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# Neural responses to negative events and subsequent persistence behavior differ in individuals recovering from opioid use disorder compared to controls

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## ABSTRACT

**Background:** Negative emotion is associated with substance craving and use in individuals recovering from substance use disorders, including prescription opioid use disorder (POUD). Decisions to abandon or persist towards a goal after negative emotion-eliciting events, and neural responses that shape such decisions, may be important in maintaining recovery from POUD.

**Objectives:** We examined differences in neural responses to negative events and subsequent persistence decisions in individuals recovering from POUD without a history of a substance use disorder.

**Methods:** 20 individuals with POUD (POUD group: 4 females, abstinent 2–3 weeks after admission to an inpatient treatment facility post-detoxification, no other substance use disorder), and 20 individuals with no substance use history (control group: 6 females) completed a persistence-after-setbacks task during functional magnetic resonance imaging. Participants advanced along a path toward a reward; after encountering each negative event (i.e., progress-erasing setback), participants made decisions to persist or abandon the path. Persistence decision rates were compared between groups and blood-oxygen-level-dependent **signal** to negative events was analyzed within a striatum region of interest (ROI) as well as whole-brain.

**Results:** The POUD group persisted less ( $t(38) = 2.293, p = .028, d = .725$ ) and showed lower striatum (left ventral putamen) signal to negative events compared to the control group ( $p < .05$ , corrected for striatum ROI).

**Conclusions:** In POUD, neural and behavioral responses to negative events differ from controls. These differences are a target for research to address whether POUD treatment increases persistence and striatum responses to negative events and improves recovery outcomes.

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## Introduction

The way that people feel and behave in response to negative events, such as outcomes that impede or undo progress toward a goal, is critical for understanding recovery from substance use disorder. For example, a negative event during treatment (e.g., life circumstances causing a missed support group meeting) may elicit negative feelings that cause an individual recovering from substance use disorder to disengage from treatment goals and increase risk of relapse. Increased negative affect and decreased positive affect are consistently associated with increased substance craving and use for a variety of substances (1,2). In particular, negative affect is linked to increased craving and relapse in individuals recovering from substance use disorders after withdrawal (3,4), including increased craving in individuals recovering from prescription opioid use disorder (POUD) (5,6). Negative events are an inevitable

part of daily life. Thus, recovery from substance use disorders including POUD requires that individuals respond to negative events in ways that do not lead to relapse. Here, we focus on negative events that impede goal pursuit and prompt decisions to persist or abandon goals. It is critical to understand responses to such negative events and the underlying mechanisms in order to promote responses (e.g., persistence decisions) that may sustain recovery from POUD.

Research suggests that coping strategies involving disengagement lead to increased risk of relapse (3). On the other hand, persistence (i.e., sustained engagement to maintain a goal) is a protective factor for maintaining recovery in smokers and other substance users (7–11). Therefore, the ability to respond to negative events by deciding to persist with a goal, rather than abandon it, may be advantageous for individuals recovering from POUD. However, prior research has not examined

persistence decisions following negative events in POUD. Neuroimaging research in healthy individuals suggests that striatum, as well as ventromedial prefrontal cortex, responses to negative events can shape subsequent decisions to persist with a goal (12,13). Striatum signal decreases in response to negative events are hypothesized to carry a learning signal that steers behavior away from further punishments (14,15), but individuals are actually more persistent when negative events are informative and evoke larger striatal decreases, consistent with a “correct mistakes and try again” strategy (12). This association between neural incentive processing circuitry and behavioral responses to negative events, together with observations that ventral striatal structure and function may differ in opioid using individuals compared to controls (16–18), suggests that behavioral responses to negative events (i.e., persistence decisions) may differ in POUD compared to individuals with no drug use history.

In the current study, we examine how individuals recovering from POUD respond to negative events, focusing on mechanisms that underlie decisions to persist with a goal after experiencing a negative event during goal pursuit (i.e., a setback that impedes goal progress). Utilizing a paradigm developed to measure neural, behavioral, and affective responses to negative events (12,19), we first test the hypothesis that individuals recovering from POUD, compared to healthy control participants with no history of substance use, will make less decisions to persist after experiencing negative events. Next, we examine whether negative affective experience (i.e., reported feelings in response to negative events) relates to subsequent decisions (i.e., do more negative feelings relate to increased or decreased persistence?). Finally, we examine differences in neural responses to negative events between individuals recovering from POUD compared to control participants, focusing on striatum responses that may represent the affective value of events and shape subsequent behavior (12,14,15).

## Methods

### Participants

Twenty (16 M; 4 F) individuals with POUD in the first 3 weeks of a 6-month long inpatient residential treatment program (POUD group) and 20 (14 M; 6 F) healthy volunteers with no history of substance use (control group) matched for age, education, and ethnic background met criteria for inclusion in the study (Table 1). Participants were included only if they were between 21 and 54 years of age, English was their

primary language, they were right-handed, and they had near 20/20 vision (or corrected). Exclusion criteria were any serious physical illness, history of childhood learning disability or current special education, presence of any serious psychiatric illness, MRI contraindications, claustrophobia, abnormal hearing, history of loss of consciousness for more than 30 minutes, alcohol abuse and dependence including past dependence, and for women, pregnancy. Additionally, participants were excluded if they did not understand or complete the experimental task (1 POUD and 1 control participant excluded). Control group participants had no current or past substance use history. Inclusion in the POUD group required a history of using prescription opioid (PO) pills for at least the past 1 year and the POUD participants had to meet DSM-5 criteria for moderate-to-severe POUD, according to a structured clinical interview (SCID-5). Participants were excluded if they had co-occurring POUD and any other substance use disorder (including tobacco use) at a moderate-to-severe level.

POUD participants were recruited from Integrity House’s inpatient addiction treatment center in Newark, New Jersey. Patients were detoxified before admission to this facility, were screened for study eligibility in their first week after admission, and completed participation during the first 2–3 weeks since admission. Control participants were recruited by advertising in North Jersey Craigslist and word-of-mouth. Groups did not differ in alcohol use history. On the day of scanning (1 to 2 weeks after screening), POUD participants reported greater use of tobacco cigarettes in the last week compared to control participants (difference in number of cigarettes smoked per day in the last week: mean = 5.700, 95% confidence interval (CI) = [3.013, 8.387]). A comparable smoking behavior measure was not available for the time before admission to the treatment center. Thus, the difference may be due to continuance of smoking behavior that did not meet the moderate tobacco use disorder screening exclusion criterion, or increased smoking behavior in the residential treatment program in the absence of opioids. Analyses including smoking (cigarettes per day in the week before scanning) as a covariate are included in the Supplemental Online Material (Table S1), however, only one control participant reported any smoking in the last week, whereas 14 out of 20 POUD participants reported smoking in the last week. Thus, analyses are underpowered to detect separable effects of smoking in the prior week that are not attributable to POUD versus control group membership. On the day of scanning, participants provided written informed consent approved by the Rutgers University Institutional Review Board, and were administered a urine screen to

**Table 1.** Demographic and substance use information for individuals with prescription opioid use disorder (POUD) and healthy controls.

	POUD (n=20) Mean, Range (SD)	Control (n=20) Mean, Range (SD)	t-stat	p
Age (yrs.)	31, 22-48 (6.3)	33, 21-54 (6.5)	-0.74	0.46
Education (yrs.)	12, 3-20 (2.4)	13, 7-20 (2.1)	-1.04	0.3
Race/Ethnicity				
Caucasian	9	7		
African American	10	11		
Hispanic	1	2		
Female (n)	4	6		
Prescription Opioid Use				
Frequency (days/week)	6.8, 3-7 (.38)	na		
Duration of use (yrs.)	5.5, 2-20 (3.35)	na		
Money spent (\$/week)	\$739, \$70-2,500 (483)	na		
DSM-5 criteria for POUD				
Number of criteria met	8.75, 4-11 (2.10)	0		
Cigarette use among participants who reported any smoking in the week before scanning:				
Number reporting any smoking	14	1		
Frequency (days/week)	7	7		
Quantity (cigarettes/day)	8.6, 2-20 (4.0)	7		
Cigarette use (means including participants who reported no smoking):				
Frequency (days/week)	4.9, 0-7 (3.29)	.35, 0-7 (1.57)	5.58	<.001
Quantity (cigarettes/day)	6.05, 0-20 (5.73)	.35, 0-7 (1.57)	4.29	<.001

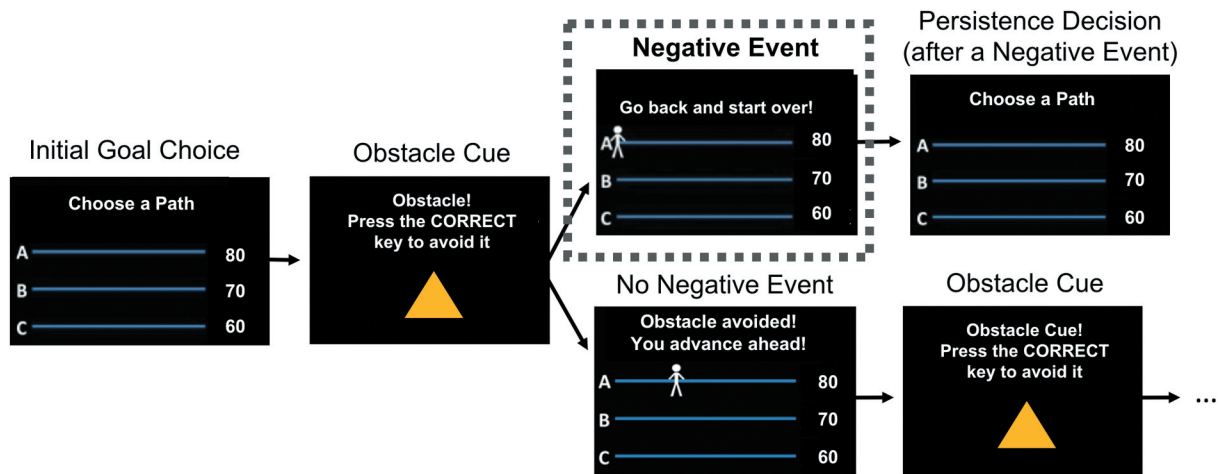
No subjects met tobacco use disorder criteria (it was an exclusion criterion), smoking measure is based on reported behavior in the week before scanning (after screening).

rule out pregnancy in women, and to ensure negative urine toxicology for cocaine, methamphetamine, THC, opiate, and benzodiazepines (One Step Multi-Drug Screen Test Panel). They were assessed for recent alcohol use with a breathalyzer. After the session, participants received a 100 USD gift certificate for participation. They further received a performance bonus based on the experimental task described below.

### **Persistence After Setbacks (PAS) Task**

The findings reported here are from a task included in a larger MR study that examined brain white matter connectivity using diffusion tensor imaging and resting state functional connectivity in POUD and control group participants. Participants performed the PAS task in the final functional scan of their session. Versions of this task have previously been used to examine neural responses underlying persistence (12) and effects of acute stress on persistence (19). In the task completed here, participants played a “path decision game” in which they chose a path and tried to earn points by advancing a stick figure through obstacles to the end of the path. The game was structured in 10 rounds. In each round participants tried to reach the points at the end of any path by advancing through obstacles on a chosen path. Each round ended when a participant reached the end of a path (6 out of 10 rounds) or ran out of time before reaching the end of

a path (4 out of 10 rounds). To start each round, participants chose between three paths with a point value at the end (80, 70, or 60 points; “Initial Goal Choice” in Figure 1). Participants then encountered obstacles (purple or orange triangles) while taking steps along the chosen path, and pressed a button to see if the obstacles resulted in a negative event received (62.5% of obstacles, figure is sent back to the beginning of the path) or negative event avoided (37.5% of obstacles, figure advances one step toward along the path, which was three steps long). After receiving a negative event, participants made a decision to persist with their previously chosen path (i.e., the path where they just received a negative event) or choose a different path. Persistence behavior was calculated as the proportion of choices to persist with the same path. This operationalization defines persistence as the continuance of a course of action to achieve a goal, despite difficulty (20,21), and allows that people may persist on high- or low-value goals, as is true in daily life. In recognition that persistence decisions are sometimes optimal and sometimes suboptimal, we also define a more specific “high-value persistence” measure to focus exclusively on optimal decisions to persist on the highest value path after a negative event. This measure is calculated as the proportion of choices to persist with the highest value path out of all choices following a negative event on the highest value path. High-value persistence decisions are optimal because the paths are equivalent except for



**Figure 1.** Task trial structure and timing. Initial Goal Choice: Participants chose a path to pursue then advanced through further events (Progress Cue or Obstacle Cue). Progress Cue (not pictured): a green triangle indicates that the character will advance one step toward the end of the path. Obstacle Cue: Participants encountered obstacles and made a key press to see if they then receive a pseudorandomly determined negative event (the character returns to the beginning of the chosen path and the next screen prompts a decision to persist or switch to a different path). If the obstacle is avoided there is no Persistence Decision (character advances one step). Analysis of fMRI signal focused on the “Negative Event” time period highlighted by the dashed line box.

the point value at the end of the path, thus, maximum points can be earned by always persisting on the high-value path. Participants were instructed to earn as many points as possible and a bonus payment would be based on points (1 cent/point, rounded to the nearest 5 USD such that all participants earned a 5 USD bonus). Participants were instructed that path difficulty (i.e., likelihood of a negative event) was not necessarily related to point value, and a negative event will not necessarily be repeated if the path is chosen again. A round ended when the player reached the end of a path or time ran out (after a pseudorandomly determined number of events). An end-of-round screen showed either “You won the points!”, or “You ran out of time!” To facilitate participants reaching the end of a path on 60% of rounds (6 out of the 10 rounds), they were occasionally presented with a third “advance” cue (green triangle), which moved the stick figure one step forward. Events in the task (path choice, obstacle cue, negative event received/avoided, end of round) were separated in time by a fixation screen (50% 2s, 25% 4s, or 25% 6s duration). Participants received 20 negative events (1 to 3 negative events per round) equally distributed across each path. This distribution meant that negative events were equally likely on any path, and the only difference between paths was the number of points available. Thus, the best strategy was to always persist on the highest value path. The distribution of negative events was predetermined to ensure the same amount of trials and chances to persist. Before entering the scanner, participants completed two practice rounds of the PAS task to become familiar with the timing of

events (see Supplemental Online Material for task instructions and practice round details).

Instructions for the task stated that the color of the obstacle (purple or orange) indicated whether it was a “controllable” or “uncontrollable” obstacle. After completing the task, participants rated their affective responses to each type of obstacle (Valence: “How negative or positive did you feel?” presented with picture of a controllable or uncontrollable obstacle cue and text “when you were sent back by [a controllable]/[an uncontrollable] obstacle”; Perception of Control: “How much control did you feel?” presented with picture of a controllable or uncontrollable obstacle cue and text “when you encountered [a controllable]/[an uncontrollable] obstacle”) to the task events on 7-point scales (Valence: scale endpoints were “extremely negative” and “extremely positive” and responses were coded as  $-3$  to  $+3$ ; Perception of Control: scale endpoints were “no control at all” and “a great amount of control” and responses were coded as 1 to 7). These ratings were assessed after task completion to limit potential influences of the rating process itself on the primary behavioral measure in the task, persistence. For “controllable” obstacles, participants were instructed to “use trial and error” to press the “correct” button (1 of 4 possible buttons) to avoid the negative event; whereas for “uncontrollable” negative events they were instructed to press a button to see the randomly determined outcome. Thus, both obstacle types were randomly determined but instructions emphasized that “controllable” obstacles could be overcome by learning the (randomly determined) “correct” response. The two types of obstacles were included to examine possible



effects of framing obstacles as “controllable” or “uncontrollable.” However, participants appeared to recognize the similarity of the two obstacle types: Perception of Control ratings did not differ between obstacle types (POUD “controllable”-“uncontrollable” mean difference = .526, 95% CI = [-.507,1.560],  $t(19) = 1.070$ ,  $p = .299$ ; control group mean difference = .650, 95% CI = [-.314, 1.614],  $t(19) = 1.412$ ,  $p = .174$ ) and Valence ratings did not differ between obstacle types (POUD “controllable”-“uncontrollable” mean difference = .500, 95% CI = [-.204,1.204],  $t(19) = 1.486$ ,  $p = .154$ ; control group mean difference = -.150, 95% CI = [-.763, .463],  $t(19) = 1.276$ ,  $p = .614$ ). For this reason, data for “controllable” and “uncontrollable” negative events were collapsed to examine behavioral, affective, and neural responses to all negative events. After completion, participants were debriefed to probe for lasting negative affect (none reported) and it was explained that the rate of negative events in the task was predetermined and necessary for the purpose of measuring goal decisions after negative outcomes.

### Behavioral analysis

Behavior in the PAS Task yielded individual measures of persistence behavior (proportion of decisions to persist after a negative event), affective response to negative events, as well as mean response time for decisions and mean response time for obstacles. These measures were submitted to two-sample t-tests to examine differences between POUD and control groups. Persistence behavior was not normally distributed (Shapiro–Wilk test,  $W = .918$ ,  $p = .007$ ), thus, group differences in persistence behavior were verified by nonparametric permutation test (22) with 10,000 permutations, and associations between persistence behavior and other variables are measured with the nonparametric Spearman  $\rho$  correlation coefficient (23).

### Neuroimaging acquisition and analysis

Images were collected on a 3.0-T Siemens TRIO scanner. Structural images were acquired with a T1-weighted MPRAGE sequence (256x256 matrix, FOV 256 mm, 176 1-mm sagittal slices). Blood-oxygen-level-dependent functional images were acquired with a multi-band echo-planar imaging sequence (TR = 600 ms, TE = 28.2 ms, FOV = 208 mm, flip angle 30°, echo spacing = 0.41 ms, multiband acceleration factor 5, 35 axial slices, voxel size 1.53 × 1.53 × 3.99 mm). A field map sequence acquired prior to functional imaging was used to correct geometrical distortion in the functional images. The *Fmriprep*

(24) pipeline was used for geometrical distortion correction, head motion and slice-timing correction, and normalization of images to MNI standard space (details in Supplemental Online Material). For each subject, a General Linear Model was fit to the functional data to estimate signal change related to the experience of negative events (using FMRIB’s Software Library version 5.0, <http://www.fmrib.ox.ac.uk/fsl/> (25,26)).

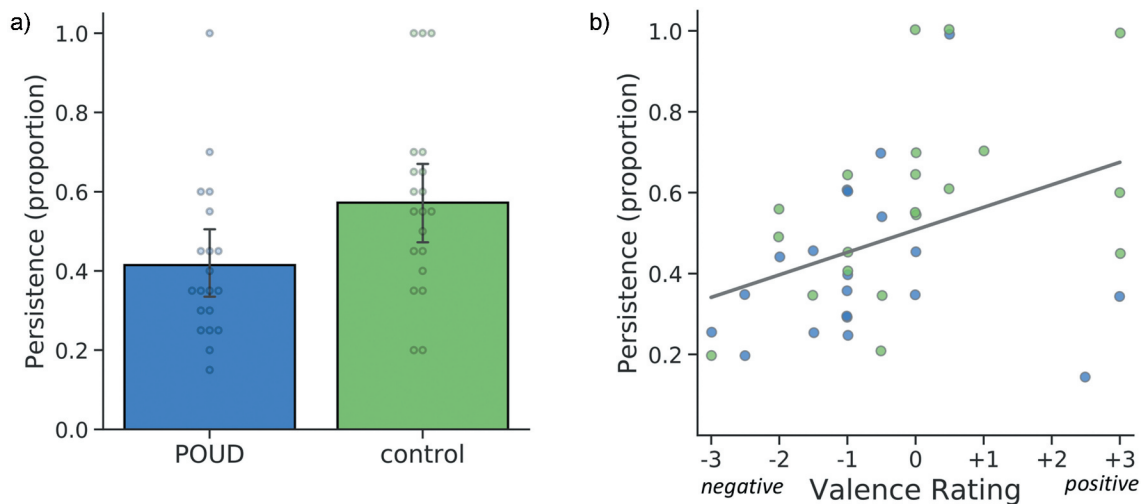
### GLM specification

The GLM consisted of two regressors identifying two possible outcomes after an obstacle was encountered: (1) negative event received and (2) obstacle avoided. Additional regressors modeled other task events (e.g., path choices, “advance” cues, missed responses) and head motion-related confounds (see Supplemental Online Material for complete GLM specification). These regressors (except head motion-related confounds) were convolved with a canonical double-gamma response function in FSL’s FEAT analysis package. Group differences were examined by submitting individual maps (parameter estimates) of the response to negative events to a nonparametric permutation-based test of the group difference (10,000 permutations with FSL’s *randomize* tool). The results were thresholded at  $p < .05$ , corrected for the striatum region of interest (FSL threshold-free cluster enhancement (27)). The striatum region of interest was defined by a meta-analytic contrast of brain responses to positive subjective value versus negative subjective value stimuli (28) intersected with a structural definition of striatum voxels from the Harvard-Oxford Probabilistic Atlas (29).

## Results

### Behavioral responses to negative events: POUD group makes less decisions to persist with a goal

Decisions in the PAS Task were classified as persistence decisions if the participant chose to continue on the same path after having just experienced a negative event on that path. The proportion of decisions to persist out of all decisions made after a negative event was greater in control compared to POUD participants (mean (s.d.): control = .572 (.228), POUD = .415 (.194); difference = .158, 95% CI = [.018, .297],  $t(38) = 2.293$ ,  $p = .028$ ,  $d = .725$ , permutation test  $p = .027$ ; Figure 2A). On the more specific measure of high-value persistence, control participants similarly chose to persist on the highest value path more than POUD participants (mean proportion of choices after a negative event on the highest value path (s.d.): control = .670 (.357), POUD = .428 (.271); difference = .242, 95% CI = [.034, .450],  $t(38) = 2.355$ ,  $p = .024$ ,  $d = .745$ ,



**Figure 2.** Persistence decisions and affective responses. (a) Proportion of persistence decisions was lower in POUD than in the control group. Vertical axis represents the proportion of decisions where participants chose to persist with the initially chosen path. Filled bars show mean value for each group, error bars represent 95% confidence interval, and points represent individual participant values. (b) Greater negative affect correlated with lower persistence across all participants. The proportion of persistence decisions is plotted against self-reported affective responses to negative events in the task.

permutation test  $p = .024$ ). Furthermore, the groups did not significantly differ in choices to start a round on the highest value path (mean (s.d.): control = .620 (.252), POUD = .570 (.297);  $t(38) = 0.560$ ,  $p = .579$ ,  $d = .177$ , permutation test  $p = .546$ ), but POUD participants were more likely to switch from any of the higher value paths to a lower value path (details in Supplementary Table S2). These observations are consistent with a suboptimal pattern of lower persistence in the POUD compared to the control group. Response times for decisions did not differ between groups (mean (s.d.): control = 856 ms (235 ms), POUD = 844 ms (201 ms); difference = 12 ms, 95% CI = [-132, 156],  $t(38) = 0.170$ ,  $p = .866$ ). Response times for button presses in response to the obstacles also did not differ between groups (mean (s.d.): control = 978 ms (208 ms), POUD = 991 ms (178 ms); difference = 13 ms, 95% CI = [-140, 114],  $t = 0.204$ ,  $p = .840$ ).

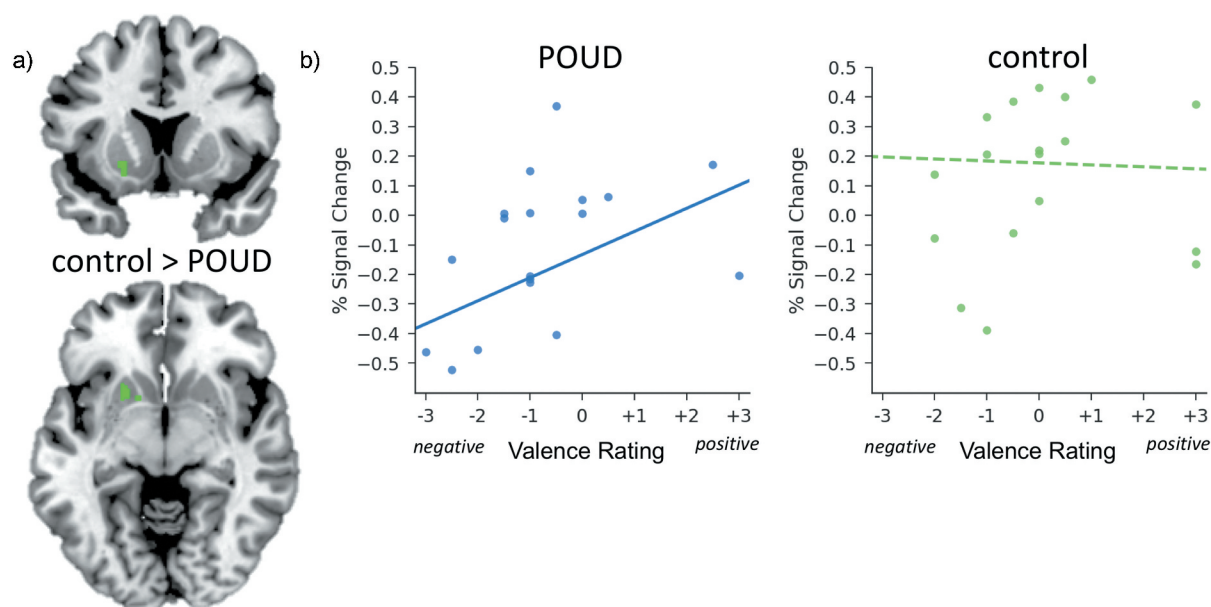
### **Affective responses to negative events correlate with persistence behavior**

We hypothesized that individuals are more persistent when they experience more positive and less negative affect. We tested this hypothesis by examining self-reported affect in response to negative events, and its relation to persistence decisions. Across all subjects, subjective feeling valence significantly correlated with the proportion of persistence decisions (Spearman  $\rho = .471$ ,  $p = .002$ , Figure 2B), indicating that individuals who felt more negative (less positive) in response to negative

events were less persistent. The relation between feeling valence and persistence did not significantly differ between groups (POUD  $\rho = .282$ ; control  $\rho = .589$ ; Fisher  $r$ -to- $z$  (30,31):  $z = 1.123$ ,  $p = .261$ ). Subjective feeling valence did not significantly differ between groups (mean (s.d.) on scale from -3 to 3: control = -.075 (1.599), POUD = -.750 (1.445); difference = .675, 95% CI for difference = [-.326, 1.676],  $t(38) = 1.365$ ,  $p = .180$ ).

### **Left Putamen response to negative events differs in POUD**

We hypothesized that striatum responses to negative events would differ between POUD and control participants due to the role of the striatum in forming a behavioral response to negative events (14,15). In the group-level contrast of neural responses to negative events in control compared to POUD participants, a cluster of voxels in left ventral putamen (i.e., the lateral and ventral aspect of the striatum) showed a greater response to negative events in control compared to POUD participants (Figure 3A, peak voxel at  $x, y, z = [-20, 12, -8]$ ,  $p < .05$ , corrected for striatum volume). In a whole brain exploratory analysis, no other voxels showed a difference at the whole brain corrected threshold. Although the timing of task events was structured to isolate responses to the negative events, participants expected a decision after every negative event. Therefore, neural responses to negative events may represent a combination of the reaction to the events as well as



**Figure 3.** Left putamen response to negative events differs between POUD and control groups. (a) Green cluster indicates voxels that show a significantly greater response to negative events in control compared to POUD participants ( $p < .05$ , corrected for striatum volume). (b) Scatter plots show left putamen response to negative events (vertical axis) plotted against self-reported affective responses to negative events.

the formulation of a behavioral response to it. For this reason, we next examined how individual differences in the left putamen response related to affective responses and persistence decisions.

#### **Affective responses to negative events correlate with left putamen responses in the POUD group**

We hypothesized that the striatum response (including ventral putamen) to negative events in the PAS task is part of how individuals form a behavioral response to negative events. If this is the case then individual responses to negative events in the striatum may correlate with affective responses and, consequently, persistence decisions. We examined correlations of individuals' responses to negative events in the left putamen region identified in the group contrast with (a) self-reported affective responses to negative events and (b) persistence decisions. In POUD participants, there was a positive correlation between left ventral putamen signal change and affective responses to negative events such that greater negative (less positive) affect related to lower left ventral putamen signal change (Spearman  $\rho = .509$ ,  $p = .022$ , Figure 3B), but there was no significant association of the neural response with persistence decisions (Spearman  $\rho = .200$ ,  $p = .398$ ). In control participants, there was no significant association of left putamen responses with affective responses to negative events (Spearman  $\rho = .048$ ,  $p = .840$ ) or with persistence decisions (Spearman  $\rho = .137$ ,  $p = .565$ ).

To examine the possibility that differences in tobacco cigarette smoking may underlie group differences in persistence behavior and striatum response to negative events, (a) group comparisons were repeated with the inclusion of a smoking behavior covariate, (b) correlations between smoking behavior and the measures were examined in the POUD group, and (c) the measures were compared between nonsmoking POUD participants and those with any smoking. Although group differences are no longer significant after including a smoking behavior covariate, collinearity between smoking behavior and group membership reduces power in these comparisons (see Results in Supplemental Online Materials). The lack of smoking behavior correlations or differences between nonsmokers and smokers (all  $p > .5$ , Table S1) suggests that the loss of significance in comparisons that include a smoking behavior covariate reflects loss of power rather than a relation between smoking behavior and the key measures (persistence and striatum response to negative events).

#### **Discussion**

In individuals recovering from POUD, similar to disorders involving other addictive substances, negative affect is related to increased substance craving (1–6). Behavioral responses to negative events that elicit negative affect are therefore an important factor that may influence recovery and likelihood of relapse. The current study examined specifically how individuals recovering from POUD form



behavioral responses to negative events, that is, whether they decide to persist or abandon a goal after experiencing a negative event during goal pursuit. Findings showed that individuals recovering from POUD were less likely to persist with a goal after experiencing a negative event. More specifically, individuals recovering from POUD made less optimal persistence choices, that is, less choices to persist with the highest value goal, compared to the control group. Across all participants, greater negative (less positive) affect in response to negative events was related to lower persistence. Neuroimaging results showed that left ventral putamen responses to negative events were lower in POUD and individual differences related to affect, such that greater negative (less positive) affect related to lower left ventral putamen signal in POUD participants. These findings provide initial evidence that individuals in recovery from POUD respond differently to negative events that are unrelated to substance use. This difference in responses to negative events may be important to understanding recovery from POUD, as greater persistence relates to improved recovery outcomes for smokers and samples of individuals with substance use disorder not specific to one substance (e.g., alcohol, heroin, cocaine) (7–11).

The current findings build upon a body of research showing an association between persistence (also referred to as distress tolerance, e.g., see (11)) and a variety of measures of addictive behaviors in smokers and populations with nonspecific substance use disorders (i.e., alcohol/heroin/cocaine/PCP) (7–11). The unique contributions of the current findings are that (a) behavioral and neural responses to negative events differ in POUD compared to control participants, and (b) the affective response to negative events may partly determine decisions to persist with a goal, such that stronger negative feelings are correlated with less persistence. This knowledge is important to inform interventions that target strategies for coping with negative affect and stress (32), as well as those that target persistence behavior to prolong abstinence (7). Prior interventions that target negative affective responses and persistence behavior (e.g., in smokers) have aimed to increase an individual's ability to tolerate distress by exposing them to negative feelings (e.g., remembering negative events) and focusing on strategies to cope with these negative feelings to replace avoidance-based strategies that may lead to substance use (7,8). The current study provides some evidence that such interventions have promise in a POUD population and provides a methodology to measure the success of such interventions in normalizing responses to negative events.

Prior research suggests that decisions under uncertainty differ between control participants and individuals with substance use disorders (33). For example, in individuals in treatment for methamphetamine dependence, risk-taking decisions are increased and negative outcomes may have a lesser impact on risk choices, compared to controls (34). Though the current findings also suggest differences (between substance disorder and control participants) in decision-making under uncertainty, comparison of the current persistence decisions with risky choices is difficult because the current task does not distinguish risky from safe decisions. Specifically, while we observed that POUD participants were less persistent on the highest value path after a negative outcome, such decisions cannot be deemed either risky or safe because negative outcomes were presented with equal probability on each path, and there was no guaranteed safe outcome. This study and prior work suggest that responses to negative outcomes and subsequent decisions are an important area of research to understand decisions in individuals recovering from substance use disorders.

The current study also provides preliminary evidence of a neural mechanism that may contribute to lower persistence in response to negative events in individuals recovering from POUD. Left ventral putamen, in the ventrolateral area of the striatum, showed responses to negative events that differed between groups and correlated with negative affective experience such that lower responses related to greater negative affect in individuals recovering from POUD. Greater negative affect is also related to lower persistence. Thus, lower left putamen signal in response to negative events in POUD may underlie a tendency to respond maladaptively to negative events by getting upset and quitting a goal. Neural responses to negative events in the striatum may be a target for further research to identify the basis for impaired persistence in individuals that struggle with addictive substance use. This knowledge can increase awareness of the many factors that contribute to POUD as well as increase support for potential intervention targets. For example, interventions may aim to normalize striatum responses to negative events or provide strategies for better coping with negative affect to promote normalized persistence (32).

Findings in the current study differ in two key ways from research with a variation of this paradigm in a sample with no history of substance use. First, prior research showed that the relation between affect and persistence depended on contextual factors including perceived control (12) and acute physiological stress (19), however, the participants did not perceive different

levels of control over obstacles in this study and physiological stress was not assessed. Second, no relation was found between persistence and striatal signal in the current study, but prior research (in a sample with no history of substance use) showed that decreases in ventromedial striatum (nucleus accumbens) reflected information gained from a controllable negative event, and larger decreases correlated with persistence behavior (12). The region of striatum that showed a group difference in the current study was a more lateral region of the striatum (ventral putamen), which may not be directly related to persistence behavior. Instead, we found that activity in this region correlated with affective responses to negative events. Further research is necessary to understand these sub-regions, their responses to negative events, and their contribution to persistence decisions.

The current study examined negative events unrelated to substance use in order to probe behavioral and neural differences in general affective responses, rather than responses that are specific to addiction recovery (e.g., negative events encountered in pursuit of recovery goals). This approach was preferred for several reasons. First, any source of negative affect can be a risk factor for substance use, not only negative events that are encountered during pursuit of a recovery goal (1,2). That is, negative feelings can motivate substance-seeking as a method of coping, regardless of the cause of negative affect (e.g., a recovery-related cause such as a missed treatment meeting or an unrelated cause such as a family argument). Second, while it was not possible to manipulate negative events that might endanger recovery goals, the current paradigm allowed for the manipulation of negative events and measurement of persistence with simple short-term goals. Prior research has used a number of distinct methods such as repeated tries in a mirror-tracing task, or duration of breath holding, and demonstrated that greater persistence related to less lapses when quitting tobacco smoking (9,11). Key features of these measures are that participants experience negative affect while maintaining a non-drug-related goal, and their persistence is measured. The current paradigm retains these common features and prior work shows that behavior in the paradigm is related to self-reported trait-level persistence (19). Finally, the paradigm was designed to allow measurement of neural responses, which required that the negative events and persistence decisions be repeated many times within the session. This approach allowed us

to measure a potential neural mechanism underlying persistence after negative events.

A new approach was used here to understand persistence behavior in POUD, thus there are important limitations. In the task examined here, individuals recovering from POUD were less likely to persist with a goal after a negative event and, relatedly, more likely to switch to a lower value goal. Due to the structure of negative events in this task, this behavior was always disadvantageous, whereas persistence with the high-value goal was always advantageous. However, persistence is not advantageous in some situations in daily life, for example, when the goal is unachievable or too costly. The likelihood of achieving the goal was held constant across paths in the current research, thus, these situations were not examined. An important question for further research is whether better recovery outcomes are associated with indiscriminate persistence, or with judicious persistence only when negative events are likely to be temporary or changeable. A related question is whether the task-specific behavior here is related to critical recovery behaviors, such as repeated (i.e., persistent) enrollments in treatment. The current study does not address this question. Instead, the experiment is highly focused on behavioral decisions immediately following negative events, and the neural and affective responses to negative events that may shape those decisions in individuals recovering from POUD compared to a control group.

An additional limitation is that control participants were not matched on tobacco smoking behavior at the time of experimental measures. Thus, effects of group (POUD or control) are difficult to distinguish from reported smoking frequency during the week before scanning. Within the POUD group, however, the primary measures of persistence behavior, affective response to negative outcomes, and left putamen response to negative outcomes were unrelated to reported smoking behavior during the week before scanning. Persistence is linked to quitting tobacco smoking (i.e., high persistence relates to longer abstinence (8,9,11)), as well as treatment for other substance use disorders (i.e., increased persistence relates to staying in treatment longer and greater improvement in substance abuse treatment patients not specific to any one substance (7,10)). With the caveat that persistence is measured differently in these studies, this pattern suggests that the difference in persistence here may not be attributable to a specific substance but instead to a more general factor related to addictive substance use. Importantly,

the current study provides a foundation for examining neural, behavioral, and affective responses to negative events in substance use disorders.

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