLD response in right cmAmyg for the 'Explode – Successful_Gamble' contrast demonstrated "good" test quality for both classification methods (with AUCs of 0.839 and 0.864 for abstinence versus use and abstinence/lapse versus relapse, respectively).

Table S1 Summary of self-report and additional cognitive-behavioral measures: descriptive statistics and correlation with SUM.

Table S2a Response to BART Decision and Outcome Events – Basic Event-Related Contrasts.

Table S2b Response to BART Decision and Outcome Events – Parametric Modulator Contrasts (Positive Correlations).

Table S2c Response to BART Decision and Outcome Events – Parametric Modulator Contrasts (Negative Correlations).

Table S3 Summary of predictive model performance for spherical ROIs defined in bilateral corticomedial amygdala ($n = 23$).

Table S4 Summary of supplemental predictive models examining treatment setting as a covariate within peak ROIs identified through leave-one-out cross-validation analysis ($n = 23$).