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Using ecological momentary assessments of negative affect and craving during residential opioid use disorder treatment to predict patients' relapse to substance use

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ABSTRACT

Background: Negative affect (NA) and craving are often independently examined as precipitators of relapse among individuals with substance use disorders, including opioid use disorder (OUD). Recent ecological momentary assessment (EMA) research has revealed that NA and craving frequently co-occur within individuals. Yet we know little about the general patterns of, and variability in, within-person associations between NA and craving, as well as whether the nature and degree of within-person NA-craving coupling predicts post-treatment time-to-relapse.

Methods: Seventy-three patients (77 % male, $M_{age} = 30.10$, *Range* = 19–61) in residential treatment for OUD took part in a 12-day, 4× daily smartphone-based EMA study. Linear mixed-effects models tested within-person, day-level associations between self-reported NA and craving during treatment. The study used Person-specific slopes (i.e., average within-person NA-craving coupling for each participant) estimated from the mixed-effects model in survival analyses with Cox proportional hazards regression models to determine if between-person differences in the within-person coupling predicted post-treatment time-to-relapse (operationalized as the return to problematic use of any substance except tobacco), and whether this prediction was similar across patients' average levels of NA and craving intensity. The study monitored relapse through a combination of hair samples and reports from patients or alternative contacts via a voice response system twice a month for up to 120 days or more following discharge.

Results: Among the 61 participants with time-to-relapse data, those with stronger positive within-person NA-craving coupling on average during residential OUD treatment had a lower hazard of relapsing (slower time to relapse) post-treatment than participants with weaker NA-craving slopes. The significant association held after controlling for interindividual differences in age, sex, and average levels of NA and craving intensity. Average NA and craving intensity did not moderate the association between NA-craving coupling and time-to-relapse.

Conclusions: Interindividual differences in average within-person, day-level NA-craving coupling during residential treatment predict OUD patients' post-treatment time-to-relapse.

1. Introduction

Addictions to prescription opioids in the United States have increased substantially over the last 20 years (SAMHSA, 2019). Unfortunately, one of the most common outcomes following treatment for opioid use disorder (OUD) is still relapse (Zhu et al., 2018). Negative affect and craving have long been associated both with each other and with relapse risk in the addiction literature broadly, as well as the OUD

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literature specifically (e.g., Epstein et al., 2009). Theoretically, negative affect has been posited as both a causal factor in craving (Cooney et al., 1997; Fox et al., 2007) and as an outcome of delayed or frustrated craving (Kavanagh et al., 2005; Stasiewicz & Maisto, 1993). Recent evidence suggests that negative affect is more likely to precede craving than vice versa, at least among alcohol-dependent outpatients (Waters et al., 2020). The direction of effect notwithstanding, it is clear that associations between these intra-personal states can play an important role in addiction (Cyr et al., 2022).

In this study, we first focused on the within-day associations between negative affect and craving during residential treatment for OUD and time-to-relapse (defined as the return to problematic use of any substance except tobacco following treatment). More specifically, this study first characterized the general patterns of, and between-person variability in, the within-person associations between daily fluctuations in negative affect and craving reported via ecological momentary assessment (EMA; Shiffman et al., 2008). Second, it used individual-level, within-person associations between negative affect and craving derived from the first set of analyses to predict time-to-relapse and investigate whether such prediction varied by patients' average levels of negative affect or craving intensity.

1.1. Associations among negative affect, craving, and relapse

Negative affect has been defined as a negative and subjective evaluative feeling state in response to internal or external stimuli (Kassel, 2010). A large literature demonstrates a strong association between negative affect and different substance use outcomes (Baker et al., 2004; for review see Witkiewitz & Marlatt, 2004 and Hogarth, 2020). This literature is strongly influenced by negative reinforcement theory, which posits that drug use is motivated by the desire to reduce negative mood states (Baker et al., 2004).

Craving—often described as a subjective urge or desire to use substances (Kozlowski & Wilkinson, 1987)—has been linked to the use of all drugs, including cigarettes (Catley et al., 2000) and alcohol (Litt et al., 2000). Within a laboratory setting, stress-induced increases in drug craving have predicted relapse to alcohol use (Brady et al., 2006; Cooney et al., 1997; Higley et al., 2011; Sinha et al., 2011) and cocaine (Back et al., 2010; Sinha et al., 2006). Studies that do not employ lab-based, cue-induced operationalizations of craving have been less consistent in finding associations between craving and relapse, leading some researchers to question the utility of unidimensional assessments of craving (e.g., Anton, 2000; McEvoy et al., 2004) and call for considering the construct's multi-dimensionality. More recently, however, studies applying EMA of craving have shown that craving precedes drug use among individuals being treated for cocaine and heroin use specifically (Preston & Epstein, 2011) as well as OUD (Preston, Kowalczyk, Phillips, Jobes, et al., 2018b) and substance use disorder (Vafaie & Kober, 2022) more broadly. We agree that a full understanding of craving and its association with relapse should include its multi-dimensionality. However, based on the recent work of Preston and colleagues, we also believe that EMA approaches to assess craving among treatment populations hold considerable promise.

EMA is an ideal methodology for capturing the temporal dynamics of craving, negative affect, and substance use (for review, see Serre et al., 2015). Studies using EMA methodology have revealed complex associations between craving and negative affect in the context of abstinence. For example, using hourly survey responses across the first 24 h of smoking abstinence, Bujarski et al. (2015) examined relationships between individuals' levels of negative affect and craving and the rates of change of these intrapersonal states. This study found that whereas average levels of negative affect were positively associated with craving, the person-level slope (i.e., change trajectory) for negative affect was only significantly and positively correlated to the corresponding craving slope during the first 6–8 h after participants' last cigarette. These time-specific findings demonstrate EMA methods' ability to document the complexity of negative affect—craving associations.

Despite the recent proliferation of EMA research examining negative affect and craving, most studies consider how they impose risk for substance use *independently of one another*. Theoretical models postulate that fluctuations in internal states, and their within-person correlates and consequences, are critical for understanding processes such as self-regulation (e.g., Roos & Witkiewitz, 2017) and relapse prevention (e.g., Hendershot et al., 2011) during addiction recovery. Thus, we posit that treatment research and practice could benefit from a fuller understanding of the nature and consequences of interindividual differences in the way negative affect and craving are mutually related (i.e., their relative independence or co-occurrence) within individuals. For example, previous EMA research with individuals in OUD treatment has documented concurrent and prospective links between negative affect and opioid use (Epstein et al., 2009; Epstein & Preston, 2012; Kowalczyk et al., 2018; Preston et al., 2018c; Preston, Kowalczyk, Phillips, Jobes, et al., 2018a; Preston, Kowalczyk, Phillips, Jobes, et al., 2018b), craving, and stress (Epstein et al., 2009; Preston et al., 2018a, 2018b, 2018c; Serre et al., 2015). These findings can be built upon by considering the within-person co-occurrence (i.e., coupling or association) of negative affect and craving and how interindividual differences in these intra-individual associations may be related to future substance use (i.e., relapse). Previous research has demonstrated the utility of using within-person associations (i.e. slopes) among stressors, affect, and behaviors to predict future health outcomes, including physical health (Piazza et al., 2013) and mental health conditions (Charles et al., 2013), as well as future alcohol problems among adults (Mohr et al., 2013) and university students (Russell et al., 2017). To our knowledge, however, no prior studies have examined within-person associations between negative affect and craving among individuals in treatment for OUD as predictors of post-treatment relapse.

1.2. The current study

The goal of the current study was to investigate whether EMA data on craving and negative affect collected from patients with opioid use disorder (OUD) via smartphones during residential treatment could be used to predict time-to-relapse following treatment. Specifically, the current study used 12 days of EMA data collected during residential treatment for OUD to understand within-person associations between fluctuations in negative affect and craving during treatment, and to determine if between-person differences in these within-person associations predicted time-to-relapse within approximately 120 days post-discharge from residential treatment. We expected to find that days characterized by higher-than-average negative affect would also be characterized by higher levels of craving. We also expected, however, to find considerable interindividual variability in this association. In other words, although we expected some patients' daily negative affect fluctuations to be strongly and positively associated with their daily craving intensity, we expected other patients to have weak, absent, or even negative associations between their reported experiences of daily fluctuations in negative affect and craving. For the sake of clarity, we refer to the variable that was constructed from each patient's average within-person association between negative affect and daily craving intensity as the "NA-craving coupling" and use the term association for results of the models predicting time-to-relapse.

The primary hypothesis examined was that NA-craving coupling would predict time-to-relapse such that individuals with stronger NA-craving coupling would have increased hazards of relapsing relative to individuals with weaker within-person coupling between negative affect and craving. Analyses also examined whether the association between NA-craving coupling and time-to-relapse held after controlling for patients' age, sex, and average levels of negative affect and craving intensity and whether patients' average levels of either negative affect or craving moderated associations between NA-craving coupling and time-to-relapse. The study also tested the three-way interaction between

negative affect, craving, and NA-craving coupling.

2. Material and methods

The EMA and relapse data used for this study were drawn from a larger study evaluating changes in neurophysiological function, affect, and stress across time among patients in residential treatment for prescription OUD. Comprehensive information about the larger study, including information about participants' psychiatric comorbidity, addiction history, and concurrent medication use, has been published elsewhere (Huhn et al., 2016; Lydon-Staley et al., 2017). This article provides details relevant to the current investigation below.

2.1. Participants

Participants ($N = 73$, 77 % male, $M_{age} = 30.10$, $SD_{age} = 10.13$, Range = 19–61) were patients at Caron Treatment Centers (CaronTC), a residential drug and alcohol treatment facility, who were recruited if: a) they met criteria for prescription opioid use disorder as determined by the Structured Clinical Interview for DSM-IV-TR (SCID; First et al., 2002), and Form-90D (Westerberg et al., 1998), and b) prescription opioids were the primary substance used and the focus of treatment. All participants completed medically assisted withdrawal approximately 10–14 days prior to the start of data collection. Other inclusion criteria included being over the age of 18, scheduled to stay in residential treatment for at least 28 days, and willingness to comply with the research protocol. Patients were excluded from participation if they had any 1) current moderate to severe major depressive disorder, psychosis, bipolar disorder, or any psychiatric disorder that would compromise the patient's ability to complete the study; 2) current or projected use of approved opioid agonist or antagonist maintenance treatment while enrolled in the study; 3) any significant problem which, in the opinion of the clinical research directors, would compromise or confound the data collection procedures over the course of the study.

2.2. Procedure

All participants provided IRB-approved written informed consent after study staff fully explained the study protocol to them. Participants who met study criteria were asked to begin completing smartphone-based surveys at four fixed times per day for 12 consecutive days. A preset alarm notified participants that a survey was ready to be taken at early morning, late morning, mid-afternoon, and evening times that did not conflict with their treatment programs. Each survey took approximately 2–3 min to complete. If participants did not choose to take the survey after the first notification, they were given reminders every 15 min for up to one hour, after which the survey was closed until the next measurement occasion. The university Institutional Review Board approved all study procedures.

Based upon staff recommendations and patient decisions, participants either left primary residential treatment after 28 days or stayed in extended residential care for as long as four months. After leaving residential treatment, all patients received a continuing treatment plan that provided for either time in a half-way house or regular outpatient care.

2.3. Measures

2.3.1. Craving

The study measured craving during each of the four assessments per day across 12 consecutive days using items adapted from the Desires for Alcohol Scale (Love et al., 1998) to accommodate daily assessment and polydrug use. As part of each EMA survey, participants completed three items of the form, "Since last data entry [Since waking]… 'the idea of using drugs has intruded upon my thoughts'; 'I have missed the feeling drugs can give me'; and 'I have thought about how satisfying drugs can be' using a five-point scale ranging from "strongly disagree" to "strongly agree". A composite craving score was calculated for each participant for each assessment as the average of the three responses. Craving was then averaged across the four assessments for each day to create a day-level mean craving score. Each participants' day-level craving scores were averaged across all days to create a person-level mean craving score. The day-level composite provided reliable assessment of within-person change, $R_c = 0.89$ (as per the generalizability theory approach for intensive repeated measures data, see Bolger & Laurenceau, 2013).

2.3.2. Negative affect

The study also measured negative affect (NA) during each of the four within-day assessments using items adapted from the Positive and Negative Affect Scale (PANAS) (Watson et al., 1988) for repeated assessment. As part of each EMA survey, participants completed eight items of the form, "Since last data entry [Since waking] have you felt… 'angry', 'irritable', 'lonely', 'sad', 'guilty', 'ashamed', 'anxious', and 'stressed'" using a continuous touchpoint (slider-type) scale with endpoint anchors 0-Not at all and 100-Very. The research team calculated a composite NA score for each participant for each assessment as the average of the eight responses. We then averaged NA across the four assessments for each day to create a day-level mean NA score (daily $R_c = 0.82$), and we averaged day-level NA scores across all days for each participant to create a person-level mean NA score.

2.3.3. Time-to-relapse

Although all participants were in treatment for OUD, such OUD patients commonly have histories of disordered use to several substances (information on participants' substance use disorder histories collected at treatment intake is included in Table 1). As such, a major focus of the treatment program was to maintain abstinence from the problematic use of any substance (including, but not limited to, opioids), and participants were required to abstain from all substances except tobacco throughout the duration of the study, as a function of staying at the residential treatment facility (tobacco cessation was strongly encouraged, but was not mandatory). The study operationalized relapse as the misuse of prescribed opioids; any use of nonprescribed opioids, illicit drugs, marijuana, or amphetamines; or return to heavy alcohol use (Falk et al., 2010; Sobell et al., 2003) following patients' discharge from residential treatment. Alcohol, as a legal substance, was not identified as a problem or treatment goal unless the patient had a diagnosis of misuse. The study counted heavy alcohol use after treatment as a "relapse" if it was identified as a treatment target ($n = 8$). As marijuana use was illegal at the time of primary and follow-up data collection, and use constituted a legal violation, we also defined subsequent use of marijuana as relapse ($n = 1$).

Upon leaving residential treatment, the study collected treatment outcome data from patients up to approximately 120 days following discharge. The plan at the study's outset was to follow participants for

Table 1
Participant lifetime substance use disorder at treatment intake.

Lifetime substance use disorder	N
Opioid only	5
Alcohol	24
Tobacco	46
Cannabis	42
Tranquilizer	9
Sedative	18
Steroid	2
Stimulant	17
Cocaine	16
Hallucinogen	2
Inhalant	1
Other	2
Missing	9

Note. N = 73 total patients.

90 days post-discharge. When data from early participants indicated that some relapse events occurred near the 90-day mark, the research team made the decision to keep tracking willing participants for up to 120 days. In a little over a dozen cases, the study followed participants beyond 120 days. Research staff used a combination of factors to determine patient status: 1) patients were followed on a twice monthly basis via an Interactive Voice Response System (patients also provided the name of an alternate contact to communicate by telephone if they could not be reached); and, 2) patients were asked to provide hair samples at 30 and 90 days post residential treatment at their local Quest Diagnostics Center; a five-panel opioid screen was performed on each sample (Quest Diagnostics; Madison, New Jersey). In addition, the CaronTC provided the research staff with random (up to four a month) urine drug screening results from their Recovery Care Services (RCS) for the first 17 weeks (120 days) following discharge. The final decision to assign a value for relapse was made with all available data by a six-member committee, including a research psychiatrist, two clinical psychologists, and the research staff involved in the study (Klein et al., 1994). In cases where hair samples and self-report yielded conflicting results (i.e., hair samples indicated relapse and self-report indicated no relapse, or vice versa), the team made the decision to assign a value of relapse. Assessment of treatment outcome began when the patient left residential treatment and began reintegration into the community. The study operationalized time-to-relapse as the number of days between leaving residential treatment and the committee's "best estimate" of when that relapse occurred.

2.4. Data analysis

The first set of analyses used multilevel models (MLM; Bolger & Laurenceau, 2013; Raudenbush & Bryk, 2002) to calculate the within-person, same-day coupling between day-level deviations in NA from person-mean levels and day-mean craving (hereinafter "day-level"), controlling for day of study, fluctuations in prior-day craving, and individual differences in average NA intensity. Next, person-specific parameters (i.e., slopes) capturing the average within-person, day-level NA-craving coupling for each participant were estimated from the MLM by adding the fixed and random effects parameters together. We then exported these person-specific NA-Craving slopes and used them as independent variables in survival analysis with Cox proportional hazards regression models to determine if between-person differences in the within-person couplings between negative affect fluctuations and craving could predict time-to-relapse following residential treatment.

2.4.1. Association between negative affect and craving

Eq. (1) provides the MLM model that we used to estimate within-person, day-level associations between deviations from person-level averages of NA and craving, accounting for study day, carryover in craving from the prior day, and individual differences in average NA intensity.

$$\begin{aligned}
&\text{Level 1}: \text{Craving}_{it} = \text{B}_{0i} + \text{B}_{1i}(\text{Day}_{it}) + \text{B}_{2i}(\text{Craving}_{it-1}) + \text{B}_{3i}(\text{NA}_{it}) + \varepsilon_{it} \\
&\text{Level 2}: \text{B}_{0i} = \gamma_{00} + \gamma_{01}\text{iNA}_i + \nu_{0i} \\
&\text{B}_{1i} = \gamma_{10} \\
&\text{B}_{2i} = \gamma_{20} \\
&\text{B}_{3i} = \gamma_{30} + \nu_{3i}
\end{aligned} \tag{1}$$

In Eq. (1), a random person-level intercept (ν_{0i}) accounts for the nesting of days (Level 1) within people (Level 2). Of particular importance in this model are (a) the γ_{30} fixed slope, which describes the sample average day-level association between deviations in levels of NA from average and craving, adjusting for study day, fluctuations in prior-day craving, and individual differences in average NA intensity; and (b) the ν_{3i} random slope, which captures individual differences in the γ_{30} fixed slope. The day-mean NA variable was person-mean centered, following proposed guidelines for appropriately estimating within-person couplings in a multilevel framework (see, e.g., Neubauer et al., 2020) to disentangle the within-person association from between-person variability. We also included each person's mean NA across all days—γ_{01}—to account for between-person differences in average NA intensity. Person-mean NA was centered on the overall mean prior to model entry. γ_{20} controls for the fixed effect of prior day's craving fluctuation on today's craving, and was person-mean centered. γ_{10} controls for the fixed effect of day of study on craving—given the treatment context of the data collection, the study expected craving to decrease over the course of the study (as demonstrated in prior work; see Cleveland et al., 2021). The day of study variable was centered such that the zero-point corresponded to the first day for each participant.

The level 1 association between (deviations from average levels of) NA and craving is interpreted as the within-person, day-level association, adjusted for person-level NA, prior day's craving fluctuation, and day of study; the level 2 association is interpreted as the between-person association. The MLM was fit in R using restricted maximum likelihood estimation in the nlme package (Pinheiro et al., 2015), with missing data handled using listwise deletion. We allowed residuals to autocorrelate (AR1).

2.4.2. Within-person coupling reliability

The study team used MLM results to estimate average NA-craving slopes for each participant. We calculated these slopes based on Eq. (1), using day's NA (person-mean centered) as the predictor of that day's craving, then adding the fixed slope describing the average association between (deviations from average levels of) NA and craving among participants (controlling for study day, previous day's craving fluctuation, and person-mean NA; γ_{30} in the equation) to the model-estimated best linear unbiased predictor, calculated from the ν_{3i} random effect for each participant. To avoid spurious results, we estimated within-person NA-craving slopes in this way only for participants who reported at least some intraindividual variance in both NA and craving across assessments.

Importantly, the two-step approach applied here (i.e., estimating NA-craving slopes for each person in one model and using these estimates to predict time-to-relapse in a second model) may introduce bias by ignoring the error around the estimation of the slope parameters in the first step (Liu et al., 2019). To examine whether interindividual differences in intraindividual NA-craving couplings were estimated with sufficient reliability before treating the person-level average coupling as an observed variable in subsequent Cox regression models, we computed within-person coupling reliability (WPCR) estimates using an approach developed by Neubauer and colleagues (Neubauer et al., 2020). The person-specific reliability index for interindividual differences in intraindividual couplings was defined per Eq. (2).

$$\text{WPCR}i = \frac{\sigma_{33}}{\sigma_{33} + \frac{\sigma_\varepsilon^2}{\sigma_x^2 * (T_i - 1)}} \tag{2}$$

where σ_{33} represents the level 2 random slope variance of NA, σ_ε^2 represents the level 1 residual variance, σ_x^2 represents the within-person (level 1) variance of person-mean centered NA, and T_i represents the number of repeated measurement occasions (i.e., days) for each individual. The sample reliability estimate, WPCR, was derived per Eq. (3) as the average of all person-specific reliability estimates:

$$\text{WPCR} = \frac{1}{N}\sum_{i=1}^{N} WPCR_i \tag{3}$$

2.4.3. Prediction of time-to-relapse from person-specific NA-craving slopes

Using the individual slopes estimated above, the team used survival analyses with Cox regression models to test the hypothesis that between-person differences in the within-person, day-level NA-craving association during residential treatment would predict post-treatment time-to-

relapse. At each time point, survival analysis compares individuals who relapsed at that point to all individuals who were still maintaining abstinence and therefore still at risk of relapsing.

We also ran sensitivity analyses (1) controlling for participants' age, sex, and usual NA and usual craving intensities, and (2) testing interactions among person-specific NA-craving slopes, usual NA, and usual craving to check if the prediction of time-to-relapse from the person-specific NA-craving slope term differed depending on participants' person-mean levels of NA or craving intensity. Usual NA and craving were defined as the mean level of NA/craving reported by each participant across all days. We standardized the scores for person-specific NA-craving slopes, usual NA, and usual craving levels ($M = 0$, $SD = 1$) prior to entry into Cox regression models to facilitate interpretation and comparison. We report results as hazard ratios with 95 % confidence intervals.

3. Results

3.1. Descriptive statistics

Table 2 reports descriptive statistics. The full sample of participants reported an average day-mean craving of M = 2.08 (SD = 1.12, Range = 1–5) and an average day-mean NA of M = 34.83 (SD = 20.46, Range = 0–98.50) across four momentary assessments collected each day. Intraclass correlation coefficients (ICCs) indicated that roughly 70 % of the variance in day-mean craving and 67.5 % of the variance in day-mean NA was between-person variance, leaving 30 % and 32.5 %, respectively, at the within-person level. The within-person (level 1) variance of the focal predictor, person-mean centered day-level NA, was 121.91.

On average, participants provided craving data on M = 9.66 (SD = 2.58, Median = 10, Range = 1–12) days, and NA data on M = 9.64 (SD = 2.57, Median = 10, Range = 1–12) days. Approximately 60 % of the sample had 10 or more days of data on craving and NA; $n = 2$ participants had two or fewer days of craving data and we thus excluded from MLM analyses, leaving $n = 71$ participants.

3.2. Association between negative affect and craving

Fig. 1 provides a descriptive view of within-person coupling of daily NA and craving across days for a subsample of six participants. Prior to interpreting the final MLM, we compared models (1) with and without prior-day craving fluctuation, and (2) with and without a random slope for day-level NA, to determine which model provided the most optimal fit to the data and/or explained the most variance in day-level craving. The model with prior-day craving fluctuation demonstrated better fit to the data (AIC = 1218.97 vs. 1494.43; BIC = 1262.76 vs. 1535.39), explained more overall variance (conditional pseudo-R^2 = 0.79 vs. 0.76), and resulted in a more reliable within-person NA-craving coupling estimate than the model without prior day craving fluctuation (WPCR = 0.49 vs. 0.42; described in more detail below). Comparing models with and without random slopes, the random slope model (a) yielded a random slope that was significantly different from zero, (b) fit the data significantly better (likelihood ratio test $\chi^2 = 21.31$, $p < 0.0001$), and (c) explained more variance (conditional pseudo-R2 = 0.79 vs. 0.77) than the model without a random slope. Thus, the study team selected the model with prior-day craving fluctuation and a random slope for NA for interpretation and further analysis.

Table 3 provides results of the MLM testing the day-level association between (deviations from average levels of) NA and craving. First, a significant random effect for the intercept ($\nu = 0.76$, 95 % CI = 0.53, 1.09) indicated that, as expected, participants exhibited variation in average craving. Second, a significant within-person, day-level fixed effect association between deviations from average levels of NA and craving (B = 0.02, 95 % CI = 0.01, 0.03) indicated that, as expected, participants' craving was on average significantly higher on days when they experienced higher NA than usual, adjusting for day of study, prior day's craving fluctuation, and usual NA level. Third, a significant random slope for day-level NA fluctuation ($\nu = 0.0003$, 95 % CI = 0.0002, 0.001) indicated that the strength of the day-level NA-craving association varied randomly between participants (i.e., craving was more strongly associated with NA fluctuations for some participants than others). Fourth, a significant person-level fixed effect association occurred between NA and craving (B = 0.03, 95 % CI = 0.01, 0.04), showing that between-person differences existed, whereby participants who experienced higher average NA also exhibited higher craving on average. Finally, the fixed effect of day of study was significant and negative (B = −0.03, 95 % CI = −0.05, −0.02), capturing a linear decrease in craving over the 12 days of the study (see Cleveland et al., 2021). The fixed effects portion of the model collectively explained approximately 19.7 % of the variance in day-level craving (marginal pseudo-R2 = 0.1970); the entire model (fixed and random effects) explained approximately 79.5 % of the variance (conditional pseudo-R2 = 0.7946).

Table 2
Correlations and descriptive statistics for study variables between- and within-subjects.

Between-Subjects									
	1	2	3	4	5	6	M	SD	Range
1. Age							29.90	10.10	19–61
2. Sex	−0.32**						0.76	0.43	0–1
3. Relapse status (1 = relapsed)	0.20	−0.17					0.50	0.50	0–1
4. Time-to-relapse	−0.17	0.24	−0.73***				101.89	74.94	0–315
5. PM Negative affect (uncentered)	0.08	−0.10	0.03	−0.05			35.46	17.15	4.11–92.42
6. PM Craving (uncentered)	−0.15	−0.16	−0.05	0.01	0.45***		2.16	1.02	1–5
7. Negative affect-Craving Slope	−0.11	−0.05	−0.29*	0.28*	0.06	−0.08	0.02	0.01	−0.01–0.07
8. PM Negative affect (GMC)							0.00	17.15	−31.35–56.97
9. PM Craving (GMC)							0.00	1.02	−1.16–2.84
Within-Subjects									
1. DM Negative affect (uncentered)							34.83	20.45	0–98.50
2. DM Craving (uncentered)	0.41***						2.08	1.12	1–5
3. DM Negative affect (PMC)							0.00	11.04	−36.22–47.76
4. DM Craving (PMC)			0.35***				0.00	0.60	−1.92–3.54

Note. Descriptive statistics are presented for this study's analytic sample only ($N_{persons} = 71$). M = Mean. SD = Standard deviation. PM = Person-mean. DM = Day-mean. GMC = Grand-mean centered. PMC = Person-mean centered.

*** $p < 0.001$.

** $p < 0.01$.

* $p < 0.05$.

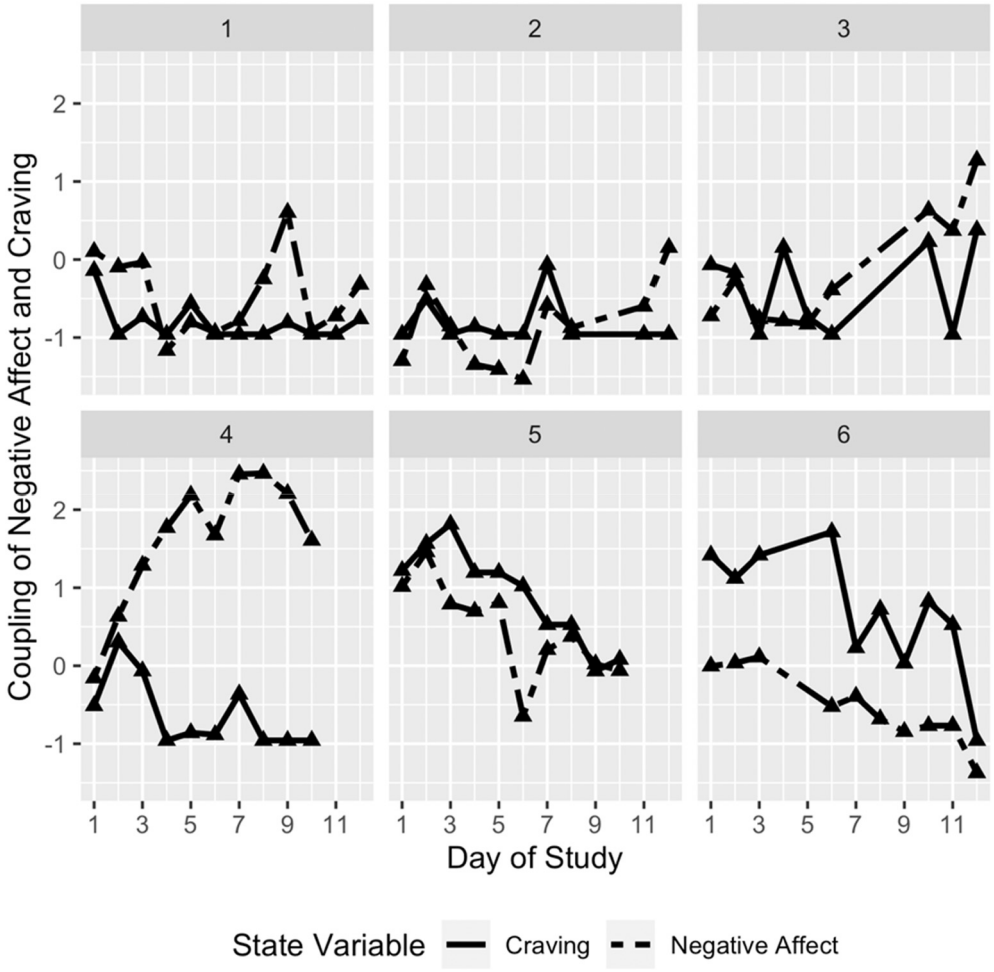

Fig. 1. Within-person coupling of negative affect and craving across days for six individual participants, demonstrating between-person variability in the within-person coupling of negative affect and craving. Note: Only complete data is plotted. Negative affect and craving variables were both *Z*-scored for this plot.

Table 3
Multilevel model testing associations between negative affect and craving.

Fixed effects	Est.	SE	*p*	95 % CI
Intercept	2.27	0.12	<0.0001	[2.05, 2.50]
Day of study	−0.03	0.01	0.0002	[−0.05, −0.02]
Prior-day craving (PMC)	−0.05	0.04	0.2208	[−0.12, 0.03]
Day-mean NA (PMC)	0.02	0.003	<0.0001	[0.01, 0.03]
Person-mean NA (GMC)	0.03	0.01	0.0001	[0.02, 0.04]
Random effects	Est.		95 % CI	
Intercept variance	0.76		[0.53, 1.09]	
Day-mean NA slope variance	0.0003		[0.0002, 0.001]	
Intercept, day-mean NA slope correlation	−0.07		[−0.41, 0.28]	
Residual AR(1)	0.08		[−0.11, 0.27]	
Level 1 residual variance	0.27		[0.24, 0.32]	

Note: N persons = 71; N days = 594. SE = Standard error. CI = Confidence interval. PMC = Person-mean centered. NA = Negative affect. GMC = Grand-mean centered.

3.3. Within-person coupling reliability

First, we calculated intraindividual NA and craving variances for the $n = 71$ participants available for MLM analyses to identify participants who reported the same value for all of their NA reports ($n = 0$) and/or all of their craving reports ($n = 2$). Of the two participants with zero craving variance, one reported no craving across all assessments and one reported the maximum level of craving across all assessments. The study did not include these participants when estimating person-specific slopes; instead, the study assigned them a slope of zero for analyses predicting time-to-relapse.

Additionally, we computed person-specific reliability estimates of the within-person NA-craving coupling (Eq. (2)) and averaged these estimates to obtain a sample reliability estimate (Eq. (3)) for the n = 71 participants included in the MLM analyses. Results revealed mean WPCR = 0.495, with a standard deviation of 0.123, a median of 0.537, a minimum of 0, and a maximum of 0.592. A histogram of the person-specific WPCR estimates in the sample is shown in Fig. 2. As the figure shows, the majority of participants ($n = 48$; 67.6 %) had a WPCR estimate between 0.5 and 0.6. One individual had an estimated WPCR = 0 due to having only a single day of data available; thus, this individual was assigned a NA-craving slope parameter of zero for analyses predicting time-to-relapse (in addition to the $n = 2$ participants assigned a slope parameter of zero because they did not report any variability in craving over the course of the study). Although the very limited amount of previous research examining WPCR makes it difficult to contextualize our findings, our results suggest that NA-craving coupling was estimated with a moderate level of reliability for most participants, and are roughly consistent with recent WPCR work (see Neubauer et al., 2020).

Fig. 3 shows the distribution of person-specific NA-craving slopes obtained from combining the fixed and random components of the MLM across the full sample of 71 participants. This figure illustrates that the mean of the NA-craving slope terms was positive (mean = 0.019), with $n = 3$ participants exhibiting a negative association between NA and craving on average. To examine the strength of association between

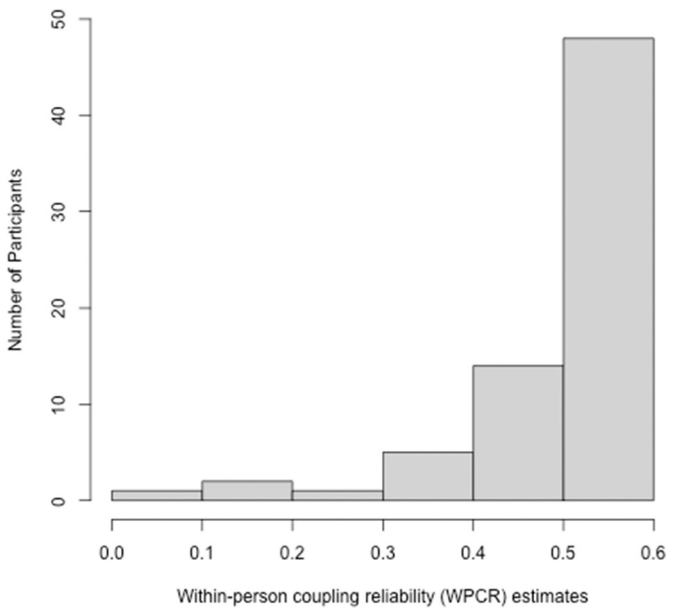

Fig. 2. Histogram of the person-specific within-person coupling reliability (WPCR) estimates for daily negative affect and craving coupling in the sample ($N = 71$). $N = 48$ participants (67.6 %) had a WPCR estimate between 0.5 and 0.6.

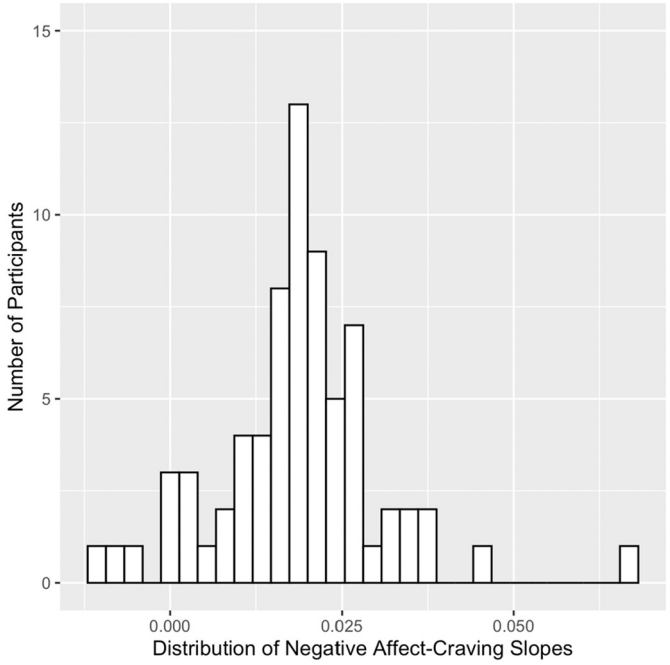

Fig. 3. Distribution of person-specific within-person negative affect-craving slope parameters estimated from the multilevel model (N = 71).

(deviations from average levels of) NA and craving based on the estimates obtained from the MLM, the study calculated an effect size as the estimate for the within-person fixed effect association between NA fluctuations and craving (0.019; see Table 3) divided by the standard deviation (SD) of the person-mean centered outcome variable (i.e., daily craving), which we found to be 0.60 (see the last row of Table 2). The resulting effect size estimate represents the number of SDs for every one-unit change in the predictor, analogous to Cohen's d. With a value of 0.03 (0.019/0.60) this effect size is modest. What is more important, however, is that these parameters documented differences, from −0.01 to 0.07 (see Fig. 3), in the within-person coupling between these variables across individuals, providing the opportunity to investigate if the degree of coupling between daily deviations in NA and craving have implications for time-to-relapse.

3.4. Prediction of time-to-relapse from person-specific NA-craving slopes

Relapse data were available for a subset of $n = 68$ of the $n = 71$ participants available for MLM analyses who transitioned to home environments, outpatient care, or step-down care following discharge from residential treatment, rather than transitioning to a second residential facility. Data on number of days until relapse were available for $n = 61$ of these participants, which composed the final analytic sample for survival analyses.

Nearly half ($n = 28$, ~46 %) of the 61 participants relapsed to any substance use within approximately 120 days following discharge from residential treatment. The median overall survival time was 91.0 days. Among those who relapsed, the median time-to-relapse was 34.5 days. The maximum number of days before relapse was 109; three participants reported relapse before or within a day of release from treatment (coded as zero days). Time-to-relapse was considered right-censored for the remaining 33 participants who the study followed for an average of 151.88 days after discharge (Median = 123, Range = 66–315).

Results investigating time-to-relapse prediction are shown in Table 4. Model 1 examined main effects that addressed our hypothesis that interindividual differences in intraindividual NA-craving slopes would predict time-to-relapse. The association between NA-craving slopes and time-to-relapse was significant. Stronger positive within-person NA-craving coupling during residential OUD treatment was associated with a decreased hazard of relapsing (slower time to relapse) post-treatment. The exponentiated coefficient (i.e., hazard ratio) of 0.5772 revealed that the percent change in the hazard of relapsing (calculated by subtracting 1 and multiplying by 100) was −42.28 % for every one unit increase in NA-craving coupling. The global model was statistically significant (according to the likelihood ratio test, $\chi^2_1 = 7.27$, $p = 0.007$) with a concordance of 0.65 and R-squared of 0.112. The validity of the proportional hazards assumption was supported (according to a non-significant statistical test using Schoenfeld residuals, $\rho = 0.181$, $p = 0.373$), as well as the overall model adequacy (according to a plot of Cox-Snell residuals). Results held when excluding individuals according to post-hoc residual plots to detect influential observations ($n = 1$) and extraordinarily long survival times (n = 1; 315 days).

Sensitivity analyses indicated that the significant association between NA-craving coupling and time-to-relapse held after controlling for interindividual differences in age and sex (Model 2 in Table 4). Again, the global model was statistically significant (likelihood ratio test $\chi^2 = 8.71$, df = 3, $p = 0.03$) with a concordance of 0.67 and R-squared of 0.133, and the validity of the proportional hazards assumption was confirmed for each predictor and the global model (age $\rho = 0.080$, $p = 0.655$; sex $\rho = 0.060$, $p = 0.754$; NA-craving slope $\rho = 0.149$, $p = 0.382$; global model $p = 0.836$). Importantly, the values for concordance (an indicator of the discriminative validity of the model when applied to individual cases) in both model 1 and model 2 were slightly lower than is usually desired. However, we should note that not only did results hold when excluding the single outlier detected by post-hoc plots of model residuals, but concordance also increased to 0.66 for the unadjusted model (model 1) and to 0.72 for the adjusted model (model 2), which is similar to other published survival studies (see Panlilio et al., 2019). R-squared values also increased to 0.16 in model 1 and 0.23 in model 2 when omitting this same single outlier.

Fig. 4 displays the hazard ratios for time-to-relapse across three different values of the NA-craving slope term (−1 SD, Mean, +1 SD), representing individuals with weak, average, and strong magnitude NA-craving slopes. On average, participants with stronger positive NA-craving slopes relapsed later and less than participants with average and weak magnitude NA-craving slopes. Note that the plot in Fig. 4 is

Table 4
Survival analysis with Cox proportional hazard models predicting time-to-relapse.

	Model 1				Model 2				Model 3			
Main effects	Est	SE	*p*	95 % CI	Est	SE	*p*	95 % CI	Est	SE	*p*	95 % CI
NA-Craving Slope	0.58	0.20	0.0071	0.39, 0.86	0.58	0.22	0.0118	0.38, 0.89	0.51	0.23	0.0026	0.32, 0.79
Age					0.99	0.02	0.6842	0.95, 1.03	1.00	0.02	0.8896	0.95, 1.05
Sex					0.58	0.44	0.2160	0.24, 1.38	0.43	0.48	0.0815	0.17, 1.11
PM Craving									0.76	0.26	0.2790	0.46, 1.25
PM NA									1.19	0.22	0.4306	0.77, 1.83
Interactions												
PM Craving × Slope									0.77	0.15	0.0756	0.57, 1.03
PM NA × Slope									1.35	0.17	0.0800	0.96, 1.89
Fit Indices	Est		*p*		Est		*p*		Est		*p*	
Concordance	0.648		–		0.672		–		0.700		–	
R-squared	0.112		–		0.133		–		0.208		–	
Likelihood ratio test	7.27		0.007		8.71		0.03		14.25		0.05	
Wald test	7.24		0.007		9.32		0.03		16.70		0.02	
Score (logrank) test	6.55		0.01		8.43		0.04		18.66		0.009	

Note: N persons = 61; N relapse events = 28. Est = Exponentiated coefficient from Cox regression model (i.e., hazard ratio). SE = Standard error. CI = Confidence interval. NA = Negative affect. PM = Person mean. Slope = NA-Craving Slope. The three-way interaction was also checked and found nonsignificant.

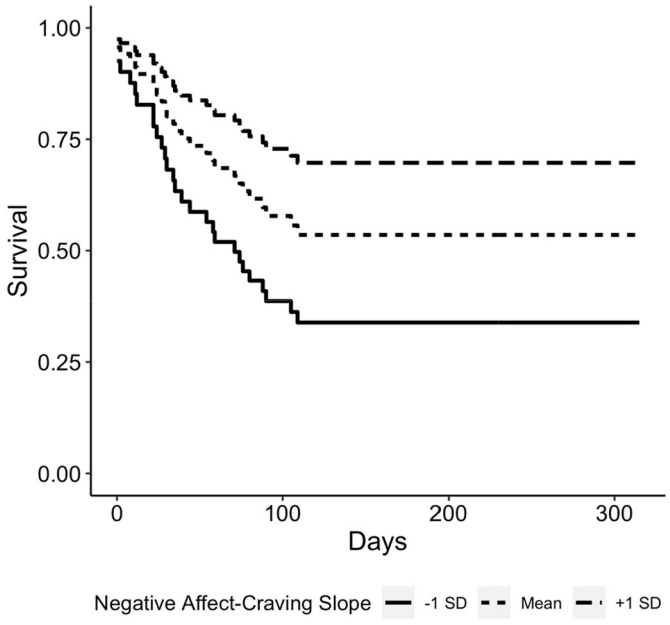

Fig. 4. Conditional survival curves by three levels of negative affect-craving slopes: weak/no association (−1 SD), average association (Mean), and stronger positive association (+1 SD). Note that the plot is derived from the unadjusted model (Model 1 in Table 4), but plots derived from adjusted models were very similar.

derived from the unadjusted model (model 1 in Table 4), but plots derived from adjusted models were very similar.

Model 3 in Table 4 includes results from the sensitivity analysis that address whether the relation between NA-craving coupling and time-to-relapse differed according to participants' usual levels of NA and/or craving. Results indicated that the association between NA-craving coupling and time-to-relapse remained significant, but there were no significant main effects for person-mean craving or NA, nor significant interactions among NA-craving slopes, person-mean craving, and person-mean NA.

Listwise deletion of the 10 cases with missing time-to-relapse data assumes missingness was due to random factors and that these cases did not differ systematically from the 61 cases that were included in the analysis in ways that could bias the results. To investigate the potential impact of missingness on the final analytic sample, we examined whether treatment duration (primary vs. extended) and discharge placement (sober living vs. home/outpatient) frequencies differed between the full sample and the final analytic sample of individuals with complete time-to-relapse data. We also examined if cases with complete time-to-relapse data differed from the full sample on the primary study predictors (PM Craving, PM NA, PM NA-Crave Slope) and other measures commonly used in addiction research, including the Hamilton Depression Scale, Snaith-Hamilton Pleasure Scale (anhedonia), and Eysenck Personality Questionnaire's neuroticism scale. Table 5 provides means and standard deviations (SDs) of these eight variables for both the full sample and final analytic sample, as well as Cohen's Ds to characterize the extent of the mean differences relative to the average sample SD. These means show very small differences, and the largest magnitude D-score was 0.08, supporting the conclusion that the 61 cases used in the final analyses did not substantially differ from the full sample. In addition, the study team used a series of statistical models, using Fisher's exact tests and logistic regressions, to predict missing time-to-relapse data from these eight variables, none of which we found to be

Table 5
Comparing the full sample and the final analytic sample on baseline variables, treatment duration and discharge, and primary study predictors.

	Full sample			Sample with Complete Time-to-Relapse Data			
Characteristic	N	M	SD	N	M	SD	Cohen's D
Treatment duration	71	0.37	0.49	61	0.33	0.47	0.08
Discharge placement	66	0.44	0.50	60	0.42	0.50	0.04
PM Craving	71	2.16	1.02	61	2.23	1.05	−0.07
PM NA	71	35.46	17.15	61	36.32	17.25	−0.05
PM NA-Crave Slope	71	0.02	0.01	61	0.02	0.01	0.00
Depression	71	10.77	5.64	61	10.79	5.18	−0.004
Anhedonia	71	1.59	1.98	61	1.70	2.07	−0.05
Neuroticism	62	14.47	6.18	52	14.73	6.05	−0.04

Note. Discharge placement is coded such that 0 = sober living facility, 1 = home/outpatient setting. Treatment duration is coded such that 1 = extended care, 0 = primary care only. Depression = Hamilton Depression Scale. Anhedonia = Snaith-Hamilton Pleasure Scale. Neuroticism = Eysenck Personality Questionnaire. N = Sample size. M = Mean. SD = Standard deviation. PM = Person-mean. NA = Negative affect.

significantly related to missingness. Based on these analyses, we concluded that listwise deletion was unlikely to have undercut the validity of the primary analyses.

As an additional check on the possible impact of dropping cases without time-to-relapse data, we ran the same logistic regression model on the full sample of participants with viable EMA and relapse status data ($n = 68$) and those participants with time-to-relapse data ($n = 61$).

By focusing just on relapse odds rather than time-to-relapse as in the Cox regression models, these logistic regression models address the possibility that missing data on the time-to-relapse variable biased the Cox regression results. Results for these models were nearly identical. In fact, the primary parameter of interest, the slope between the coupling of NA-Craving and occurrence of relapse was nearly identical, −0.70 (OR = 0.50, $p < 0.05$) vs. –0.73 (OR = 0.48, $p < 0.05$) in the $N = 68$ and $N = 61$ analyses, respectively. Results were similarly robust to subtle variations of our analytic decisions. Specifically, results were highly similar when (1) excluding three individuals in survival analyses who reported relapse before or within a day of release from treatment (as opposed to coding them as zero days; unadjusted NA-Craving Slope parameter estimate = 0.58 vs. 0.58, $ps < 0.05$); (2) excluding two individuals in survival analyses with no within-person craving variability (as opposed to including them but fixing their slopes at zero; unadjusted NA-Craving Slope parameter estimate = 0.58 vs. 0.61, $ps < 0.05$); and (3) leaving the NA variable uncentered in our MLM estimating the daily association between NA and craving, and then testing the associations between these person-level slopes and time-to-relapse (unadjusted NA-Craving Slope parameter estimate = 0.58 vs. 0.66, $ps < 0.05$).

4. Discussion

The current study used 12 days of 4×-day EMA data gathered from patients in residential treatment for OUD to characterize associations between negative affect and craving, and to use these associations to predict time-to-relapse. Given prior EMA research on negative affect and craving, including by our own group (Cleveland & Harris, 2010; Huhn et al., 2016; Lydon-Staley et al., 2017), we expected the significant within-person association between deviations from average levels of negative affect and craving that the study found. The size of the effect was modest *on average*, which was consistent with the conclusion that negative affect and craving were generally weakly to moderately (positively) associated across studies of individuals with substance-related disorders of a recent systematic review and meta-analysis (Cyr et al., 2022). Authors of this meta-analysis also concluded that the relationship between negative affect and craving, as well as the individual differences in this relationship, are important to explore further (Cyr et al., 2022). Thus, the more important contribution of initial analyses was demonstrating the significant between-person variation in the strength of the within-person negative affect-craving association, which is to say that craving was more strongly associated with deviations in negative affect from average levels for some participants than others.

Following their estimation, the study used the person-specific negative affect-craving slopes to predict time-to-relapse. Results of this analysis indicated that stronger coupling between negative affect and craving during residential treatment was significantly associated with longer time to relapse following treatment. Patients with weaker links between negative affect fluctuations and craving were at risk of earlier relapse following treatment. The association between negative affect-craving and time-to-relapse held after controlling for participant age, sex, and average levels of negative affect and craving intensity, and was not moderated by either patients' average negative affect nor their average craving intensity. These results suggest that a weaker within-person association between negative affect and craving during treatment places individuals at risk for shorter time-to-relapse, regardless of person-level differences in average negative affect or craving intensity.

The novel contribution of this study is showing that EMA data collected during residential opioid treatment can predict time-to-relapse following treatment. Although EMA is an increasingly used methodology in addiction research, we are unaware of prior studies that have used EMA collected during residential OUD treatment to predict post-treatment time-to-relapse. Taken together, our findings indicate individuals with weaker negative affect-craving coupling relapse sooner than individuals with stronger negative affect-craving coupling. That a stronger association between daily deviations from average levels of negative affect and craving could be protective may appear initially surprising. Given the lack of prior research from which to draw, it we should be cautious when interpreting this finding. With this caution in mind, patients with weaker coupling may experience less predictable craving or, perhaps, their craving is linked to something other than negative affect. Given that both negative affect and craving are demonstrated threats to abstinence in isolation, perhaps these triggers are more difficult to pinpoint and deal with when they operate independently from one another as opposed to when they co-occur. These speculations are worthy of future research.

In contrast, those patients with stronger linkages may be at lower risk for relapse due to treatment (or other) experiences that helped to increase their awareness of their negative affect and that their cravings were predictably linked to negative affect. Relatedly, perhaps a strong coupling between negative affect and craving in the absence of substance use (as a result of the residential treatment context) strengthens resolve against using and increases abstinence self-efficacy. For example, experiencing higher-than-average intensity in both negative affect and craving in one's daily life may warrant the need to consistently use self-regulation skills each day (Roos & Witkiewitz, 2017), and when provided with the time and assistance to practice these skills during residential treatment, may help one to prevent (or at least delay) relapse after treatment. The lack of significant interactions with average levels of negative affect or craving intensity suggest that attention to the linkage between negative affect and craving may be clinically beneficial for most patients. Overall, these findings suggest that future research could enhance our understanding of relapse risk by examining within-person couplings of risk factors, including negative affect and other factors that may be linked to intraindividual variability in craving, instead of focusing solely on how single factors are related to OUD treatment outcomes.

4.1. Strengths and limitations for the EMA protocol

The primary strengths of this study are based on the intensive measurement protocols used to collect data during treatment for prescription opioid use disorder. These EMA reports provided the high-density data necessary for constructing the within-person slopes used to characterize the linkage between negative affect fluctuations and craving. The study also used these high-density data to estimate person-level means for negative affect and craving. Based on multiple daily reports of these intra-personal states across 12 days these variables are likely more accurate assessments of craving than single-report measures of the same constructs that addiction research conventionally uses.

EMA approaches also carry limitations, however. One of these is that EMA studies tend to be relatively small, which reduce statistical power. Applying a power calculation developed by by Hsieh and Lavori (2000) for Cox proportional hazards regression with nonbinary covariates (using the 'powerEpiCont' function from the R package 'powerSurvEpi') demonstrated that the study had sufficient power to detect the effect of negative affect-craving coupling on time-to-relapse, $1\text{-}\beta = 0.83$. However, the sample was insufficiently powered to carry out potential analyses by other factors, such as age or sex. A limitation more specific to this study's EMA protocol was its use of a fixed-interval prompt schedule that we selected to avoid interfering with the treatment programs of the participants and other patients at the residential facility. Depending on what routinely happened at that time of day, this prompt schedule may have influenced reporting of negative affect and craving.

This study operationalized relapse as the return to problematic use of any substance (including opioids, cannabis, and alcohol when patients were diagnosed with an alcohol use disorder in addition to OUD). We believe that defining relapse in this way is the best option available for this sample based on patients being in abstinence-based treatment and that return to use of a given nonopioid substance as relapse was coded as relapse only when the patient had been diagnosed with a dependency to that substance, such as alcohol (in addition to opioids). We should acknowledge, however, that using this broader definition is not equivalent to operationalizing relapse as limited to opioid use. Finally, the generalizability of the findings should also be considered in light of patients not being treated with agonists or antagonists, that they were likely continuing to experience biological dysregulation related to having recently gone through withdrawal, and that being in a residential setting likely reduced exposure to environmental and social triggers that could impact fluctuation in negative affect and craving.

5. Conclusion

The current study found an average day-level, within-person association between the intra-personal states of negative affect and craving, as well as interindividual differences in the average intraindividual association. More importantly, the study also found that these interindividual differences in the association between negative affect and craving were uniquely associated with time to relapse following residential treatment for OUD. Patients with weaker coupling between negative affect and cravings relapsed sooner than those with stronger negative affect-craving coupling. Beyond the specific finding, however, the larger contribution of the study may be more general. By showing how a within-person temporal linkage between intrapersonal states, and not just the individual states themselves, can predict relapse, the study provides clear evidence of the utility of within-person approaches for operationalizing processes that impact substance use disorders. These approaches are useful not only for providing more reliable and more detailed assessments of constructs relevant to substance use disorders, they can also provide important insights into the processes that can either support abstinence and recovery or lead to relapse. In doing so, these within-person data can provide opportunities to not only align our analyses more with the complexity of our theoretical perspectives, they can also provide novel insights that can potentially push those perspectives forward.

CRediT authorship contribution statement

H. Harrington Cleveland: Conceptualization, Study Design and Investigation, Resources, Writing- Original draft. **Kyler S. Knapp**: Formal analysis, Writing- Original draft. **Michael J. Cleveland**: Formal analysis, Writing- Review & editing. **Erin Deneke**: Writing- Review & editing. **Scott C. Bunce**: Study Design and Investigation, Resources, Supervision, Writing- Review & editing.

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Declaration of competing interest

The authors declare that they have no conflicts of interest.

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