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A preliminary study of longitudinal neuroadaptation associated with recovery from addiction

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ABSTRACT

Background: Few studies have explored longitudinal change in event-related brain responses during early recovery from addiction. Moreover, existing findings yield evidence of both increased and decreased signaling within reward and control centers over time. The current study explored reward- and control-related signals in a risky decision-making task and specifically investigated parametric modulations of the BOLD signal, rather than signal magnitude alone. It was hypothesized that risk-related signals during decision-making and outcome evaluation would reflect recovery and that change in specific signals would correspond with improved treatment outcomes.
Methods: Twenty-one substance dependent individuals were recruited upon enrollment in community-based substance use treatment programs, wherein they received treatment-as-usual. Participants completed functional neuroimaging assessments at baseline and 3-month follow-up while performing the Balloon Analogue Risk Task (BART). Risk- and reward-sensitive signals were identified using parametric modulators. Substance use was tracked throughout the 3-month study interval using the timeline follow-back procedure.
Results: Longitudinal contrasts of parametric modulators suggested improved formation of risk-informed outcome expectations at follow-up. Specifically, a greater response to high risk (low-likelihood) positive feedback was identified in caudal anterior cingulate cortex (ACC) and a greater response to low risk (low-likelihood) negative feedback was identified in caudal ACC and inferior frontal gyrus. In addition, attenuation of a ventromedial prefrontal cortex (vmPFC) "reward-seeking" signal (i.e., increasing response with greater reward) during risky decisions at follow-up was associated with less substance use during the study interval.
Conclusions: Changes in risk- and reward-related signaling in ACC/vmPFC appear to reflect recovery and may support sobriety.

1. Introduction

Changes within primary reward circuitry and prefrontal control networks underlie the neurobiological instantiation of substance use disorders (SUDs), resulting in a disturbance of salience attribution and response inhibition that drives compulsive use (Goldstein and Volkow, 2002, 2011). Interventions for SUDs should restore functioning within these neural systems, but few studies explore longitudinal neuroadaptation during early recovery.

In a recent meta-analysis, both pharmacologic and cognitive-behavioral interventions affected the ventral striatum, orbitofrontal cortex, and inferior frontal gyrus (IFG) – regions associated with reward-learning, reward-seeking, and response inhibition, respectively (Konova et al., 2013). Cognitive-behavioral interventions also recruited control-related brain areas (e.g., anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), and middle frontal gyrus) – suggesting an added benefit of these approaches. Konova et al. primarily considered acute treatment effects and were unable to target neuroadaptive change over the longer term because few longitudinal neuroimaging studies have been conducted.

A few studies have explored longitudinal change in brain function during recovery from SUDs. DeVito et al. (2012) studied a mixed sample of substance dependent individuals

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(SDIs) receiving treatment-as-usual (with or without adjunctive cognitive-behavioral therapy) and found improved Stroop performance and reduced control-related activation in regions including ACC, IFG, and midbrain following 8 weeks of treatment – consistent with enhanced processing efficiency in these regions. Increased activation has also been reported following treatment for cocaine dependence in midbrain and thalamus – both in response to neutral and drug Stroop stimuli (Moeller et al., 2012) and during reward anticipation in a monetary incentive delay task (Balodis et al., 2016). Moeller et al. also identified a trend toward increased ACC activation to drug words, specifically. Taken together, these results suggest restoration of dopaminergic neurotransmission within the midbrain and improved recruitment and/or efficiency of dopaminergically-innervated regions associated with cognitive control and motivational salience.

Moeller et al. (2012) also report a relationship between increased midbrain activity at follow-up, reduced drug-seeking in a simulated cocaine choice paradigm, and fewer days of use during recovery – while increased dorsolateral prefrontal cortex activity was associated with less spending on cocaine during treatment. Balodis et al. (2016) also found that an increased midbrain response at follow-up was associated with reduced use, while a greater ventral striatum response during loss anticipation was associated with fewer negative urine drug screens. Correlations with treatment outcome were also explored by DeVito et al. (2012) but no significant effects were identified.

Despite the apparent importance of decision-making in substance use recovery (Larimer et al., 1999; Redish et al., 2008; Reske and Paulus, 2008), no previous work has addressed change in reward- and control-related signaling in this context. The current study specifically targeted recovery-related change in neural activation during risky decision-making in a mixed sample of SDIs during the three months following treatment engagement. Specifically, the Balloon Analogue Risk Task (BART) was selected due to its good test-retest reliability (Weafer et al., 2013; White et al., 2008), external validity with respect to real-life risky behavior (including substance use; Bogg et al., 2012; Fernie et al., 2010; Lejuez et al., 2002), and existing framework for disentangling reward-seeking, loss aversion, and infrequency effects, previously developed by our lab (please see Fukunaga et al., 2012; for details).

Our previous work identified BART-related activation in mPFC/ACC that was associated with uncontrolled substance use and substance abuse risk factors in alcohol-using undergraduates (Bogg et al., 2012). Specifically, high-risk substance use was associated with reduced mPFC/ACC signal in relation to increasingly risky decision-making and increased mPFC/ACC signal in relation to unexpected, high-risk reward. This is consistent with the notion that control-related mPFC/ACC activity biases decisions away from riskier options (Fukunaga et al., 2013, 2012; Krawitz et al., 2010) and signals predictions errors based on risk appraisal (Alexander and Brown, 2011).

We specifically hypothesized that individuals with improved recovery outcomes would exhibit remediation of these event-related signals over time (i.e., increased mPFC/ACC activity during risky decision-making and reduced signal to high-risk reward). Further, unlike previous longitudinal imaging studies of recovery, the current study investigated parametric modulations of the BOLD response that reflect dynamic sensitivity to task context (specifically, trial-to-trial variation in risk and reward). Such signals provide unique insight into the neural representation of relapse-relevant constructs (e.g., reward sensitivity, loss aversion) and may be robust to changes in processing efficiency that complicate interpretation of findings from main effect contrasts.

2. Methods

2.1. Participants and design

Twenty-six SDIs were enrolled upon treatment engagement at one of two community-based clinics; 21 completed baseline and follow-up assessments and are included in the current sample (6 female; see Table 1 for demographic and recruitment data). Participants were (1) diagnosed with alcohol, drug, or polysubstance dependence using DSM-IV criteria, (2) 18–50 years of age, (3) 1–4 weeks abstinent at time of baseline assessment, and (4) actively participating in substance use treatment. Individuals receiving replacement pharmacotherapy and those reporting contraindications to magnetic resonance imaging or a history of traumatic brain injury, other neurocognitive disorders, Bipolar disorder, or psychotic illness were excluded.

Participants received treatment-as-usual in an intensive outpatient or residential treatment program. Both programs were abstinence-oriented and utilized a twelve-step facilitation approach, as well as routine urinalysis (see Supplementary materials for additional details). Participants completed a baseline assessment and follow-up fMRI assessment at 3-months. The timeline follow-back procedure (Sobell et al., 1988) was conducted at monthly intervals to track drug and alcohol use during the 3-month period and additional narrative details (e.g., subjective intoxication) were also collected (see Supplementary materials for additional information). A breathalyzer test (AlcoSensor IV, Intoximeters, Inc., St. Louis, MO) and 6-panel urine drug screen (Alere Toxicology, Portsmouth, VA) were conducted prior to baseline and 3-month assessments. Participants who resumed use during the study were required to maintain abstinence for 48 hours prior to testing and were evaluated for signs of intoxication. Study assessments were not conducted if urinalysis results were positive for recent substance use or blood alcohol content was greater than 0.000 percent by volume. Two participants screened positive for use at 3-month follow-up; both were rescheduled and completed this assessment after providing negative urine specimen and breathalyzer results.

Lifetime problems with alcohol and other substances were assessed at baseline using the Semi-structured Assessment for the Genetics of Alcoholism (Bucholz et al., 1994). Data from the timeline follow-back were used to compute a substance use metric (SUM),[1] summarizing days of use (with and without intoxication) for each participant; values were arcsine-transformed to better approximate the normal distribution. Additional self-report (including measures of social investment, craving, anxiety, depression, and coping) and cognitive-behavioral (i.e., Go/No-Go, Delay Discounting, and Brown-Peterson tasks) measures of recovery are described in Supplementary materials and Supplementary Table 1.

2.2. fMRI procedure

Imaging datasets were acquired at baseline and 3-month follow-up using a Siemens Magnetom Trio 3-T MRI scanner and 32-channel head coil. We used a version of the BART (see Fig. 1), previously validated in neuroimaging studies of healthy individuals (Fukunaga et al., 2012), substance users (Bogg et al., 2012), and at-risk youth (Hulvershorn et al., 2015), developed from the original implemen-

[1] A substance use metric (SUM) was computed to differentially weight excessive or uncontrolled use resulting in intoxication (e.g., relapse) versus less serious use without intoxication (e.g., slip) using the following formula: [Days Alcohol Used without Intoxication + 2*(Days Alcohol Used with Intoxication) + Days Drugs Used without Intoxication + 2*(Days Drugs Used with Intoxication)]/4*Total Days (See Supplementary materials for additional information.)

Table 1
Sample demographic and recruitment data (n = 21).

Demographic Variables				
Age			27 (6.8)	
Male			15	
Total Years of Education			13 (1.9)	
Employment Status			Baseline	3 Mo.
	Employed Full Time	5	8	
	Employed Part Time	5	4	
	Unemployed	9	8	
	Student	2	1	
Recruitment Information				
Treatment Setting		*Outpatient*	12	
	Residential	9		
Referral Source		*Self*	13	
	Drug Court	5		
	Probation	3		
Clinical Variables				
Number of Times in Previous Treatment			2 (2.5)	
SSAGA Symptom Count			6.5 (0.7)	
Primary DSM-IV Diagnosis	*Alcohol dependence*			12
	Sedative, Hypnotic, or Anxiolytic dependence			1
	Cannabis dependence			1
	Amphetamine dependence			1
	Opioid dependence			2
	Polysubstance dependence			4
Additional Psychiatric Diagnoses	*Major Depressive Disorder*			4
	Generalized Anxiety Disorder			4
	Posttraumatic Stress Disorder			1
	Anxiety Disorder NOS			2
	Antisocial Personality Disorder			1
	None			7

*Correlation between wager amount and probability of explosion is $r = 0.995$

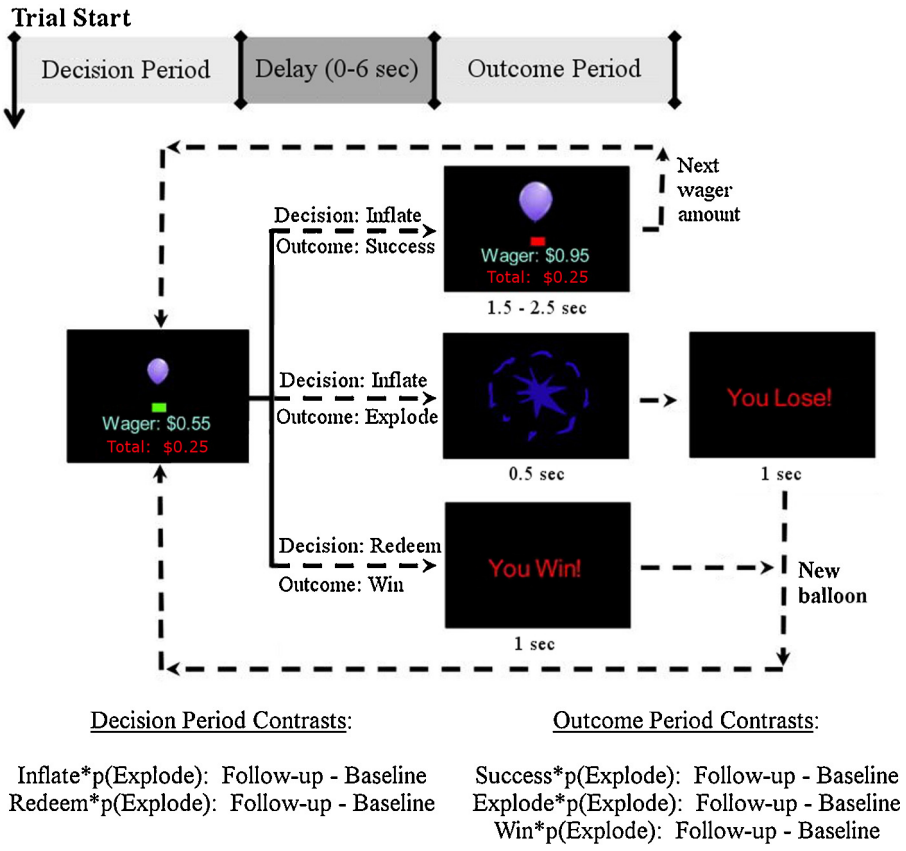

Fig. 1. Schematic representation of the Balloon Analogue Risk Task (BART).
Adapted, with permission, from Fukunaga et al. (2012).

Table 2
Wager amount and probability of explosion by inflation number.

Inflation #	Wager Amount	p(Explode)
0	$0.00	0.0%
1	$0.05	2.1%
2	$0.15	4.2%
3	$0.25	6.3%
4	$0.55	14.6%
5	$0.95	23.9%
6	$1.45	31.3%
7	$2.05	43.8%
8	$2.75	56.3%
9	$3.45	68.8%
10	$4.25	79.2%
11	$5.15	89.6%

tation of the BART for fMRI and utilizing a similar analytic approach (Rao et al., 2008). Acquisition parameters were identical to those used in Bogg et al., 2012 and are reported in Supplementary materials. Stimuli were presented using E-Prime (Psychology Software Tools, Pittsburgh, PA) and a projector to display images within the scanner bore. Each inflation sequence began with a small balloon, valued at $0.00, in the center of the screen. Participants could 'Inflate' the balloon, increasing its value in the next trial, or 'Redeem' the balloon for its current value by responding with left and right index fingers (assignment counterbalanced across participants). Each decision was preceded by a red rectangle, presented below the balloon for a pseudo-randomly-determined delay of 1.5, 2, or 2.5 s, signaling participants to withhold responses. The rectangle then turned green, indicating participants could respond when ready. Following response production, a jittered delay of 0–6 s preceded feedback such that decision and outcome intervals could be estimated separately in the general linear model (GLM).

After 'Redeem' responses, the words, "You Win!" were presented for 1 s ('Win') and the wager value was added to block winnings (visible at bottom of screen). After 'Inflate' responses, 'Success' was signaled by an increased wager value and balloon size, cueing the start of the next decision trial. Alternatively, an 'Explode' outcome (resulting in loss of the current wager) was signaled by presentation of an exploding balloon for 500 ms and the words, "You Lose!" for 1 s. An equiprobable delay of 2, 4, or 6 s preceded new inflation sequences, signaled by presentation of a new $0.00 balloon after 'Win' and 'Explode' events. Explosion probability and reward increased in parallel with each inflation, in accordance with values specified in Table 2. Participants were informed that both wager value and explosion probability increased with consecutive inflations; the rate of increase was not described. Participants completed two 8-min blocks per timepoint, each with an average of 17 inflation sequences ($SD = 2$) and 96 decisions ($SD = 9$) per block; participants were unaware that the number of balloons per block was unlimited.

Winnings were reset at the beginning of each block; participants received a monetary bonus equal to 25% of total earnings at each timepoint. While it was possible for participants to produce a different number of events for entry into the first-level GLM at each timepoint, participants generated a similar number of events of each type (see Supplementary Table 2).

2.3. Preprocessing and analysis of neuroimaging data

Preprocessing steps were identical to those reported by Bogg et al. (2012) and are described in Supplementary materials. Functional images from both timepoints were coregistered to the high resolution structural from baseline. First- and second-level statistical analyses were conducted in SPM5. Event-related BOLD responses during the BART were estimated using a GLM with a global constant and 20 regressors for each timepoint (baseline vs. follow-up): six motion regressors, two constant terms, five basic (i.e., main effect) event regressors (i.e., 'Redeem', 'Inflate', 'Explode', 'Success', and 'Win'), five parametric modulators representing explosion probability for each event, and 2 parametric modulators representing response time (RT) for 'Redeem' and 'Inflate' events. A canonical hemodynamic response function was used to model BOLD response, with decision-related regressors time-locked to RT and outcome-related regressors time-locked to feedback latency.

Due to the relationship between risk and reward in the task, parametric modulators specified with reference to explosion probability also tracked trial-to-trial variation in reward magnitude. These parametrically-modulated regressors were identical to the five basic event regressors, except that the magnitude of each modeled event was multiplied by that event's explosion probability. Each parametrically-modulated regressor was mean-centered, so that the sum of regressor values across all time points was zero. For three participants, a lower occurrence of explosions precluded unique estimation of basic event regressors and parametric modulators for 'Explode' events; this was additionally the case for one participant for 'Win' events. These participants were accordingly excluded from parametric modulator contrasts of each corresponding type.

Given our hypotheses, only the five parametric modulators representing explosion probability (designated by '*p(Explode)') were considered in second-level analyses. We specifically explored longitudinal change in parametric modulators by computing longitudinal contrasts (i.e., 3-month follow-up – baseline, hereafter FU-BL) and evaluating these contrasts using one-sample *t*-tests to assess main effects and correlation analyses to assess longitudinal change related to substance use outcomes (represented by the SUM). Longitudinal contrasts were specified at the first-level and tested at the second-level with random effects to model between-subjects variance. To exclude effects related to behavior change between sessions, the difference in mean BART inflation number between acquisition sessions (FU-BL) was included as a nuisance covariate at the second-level. Reported *p*-values for second-level analyses reflect one-tailed tests of significance.

In order to test predictions from Bogg et al. (2012) the Inflate*p(Explode) FU-BL contrast was specified to identify regions wherein longitudinal signal increased with escalating risk/reward during decision-making and the Success*p(Explode) FU-BL contrast was specified to identify regions with less signal to high-risk reward over time. Longitudinal contrasts were similarly specified for Explode*p(Explode), Win*p(Explode), and Redeem*p(Explode) parametric modulators.

Between-subject, whole-brain correlational analyses were conducted for longitudinal contrasts to identify regions wherein changes in task-related signal related to substance use outcomes (i.e., SUM). Negative correlations represent less use with increased parametrically-modulated event-related activation at follow-up, relative to baseline. Positive correlations indicate that increased parametrically-modulated signal at follow-up corresponded with more use.

We employed a whole brain search space to improve hypothesis-generating potential; however, our hypotheses specifically concerned mPFC/ACC, justifying small volume correction for that region. Clusters of 30 or more contiguous voxels, passing cluster-level correction at the 0.05 α-level (initial cluster-forming threshold of 0.001; cluster extent estimated using AFNI's 3dClustSim to achieve a type I error rate of 0.5%), were identified as regions of interest. Bonferroni correction was additionally applied for 10 whole brain correlations (5 positive and 5 negative longitudinal contrast correlations), lowering the cluster-corrected *p*-value to 0.005 for these comparisons. Correlation analyses were repeated

following exclusion of participants with SUM scores exceeding 2 standard deviations of the mean to assess the influence of extreme values.

2.4. Cognitive-behavioral and self-report data

Repeated-measures analysis of variance (ANOVA) was used to assess longitudinal change in BART performance, as well as self-report and cognitive-behavioral measures (see Supplementary materials). Pearson correlations between SUM values and longitudinal change in these variables were also calculated. Post hoc paired *t*-tests were utilized for comparison of specific conditions. Reported *p*-values reflect a two-tailed test of significance.

3. Results

3.1. BART behavior and substance use measures

BART performance and substance use outcome data are summarized in Table 3. A 2 (timepoint) × 2 (block) repeated-measures ANOVA revealed no significant effects for total balloons, exploded balloons, won balloons, average 'Redeem' inflation number, or average 'Explode' inflation number. 'Explode' events were less frequent than 'Win' at both baseline ($t(20) = 4.57$, $p < 0.001$) and follow-up ($t(20) = 5.09$, $p < 0.001$). With respect to RT, a 2 (timepoint) × 2 (block) × 2 (decision type) repeated-measures ANOVA identified a significant main effect of timepoint, with evidence of faster overall RTs at follow-up relative to baseline ($t(20) = 1.72$, $p = 0.052$). This finding supports inclusion of RT-based parametric modulators in first-level GLMs. No other significant effects were identified.

Less substance use during the study interval was associated with a greater reduction in RT from baseline to follow-up on 'Inflate' trials ($r(21) = 0.586$; $p = 0.005$) but not on 'Redeem' trials ($r(21) = 0.065$; $p = 0.780$). Longitudinal change in mean stop inflation number did not significantly correlate with SUM ($r(21) = 0.245$; $p = 0.284$). Additional self-report and cognitive-behavioral measures are summarized in Supplementary Table 1.

3.2. Longitudinal change in parametrically-modulated brain signals

Longitudinal contrast results are summarized in Table 4. FU-BL main effect contrasts for decision events revealed greater increasing parametrically-modulated risk/reward signal during 'Redeem' events (i.e., 'Redeem*p(Explode)') at follow-up in left dorsal premotor cortex (BA 6). No significant areas of decreased 'Redeem*p(Explode)' signal were identified and the 'Inflate*p(Explode)' FU-BL contrast yielded no significant effect in either direction.

For outcome events, greater increasing activity with increasing risk/reward for 'Success' feedback (i.e., 'Success*p(Explode)') at follow-up was identified between right caudal ACC and PCC (BA 24). In addition, decreasing parametrically-modulated activity from baseline to follow-up was identified for the 'Explode*p(Explode)' contrast in right IFG (BA 47) and left caudal ACC (BA 24), extending into the cingulum. Significant longitudinal change in 'Win*p(Explode)' was not identified. Outcome-related clusters are depicted in Fig. 2. Collectively, outcome-related effects suggest increased sensitivity to surprising events or prediction error (Alexander and Brown, 2011, 2014).

3.3. Whole brain correlations between FU-BL contrasts and substance use outcomes

Several regions demonstrated a significant correlation between longitudinal change in parametrically-modulated signals and substance use outcomes (i.e., greater signal modulation by risk/reward at follow-up associated with more or less use during the study interval). These are summarized in Table 4. While no arcsine-transformed SUM scores exceeded 3.25 standard deviations of the mean, we sought to test if results were robust to exclusion of extreme SUM values (exceeding 2 standard deviations of the mean). Therefore, we re-ran correlational analyses following exclusion of 2 participants with the heaviest reported use during the study interval.

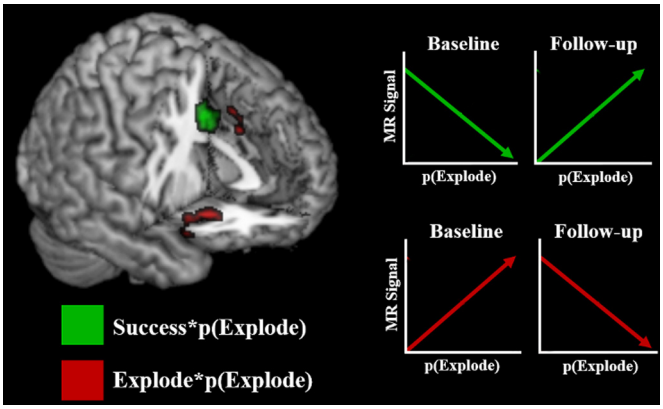

Fig. 2. Regions demonstrating longitudinal recovery of prediction error effects, as a change in signaling to positive and negative BART outcomes. A greater increasing activation to successful inflation feedback with increasing explosion probability (i.e., 'Success*p(Explode)') was identified at follow-up in right caudal ACC (peak voxel: 8, 4, 34) and a greater decreasing signal to explosion feedback with increasing explosion probability ('Explode*p(Explode)') was identified at follow-up in right IFG (peak voxel: 32, 20, −14) and left caudal ACC/cingulum (peak voxel: −18, 12, 32). Results suggest more robust signaling of unexpected (low likelihood) outcomes at follow-up which is consistent with stronger formation of risk-informed outcome expectations. Line plots at the right side of the figure are included to conceptually illustrate longitudinal parametric modulator contrasts. For the Success*p(Explode) contrast (green), there was a greater positive relationship between trial-to-trial variation in p(Explode) and the magnetic resonance (MR) signal at follow-up (i.e., stronger signal with a higher probability of an explosion (or magnitude of reward) at follow-up). For the Explode*p(Explode) contrast (red), there was a greater negative relationship between trial-to-trial variation in p(Explode) and the MR signal at follow-up (i.e., stronger signal with a lower probability of an explosion (or magnitude of reward) at follow-up). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

A single cluster between left dorsal ACC (dACC; BA 32) and ventromedial PFC (vmPFC), demonstrating a positive correlation for the Inflate*p(Explode) FU-BL contrast in the full sample, survived cluster extent thresholding when excluding the heaviest users (cluster size: 30 voxels, peak voxel: −6, 36, 10, *z*-score = 4.27) but did not pass cluster-level correction for the whole brain search volume (cluster-corrected p-value = 0.337, uncorrected p-value = 0.008). A cluster of 26 voxels passed small volume correction (p-value = 0.041) for an anatomically-defined, hypothesis-driven mask over ACC and mPFC, without Bonferroni correction for multiple comparisons. This cluster, as well as the larger cluster identified for the full sample, are depicted in Fig. 3, with scatterplots showing an increasing response to increasing risk/reward over time in association with greater use and a decreasing response to increasing risk/reward over time in association with reduced use.

While the difference in mean BART inflation number between acquisitions was controlled for in whole brain correlation analyses, we explored the relationship between Inflate*p(Explode) FU-BL signal and BART performance at each timepoint within dACC/vmPFC clusters (see Supplementary Fig. 1), applying Bonferonni correction for 2 timepoints ($\alpha = 0.025$). A positive correlation between mean stop inflation number at follow-up and parameter estimates for the Inflate*p(Explode) FU-BL contrast approached uncorrected significance for the full sample ($r(21) = 0.409$, $p = 0.066$)

Table 3
Summary of BART behavioral performance measures and substance use outcomes.

BART Behavioral Performance

Dependent Variable	Mean (SD)				*F*-statistic (*p*-value)		
	Baseline		Follow-up		Main Effect:	Main Effect:	Interaction
	Block 1	Block 2	Block 1	Block 2	Timepoint	Block	
Total # of Balloons	16.5 (1.6)	16.3 (1.9)	17.0 (2.5)	17.1 (2.8)	2.81 (0.109)	0.08 (0.785)	0.35 (0.559)
# of Balloons Exploded	5.9 (2.5)	5.9 (2.2)	6.0 (2.2)	5.8 (2.1)	0.00 (1.00)	0.09 (0.766)	0.01 (0.906)
# of Balloons Won	10.6 (3.1)	10.4 (3.0)	11.1 (3.4)	11.3 (3.7)	1.22 (0.283)	0.00 (0.946)	0.26 (0.617)
Average Stop Inflation #	6.29 (0.87)	6.34 (0.68)	6.25 (0.75)	6.22 (0.67)	0.22 (0.642)	0.01 (0.918)	0.19 (0.672)
Average Explode Inflation #	4.96 (0.82)	5.04 (1.34)	4.92 (0.86)	4.89 (0.94)	0.35 (0.559)	0.01 (0.919)	0.09 (0.769)
Choose Inflate Trial RT	1081 (458)	1036 (488)	952 (432)	952 (512)	3.24 (0.087)	0.41 (0.527)	0.78 (0.387)
Choose Win Trial RT	1115 (743)	1003 (819)	875 (494)	811 (420)	4.45 (0.048)	1.63 (0.217)	0.16 (0.690)
RT (All Trials)	1098 (583)	1019 (621)	914 (392)	882 (436)	**6.46 (0.019)****	1.49 (0.237)	0.42 (0.522)

Substance Use Outcomes

		1 Mo.	2 Mo.	3 Mo.	Total
Substance Use Metric (SUM)	Mean (SD)	0.035 (0.082)	0.069 (0.187)	0.067 (0.132)	0.057 (0.127)
	Maximum	0.283	0.717	0.567	0.519

		Alcohol	Drug	Alcohol	Drug	Alcohol	Drug	Combined
Reported Days of Use w/out Intoxication	Mean (SD)	0.3 (0.9)	1.3 (5.9)	0.1 (0.7)	1.4 (6.5)	0.1 (0.3)	1.9 (6.3)	5.1 (19.2)
	Maximum	4	27	3	30	1	26	87
Reported Days of Use w/Intoxication	Mean (SD)	0.3 (0.7)	1.0 (3.7)	1.9 (6.1)	1.5 (6.5)	1.8 (3.8)	1.3 (3.2)	7.8 (14.5)
	Maximum	3	17	28	30	17	13	50

Table 4
Regions of interest from longitudinal contrasts and whole brain correlation analysis of substance use outcomes.

Increased Parametrically-Modulated Signal at FU Relative to BL			Peak MNI Coordinates				
Contrast	Region	Cluster Size	x	y	z	*z*-value	Corrected *p*-value
FU > BL Longitudinal Contrasts ($p < 0.05$)							
Inflate*p(Explode)	n/a	–	–	–	–	–	–
Redeem*p(Explode)	L Dorsal Premotor Cortex (BA 6)	55	−48	−4	42	3.94	0.041
Explode*p(Explode)	n/a	–	–	–	–	–	–
Success*p(Explode)	R Caudal ACC/PCC (BA 24)	77	8	4	34	4.04	0.010
Win*p(Explode)	n/a	–	–	–	–	–	–
FU > BL *Correlates* with Less Use (Negative Correlation; $p < 0.005$)							
Inflate*p(Explode)	n/a	–	–	–	–	–	–
Redeem*p(Explode)	n/a	–	–	–	–	–	–
Explode*p(Explode)	R Middle/Superior Temporal Gyrus (BA 21)	338	66	−22	2	4.58	<0.001
	R Lingual Gyrus (BA 19)	184	24	−66	0	4.47	<0.001
	R ACC (BA 24)	119	6	14	22	4.40	<0.001
	R Superior Temporal Gyrus (BA 22)	196	50	−14	12	4.15	<0.001
Success*p(Explode)	R Putamen/Pallidum	156	16	−2	−6	4.51	<0.001
	L Medial Prefrontal Cortex (BA 9)	339	−18	44	24	4.42	<0.001
	R Middle Temporal Gyrus (BA 21)	143	50	−32	−2	4.36	<0.001
	L Middle Temporal Gyrus (BA 21)	179	−64	−28	−18	4.19	<0.001
	R Middle Temporal Gyrus (BA 21)	91	58	0	−26	3.98	0.002
Win*p(Explode)	n/a	–	–	–	–	–	–

Decreased Parametrically-Modulated Signal at FU Relative to BL			Peak MNI Coordinates				
Contrast	Region	Cluster Size	x	y	z	*z*-value	Corrected *p*-value
FU < BL Longitudinal Contrasts ($p < 0.05$)							
Inflate*p(Explode)	n/a	–	–	–	–	–	–
Redeem*p(Explode)	n/a	–	–	–	–	–	–
Explode*p(Explode)	R Inferior Frontal Gyrus (BA 47)	203	32	20	−14	4.84	<0.001
	L Caudal ACC (BA 24)/Cingulum	62	−18	12	32	4.43	0.040
Success*p(Explode)	n/a	–	–	–	–	–	–
Win*p(Explode)	n/a	–	–	–	–	–	–
FU < BL *Correlates* with Less Use (Positive Correlation; $p < 0.005$)							
Inflate*p(Explode)	L Putamen	116	−28	10	0	4.53	0.001
	L Middle Temporal Gyrus (BA 21)	100	−66	−30	−16	4.09	0.002
	L ACC (BA 32)/ventromedial PFC	105	−2	44	10	4.08	0.001
Redeem*p(Explode)	n/a	–	–	–	–	–	–
Explode*p(Explode)	n/a	–	–	–	–	–	–
Success*p(Explode)	R Cerebellum Posterior Lobe (Crus I)	188	30	−84	−22	4.41	<0.001
	L Paracentral Lobule (BA 6)	83	−4	−16	72	4.05	0.004
Win*p(Explode)	n/a	–	–	–	–	–	–

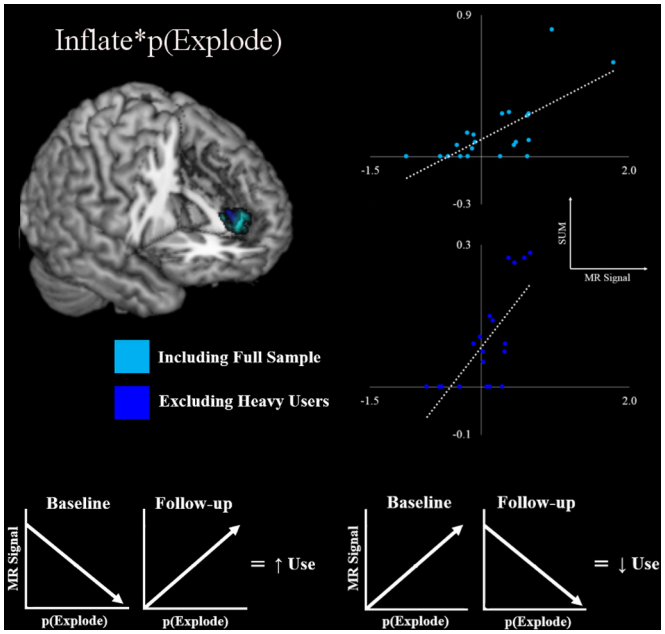

Fig. 3. Longitudinal attenuation of the "risk-seeking" signal in dACC/vmPFC during 'Inflate' decisions corresponded with decreased substance use during the study interval. Overlapping clusters were identified with (peak voxel: −2, 44, 10) and without (peak voxel: −6, 36, 10) inclusion of two participants with the heaviest reported substance use, indicating the effect was robust to the exclusion of potential outliers. A positive longitudinal contrast, indicating increased signal with increasing reward at follow-up, was associated with increased substance use. A negative longitudinal contrast, indicating decreased signal with increasing reward at follow-up, was associated with less substance use. A vmPFC-based reward-seeking signal was previously described in association with BART inflation events in healthy participants (Fukunaga et al., 2012). Longitudinal attenuation of this signal in successful early recovery may reflect improved inhibition of reward-seeking and may, in turn, be mediated by restoration of control-related functioning in other prefrontal regions.

and reached significance when excluding two participants with heaviest reported use ($r(19) = 0.534$, $p = 0.019$). Correlations between parameter estimates and mean stop inflation number at baseline were not significant (see Supplementary Fig. 1). Taken together, our findings suggest longitudinal attenuation of a risky reward-seeking signal in dACC/vmPFC in association with both decreased substance use and risk-taking in the BART at follow-up.

4. Discussion

The current study explored change in risk/reward-related modulation of the BOLD response to decision-making and outcome evaluation during early recovery from SUDs. While it was hypothesized that improved substance use outcomes would be observed in conjunction with increased parametrically-modulated risk/reward signals during inflations and decreased parametrically-modulated risk/reward signals to positive feedback in ACC/mPFC, successful recovery was instead associated with reduction in a vmPFC-based reward-seeking signal. There was also evidence of overall increased signaling to high risk/reward 'Success' outcomes in caudal ACC and increased signaling to low risk/reward 'Explode' outcomes in IFG and caudal ACC from baseline to follow-up. These results may be consistent with an increased surprise signal to unexpected outcomes (i.e., high risk successes and low risk explosions) in recovery which may, in turn, reflect formation of stronger expectancies based on previous outcomes (Alexander and Brown, 2010, 2011, 2014; Krawitz et al., 2011). However, we cannot exclude the possibility that this is a learning effect, unrelated to substance use recovery. A longitudinal increase in the Redeem*p(Explode) parametric modulator was also noted in dorsal premotor cortex, consistent with greater internally-guided motor planning (Ariani and Wurm, 2015) during safe responses in association with elevated risk/reward.

With respect to correlational analyses, improved substance use outcomes were associated with a decreasing dACC/vmPFC response to increasing risk/reward during inflations at follow-up relative to baseline. While not predicted from our previous work in substance users (Bogg et al., 2012), these results suggest recovery-related attenuation of the vmPFC "reward-seeking" signal (Kim et al., 2011), previously described for healthy controls (Fukunaga et al., 2012). Specifically, individuals with less reported substance use during the study interval exhibited less increasing vmPFC activation with increasing risk/reward at follow-up, while individuals with greater use demonstrated the opposite effect. Longitudinal change in vmPFC-based "reward-seeking" was further demonstrated to correlate with BART mean stop inflation number at follow-up such that stronger attenuation corresponded with less risk-taking in the task.

With respect to longitudinal effects that did not correlate with substance use outcomes, we cannot exclude that our results reflect learning or practice effects. However, consistent decision-making performance within and across timepoints may suggest against this interpretation. In addition, participants were informed that the risk of explosion increased with the number of inflations and did not need to learn this through trial-and-error. The established test-retest reliability of the BART (Weafer et al., 2013; White et al., 2008) also suggests rapid stabilization of performance in new task-learners – although with respect to the original behavioral paradigm rather than the modified version used herein.

While hypotheses based on Bogg et al. (2012) were not directly supported in the current study, the sample studied by Bogg et al. was comprised of non-treatment-seeking undergraduate students (ranging from modest alcohol users to heavy drinkers) and is appreciably different from the clinical sample of treatment-seeking SDIs reported here. Importantly, Bogg et al. reported reduced risk-seeking in the BART (lower mean stop inflation number) in association with both greater alcohol use and reduced ACC/mPFC signaling to increasing risk/reward. This paradoxical finding suggests that heavy substance using undergraduates are "loss averse reward takers" (Alexander et al., 2015; Bogg et al., 2012) who perform more cautiously because cognitive deficits impede their exploration and use of learned task contingencies to optimize performance. In the present study, however, an increased vmPFC "reward-seeking" signal was associated with greater risk-taking in the BART at follow-up and greater substance use during early recovery, consistent with high risk, reward-seeking rather than "loss averse reward taking."

Unfortunately, BART brain-behavior relationships cannot be conclusively targeted herein because we lack healthy and/or non-treatment-seeking comparison groups. We must also defer potentially interesting questions regarding specific SUDs due to our modest sample size and high rate of substance use comorbidity. While a limitation of the current study, a mixed substance use sample was used in a previous study of longitudinal change in recovery (DeVito et al., 2012). These findings, taken together with our own, support common mechanisms of recovery across SUDs. Differences in recovery-related neuroadaptation may also arise between outpatient versus residential treatment programs. Here, our small sample size and inability to reliably track treatment attendance/compliance precludes examination of this factor. We also note that our utilization of self-report to track substance use is suboptimal – although participants were educated about the importance of providing accurate data and did not stand to benefit from providing a false report.

Recent findings suggest that neural signatures present at the time of treatment engagement can predict substance use treatment

outcomes. For example, brain signals associated with aberrant cue and reward processing (Beck et al., 2012; Grusser et al., 2004; Jia et al., 2011; Marhe et al., 2013a; Stewart et al., 2014a,b), diminished control-related signaling (Brewer et al., 2008; Kober et al., 2014; Luo et al., 2013; Marhe et al., 2013b) and impaired decision-making (Gowin et al., 2014; Paulus et al., 2005; Stewart et al., 2014a,b) have been implicated in subsequent relapse risk. However, there is also accumulating evidence that cognitive functioning is partially restored across multiple domains during early recovery (Bates et al., 2013; Mann et al., 1999; Stavro et al., 2013) including improved cognitive control (Connolly et al., 2012) and reduced risky decision-making (De Wilde et al., 2013). The current findings suggest that reduced reward-seeking during early recovery (which may reflect improved cognitive control) may represent a protective factor against relapse.

While preliminary, our findings suggest that change in contextually-informed, neural representations of risk/reward during decision-making may support reduced risk-taking and continued abstinence. Interventions that promote such recovery may thus improve treatment outcomes in those most susceptible to relapse. To our knowledge, the current findings represent the first evidence of recovery in context-dependent modulations of brain activity that may inform risk appraisal and decision-making. The current study adds to limited extant research into neuroadaptive processes that may benefit early recovery from SUDs.

Conflict of interest statement

No conflict declared.

Role of funding source

Nothing declared.

Contributors

PRF, JWB, and SEF were responsible for the study design and concept. SEF performed all data preprocessing and analysis. SEF, JWB, and PRF contributed to the interpretation of results. SEF drafted the manuscript. SEF, JWB, and PRF participated in revision of the manuscript. All authors critically reviewed content and approved the final version for publication. SEF had full access to all the data in the study and takes responsibility for the integrity of data and the accuracy of the data analysis.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2016.08.626.

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