Craving Mediates the Effect of Impulsivity on Lapse-Risk During Alcohol Use Disorder Treatment

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Abstract

Background: Rash impulsiveness, the propensity for approach behaviour despite potential negative consequences, is associated with stronger alcohol craving in patients with Alcohol Use Disorder (AUD). This relationship is poorly understood and implications for treatment response unexamined. This study explored the relationship between rash impulsiveness, craving, and treatment response in a sample of AUD outpatients.

Design: Longitudinal study conducted over a 12-week intervention period.

Setting: University public hospital outpatient alcohol and drug clinic.

Participants: Patients attending an abstinence-based Cognitive-Behavioural Therapy program for AUD (N = 304).

Procedure: Assessments were completed pre-and-post treatment. Craving and alcohol consumption were assessed at each treatment session.

Results: Higher rash impulsiveness predicted more frequent craving over treatment (b = 0.95, 95% CI = 0.40, 1.50). Higher craving was associated with greater lapse-risk (b = 0.04, 95% CI = 0.03, 0.05). The association between craving and lapse-risk increased as treatment progressed (b = 0.01, 95% CI = 0.01, 0.02). Craving positively mediated the relationship between impulsivity and lapse-risk (μ = 0.38, 95% CI = 0.10, 0.70).

Conclusions: Craving mediates the effect of impulsivity in the prediction of lapse during abstinence-oriented treatment for AUD. Frequent assessment and management of craving during treatment is recommended to reduce alcohol lapse.

Key words: alcohol; rash impulsiveness; craving; Cognitive-Behavioural Therapy; treatment response

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Introduction

Alcohol Use Disorder (AUD) is a chronic relapsing condition among those who are severely dependent [1,2]. Several cognitive and behavioural treatments with strong empirical support are available, though no single approach has demonstrated superiority [3,4]. Research attention has shifted from the development of new interventions towards identifying the effective components of current treatments; specifically, what works for whom [5–8]. To achieve this goal predictors of treatment outcome must be identified [9] and the mechanisms that affect differential treatment response must be understood [5,10]. Alcohol craving and impulsivity have been independently related to treatment response and identified as potential targets within personalised interventions [8]. Recent research has found evidence of an association between impulsivity and alcohol craving [11–14]. This may have important implications in AUD maintenance and treatment response.

Craving is considered a subjective desire to use a substance and is prominent among those that are substance dependent [15,16]. The experience of craving can include physiological discomfort, intrusive substance-related cognitions, and affective distress [15,16]. Craving is a dynamic state, variable in intensity, frequency, and duration [17]. It may be induced by physiological, cognitive, affective, or environmental cues [18]. Temptation to drink arises from the belief that alcohol will alleviate craving-related distress [16]. Craving is a widely recognised symptom of substance dependence informing diagnosis and treatment prognosis [8,15,19,20]. Craving management is a central component of AUD interventions, with most addiction services considering craving in treatment planning [21].

Impulsivity, as it pertains to addiction, may be best represented by two core processes: (i) a heightened sensitivity to rewarding stimuli increasing the motivation to approach drugs (Reward Sensitivity/Drive); and (ii) a propensity for approach behaviour in spite of negative future consequences (Rash Impulsiveness) [22–25]. Reward drive has

similarities to *Sensation Seeking* in some models of impulsivity [26] and (agentic) *Extraversion* [22]. Rash impulsiveness is closely aligned with Zuckerman's *Impulsive Sensation Seeking* [27], *(Lack of) Premeditation* [26], and Barratt's *Impulsiveness* [28]. Both reward drive and rash impulsiveness are considered personality traits which are relatively stable over time. Where reward sensitivity is a robust predictor of constructs pertaining to alcohol approach behaviours [29–32], including cue-elicited urge to drink [12–14], rash impulsiveness is more heavily implicated in problematic use and Substance Use Disorders (SUDs) [25,33].

Rash impulsiveness is predictive of the onset of SUDs [33], higher levels of consumption [25], greater risk of lapse during treatment [34], and higher likelihood of relapse post-treatment [11,35]. Rash impulsiveness may moderate reward sensitivity in occasions of problem use, causing greater issue within treatment populations. This is consistent with neurobiological models of addiction, maintaining that while incentive salience arises from the limbic system, subsequent approach behaviour is determined by 'executive' prefrontal inhibitory systems [36–40].

Given that alcohol craving is a dynamic state of desire to drink, a person's capacity for impulse regulation is expected to moderate alcohol approach behaviour in response to craving. Patients with high trait rash impulsiveness would then be expected to be at greater risk of lapse during treatment in response to an episode of craving. No research has been identified which has examined this proposed relationship.

There is also a potential direct relationship between impulsivity and craving, with several recent cross-sectional and experimental studies finding patients with greater impulsivity experience stronger cravings. Laboratory studies have found higher impulsivity to be predictive of greater cue-induced cravings among smokers [41], social drinkers, and alcohol dependent patients [42,43]. Across three studies, Kambouropoulos and Staiger [12–14] found reward drive consistently predicted cue-elicited craving in social drinkers, while one

study showed that rash impulsiveness only predicted cue-elicited positive affect [14]. By contrast, Evren et al.[11] found high rash impulsiveness was predictive of greater alcohol craving in alcohol dependent patients. Pre-treatment craving, but not rash impulsiveness, was predictive of relapse at 12-months [11]. This prompted authors to suggest that craving may mediate the effect of rash impulsiveness on relapse.

This study aims to explore the relationships between rash impulsiveness, alcohol craving, and lapse events during abstinence-oriented Cognitive-Behaviour Therapy (CBT) for patients with established AUD. We predicted that rash impulsiveness would be significantly positively predictive of craving (*H1*). Both craving and impulsivity were expected to be associated with greater likelihood of lapse during treatment (*H2* and *H3*). Craving was expected to mediate the effects of rash impulsiveness on lapse (*H4*). Finally, higher rash impulsiveness was predicted to enhance the risk of lapse in response to craving (moderation, *H5*).

Method

Participants and Procedure

Subjects were consecutive patients (n = 304) attending a university metropolitan hospital outpatient drug and alcohol service for treatment of AUD. Sample characteristics are presented in Table 1. Referral to the alcohol and drug service was typically made by inpatient hospital referral or a community based General Practitioner. Intake interview was conducted by a nurse or social worker, who determined eligibility for the AUD treatment program and administered pre-treatment assessments. Patients were reviewed by an Addiction Medicine Physician. Pre-treatment assessments included assessment of AUD, dependence severity, baseline craving frequency, and rash impulsiveness. Inclusion in treatment required that patients meet DSM-IV criteria for alcohol dependence and commit to a goal of 12-weeks of abstinence. This clinically indicated treatment goal reflected the severity of the AUD sample

[2]. Patients were excluded from this study if they had a co-morbid substance dependence (with the exception of nicotine) or if they were taking Disulfiram or a prescribed opioid for opiate dependence. Patients were scheduled to begin treatment within 7-days following intake. The program included eight, one-hour sessions of CBT conducted over 12-weeks. Treatment was administered one-on-one by clinical psychologists with Masters or Doctoral level qualifications. Psychologists recorded drinking behaviour, craving, and adjunct pharmacotherapy (naltrexone, acamprosate, or both) at each treatment session. Human research ethics approval was obtained (HREC/12/QPAH/022, HREC/14/QPAH/664).

Measures

The Severity of Alcohol Dependence Questionnaire (SADQ)

The SADQ contains 20 self-report items on a 4-point scale from 0 (*almost never*) to 3 (*nearly always*), assessing physical withdrawal, affective withdrawal, drinking to relieve withdrawal symptoms, alcohol consumption, and rapidity of reinstatement of alcohol dependence [44]. For AUD patients scores ≤ 15 are indicative of mild dependence, scores between 16 and 30 indicate moderate dependence, and scores ≥ 31 suggest severe dependence. The SADQ has strong psychometric properties with good test-retest reliability and concurrent validity [44]. Internal consistency of the SADQ within this study was good (Cronbach's $\alpha = 0.92$, 95% CI = 0.91-0.93). The SADQ was included within the pre-treatment assessment battery at patient intake.

The Alcohol Craving Experience Questionnaire – Frequency (ACE-F)

The ACE-F is a self-report measure assessing the frequency of desire related cognitions over the previous week. The ACE-F comprises 11-items on an 11-point visual analogue scale, anchored 0 (not at all) to 10 (constantly/extremely). The ACE-F has good construct validity, predictive validity, concurrent validity, discriminant validity, internal

reliability, and test-retest reliability [45–47]. Internal consistency of the ACE-F within the current study was excellent (Cronbach's α = 0.95, 95% CI = 0.94-0.95). The ACE-F was included within the pre-treatment assessment battery at patient intake and re-administered at each treatment session.

Dickman's Impulsivity Inventory - Dysfunctional Impulsivity Scale (DIS)

Dickman's Impulsivity Inventory is a self-report questionnaire comprising two scales: Functional Impulsivity and Dysfunctional Impulsivity. The Dysfunctional Impulsivity scale (DIS) assesses the tendency to act with little forethought where this leads to negative consequences [48], and is a valid measure of rash impulsiveness [24,49]. The DIS comprises 12-items with dichotomous (True/False) response options. The DIS has demonstrated good internal reliability, construct validity, and excellent concurrent validity when compared with other established impulsivity scales [48,50]. Good internal consistency was identified within this sample (Cronbach's α = 0.84, 95% CI = 0.82 - 0.86). The DIS was included within the pre-treatment assessment battery at patient intake.

Drinking Behaviour

Guided by the Time-Line Follow-Back procedure [51] experienced clinical psychologists asked patients to recall any drinking occasions which occurred between each session, report the type of alcohol consumed, and estimate volume of consumption. Any alcohol consumption between treatment sessions was coded as a lapse.

Statistical Analysis

As craving is proposed to mediate rash impulsiveness in the prediction of lapse, there are two primary outcomes within the study, ACE-F score (craving) and lapse status (abstinent or lapsed). For each outcome, two effects were modelled: the main effects on the outcome (intercept) and effects on the trajectory of the outcome as sessions progress (slope).

Longitudinal linear mixed models (LMM) enabled both effects to be modelled while controlling for intra and inter-personal differences. LMMs are particularly well suited to psychotherapy research as they allow for incomplete and unbalanced data [52,53]. The number of sessions each patient attended was included in the analyses to model potential effects on the outcome dependent on the missing data process [53,54].

All data analysis was conducted in R version 3.3.3. LMMs were constructed by R package 'lme4' [55] using Maximum Likelihood estimation. All models included random intercepts. Random slopes were assessed and retained if found to improve model fit and affect parameter estimates. Statistical significance at $p < 0.05$ was determined by Wald estimated 95% CIs excluding zero. Session number was re-coded by subtracting one to set the lower limit to zero (e.g. Session 1 = 0, session 2 = 1). Session number and potential covariates were entered in the first step of each model, as well as 'session number × covariate' interactions to detect covariate effects on the trajectory of the outcome. Only statistically significant covariates were retained. When the interaction was significant, but not the main effect, both terms were retained. Covariates included: age, gender, dependence severity (SADQ, total number of sessions attended, days between sessions, and adjunctive pharmacotherapy [9,56,57]. As this sample includes patients enrolled in a personalised treatment condition as part of a randomised controlled trial (RCT; $n = 137$) [8], this was included as a covariate to control for potential response differences between groups [58].

Individual ordinary least squares plots and normality probability plots were inspected to assess violations of linearity and normality assumptions. To identify potential bias arising from violation of statistical assumptions, sensitivity analyses were conducted by comparing all LMMs based on Maximum Likelihood estimation to Design Adaptive Scale Tau estimation, a robust LMM variant [59,60]. Robust LMMs were constructed by R package 'robustlmm' [60]. When the estimates provided by both models were ostensibly the same, the

original model is reported. When discrepancy between the models was observed the robust model is reported.

Hypothesis Testing

H1) Rash impulsiveness will be significantly positively predictive of craving. LMMs were used to assess the relationship between pre-treatment impulsivity score and the trajectory of craving over treatment.

H2 & H3) Higher craving and rash impulsiveness will predict greater likelihood of lapse. Separate logistic LMMs were used to assess the prognostic value of pre-treatment ACE-F and DIS in the prediction of lapse-likelihood. Prediction of the slope of lapse-likelihood was also assessed by including 'predictor' x 'session number' interaction terms. Session by session ACE-F scores were included in a separate model to examine the effect of craving trajectory on the slope of lapse-likelihood over treatment.

H4) Craving will mediate the effect of rash impulsiveness in prediction of lapse. Consistent with the *joint significance procedure* [61] evidence for mediation was determined by a significant association between predictor and mediator (Path *a*), and a significant relationship between the mediator and outcome (Path *b*). Indirect effects and 95% confidence intervals (CI) were estimated by the product-of-coefficients method using R package 'Rmediation' [62,63]. As the lapse outcome variable was dichotomous, path a and b coefficients were standardized to correct for differences in mediator/outcome distributions and residual variance [64].

H5) Higher rash impulsiveness will increase the risk of lapse in response to craving. Interaction between craving and impulsivity in the prediction of lapse was assessed by adding 'impulsivity × craving and 'impulsivity × craving × Session Number' terms to a logistic LMM model.

Results

Descriptive statistics and Missing Data

The mean number of sessions (range 1-8) attended was 5.22 (*SD* = 2.20). Eighty-seven patients (29%) completed all 8 sessions or 12-weeks of treatment. Among those who completed treatment, 37 (43%) completed without lapse. Patients who completed treatment were significantly older (*M* = 46.01, *SD* = 10.45) than non-completers (*M* = 43.24, *SD* = 10.64; *t*(468) = -2.80, *p* =0.005). No other significant differences between treatment 'completers' and 'non-completers' were observed on any demographic variables or pre-treatment assessments.

Table 1. Descriptive Statistics of the Sample (*N* = 304)

	Mean	*SD*	*Range*
Age (years)	45.05	10.69	20 - 76
Alcohol Use Disorder Identification Test	27.73	8.90	0 - 40
Severity of Alcohol Dependence	22.79	12.93	0 - 58
Rash Impulsiveness	4.51	3.43	0 - 12
Pre-treatment Alcohol Craving Experience	45.10	29.13	0 - 110
	n	*%*	
Gender			
Female	104	34.21	
Male	200	65.79	
Pharmacotherapy			
Yes	122	40.13	
No	182	59.87	
Active Treatment Trial			
Yes	137	45.07	
No	167	54.93	

H1) Rash impulsiveness will be significantly positively predictive of craving.

LMMs were used to examine the relationship between the pre-treatment rash impulsiveness and craving over treatment. Covariates RCT enrolment, treatment completion, and adjunctive pharmacotherapy had no significant effect on the craving intercept or slope and were not retained. Age and gender had no significant effects on the slope of craving over treatment, so their respective session number interaction terms were excluded. Independent of covariates, craving was found to reduce over treatment in the order of 5.92 points per session (95% CI = -8.78, -3.05; = 0.20 *SDs*). Each unit increase in baseline impulsivity score was predictive of a 0.95 (95% CI = 0.40, 1.50) higher craving score. Patients scoring +1 *SD* above the mean on rash impulsiveness reported +3.26 points higher craving (= 0.11 *SD*s). No time-dependent effect of impulsivity on craving was observed (Table 2, Model 1; figure 1) so this interaction term was not retained (Table 2, Model 2). Sensitivity analyses utilising robust methods yielded consistent results, indicating that any violations to statistical assumptions did not meaningfully affect the present findings.

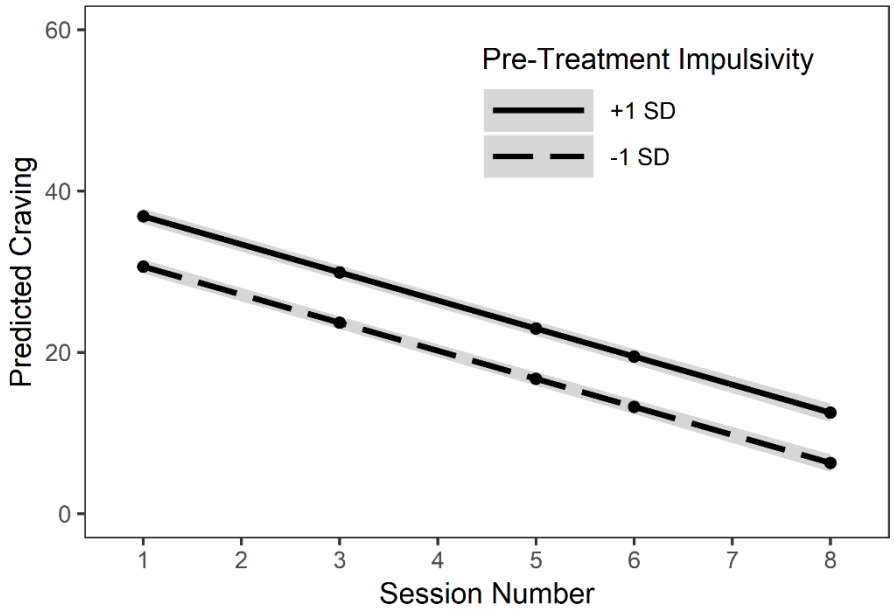

Figure 1. Trajectory of predicted craving over treatment by high (+1 SD) and low (-1 SD) pre-treatment rash impulsiveness scores. The shaded areas are standard errors. Higher impulsivity is predictive of higher craving independent of time (Table 2, Model 1).

Table 2. Summary of linear mixed-effects regression models predicting alcohol craving during treatment (N = 304).

Parameter	Model 1		Model 2	
Fixed Effects	*b (SE)*	*95% CI*	*b (SE)*	*95% CI*
Intercept	**40.75 (6.78)**	**27.47, 54.03**	**41.15 (6.74)**	**27.94, 54.36**
Session Number	**-5.80 (1.48)**	**-8.70, -2.90**	**-5.96 (1.46)**	**-8.81, -3.10**
Age	-0.21 (0.11)	-0.42, 0.002	-0.21 (0.11)	-0.42, 0.002
Severity of Dependence	**0.57 (0.10)**	**0.37, 0.77**	**0.58 (0.10)**	**0.38, 0.77**
Gender (Male)	**-7.90 (2.30)**	**-12.41, -3.39**	**-7.93 (2.30)**	**-12.43, -3.42**
Sessions Attended	**-1.26 (0.58)**	**-2.4, -0.12**	**-1.27 (0.58)**	**-2.4, -0.13**
Days Between Sessions	-0.20 (0.11)	-0.43, 0.02	-0.20 (0.11)	-0.43, 0.02
Session Number × Severity of Dependence	-0.04 (0.02)	-0.08, 0.001	-0.04 (0.02)	-0.08, 0.001
Session Number × Sessions Attended	**0.40 (0.19)**	**0.02, 0.78**	**0.40 (0.19)**	**0.03, 0.78**
Session Number × Days Between Sessions	**0.08 (0.03)**	**0.02, 0.13**	**0.08 (0.03)**	**0.02, 0.13**
Rash Impulsiveness	**1.00 (0.38)**	**0.26, 1.74**	**0.89 (0.33)**	**0.25, 1.54**
Session Number × Rash Impulsiveness	-0.04 (0.07)	-0.18, 0.10		
Random Effects	*σ2*		*σ2*	
Patient (Intercept)	283.15		282.93	
Residual	180.99		181.10	

Note: Boldface indicates $p < 0.05$ as 95% confidence intervals do not include zero. All parameters are unstandardized.

H2 & H3) Higher craving and impulsivity will predict greater likelihood of lapse.

Logistic LMMs were used in the prediction of lapse-likelihood (Table 3). Covariates age, gender, severity of dependence, combined pharmacotherapy, number of sessions attended and RCT enrolment had no significant effect on the intercept or slope of log-likelihood of lapse and were excluded. Within the baseline model each progressive session was associated with 14% increase in the probability of lapse.

Pre-treatment impulsivity was not predictive of lapse at session 1 but was predictive of greater lapse-likelihood as sessions progressed (Table 3., Model 3). When craving was added to the model impulsivity became non-significant, while craving was significant in the prediction of the slope of lapse-likelihood (Table 3., Model 5). Higher craving over treatment was associated with greater likelihood of lapse as treatment progressed (Table 3., Model 4; Figure 2).

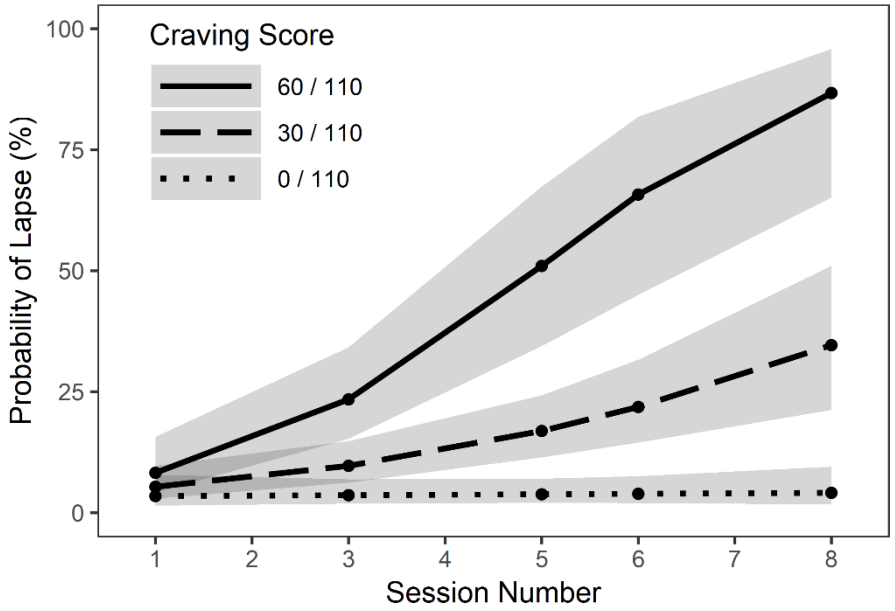

Figure 2. Probability of lapse over treatment by craving score. The shaded areas are 95% confidence intervals. Higher craving over treatment is associated with greater probability of lapse (Table 2, Model 4).

H4) Craving will mediate the effect of impulsivity in prediction of lapse.

As pre-treatment impulsivity was significantly associated with craving (*path a*) and craving was predictive of lapse-likelihood during treatment (*path b*), there is evidence for mediation under the joint-significance approach. Product-of-coefficients estimates of the indirect effect of impulsivity score on lapse-likelihood was significant ($\mu = 0.11$, $SE = 0.05$, 95% CI = 0.03, 0.23; Figure 3), supporting the hypothesised mediation.

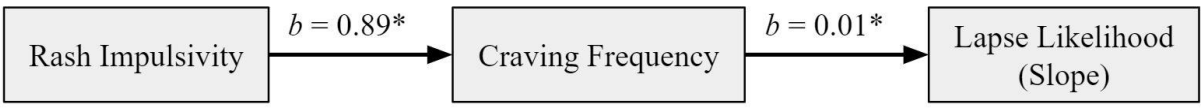

Figure 3. Mediation model of pre-treatment rash impulsiveness and craving in the prediction of lapse risk during treatment.

* 95% confidence intervals non-inclusive of zero.

H5) Higher rash impulsiveness will increase the risk of lapse in response to craving.

Interaction terms ‘craving × rash impulsiveness’ and ‘craving × rash impulsiveness × session number’ were included in a logistic LMM predicting lapse-likelihood (Table 3, Model 6). Neither interaction term was significant (Table 3., Model 6), yielding no support for moderation of craving by impulsivity in the prediction of the intercept or slope of lapse-likelihood over treatment.

Table 3. Summary of mixed-effects logistic regression models predicting lapse (N = 304).

Parameter	Model 3		Model 4		Model 5		Model 6	
Fixed Effect	*b (SE)*	*95% CI*	*b (SE)*	*95% CI*	*b (SE)*	*95% CI*	*b (SE)*	*95% CI*
Intercept	**-2.53 (0.39)**	**-3.29, -1.77**	**-3.52 (0.51)**	**-4.52, -2.52**	**-3.52 (0.58)**	**-4.66, -2.38**	**-3.43 (0.68)**	**-4.77, -2.09**
Session Number	-0.001 (0.07)	-0.14, 0.14	0.02 (0.09)	-0.16, 0.19	-0.05 (0.11)	-0.26, 0.17	-0.06 (0.14)	-0.33, 0.21
Gender (Male)	**-0.67 (0.3)**	**-1.26, -0.08**	-0.45 (0.35)	-1.15, 0.24	-0.47 (0.36)	-1.16, 0.23	-0.46 (0.36)	-1.16, 0.24
Days Between Sessions	**0.04 (0.01)**	**0.02, 0.06**	**0.05 (0.01)**	**0.02, 0.07**	**0.05 (0.01)**	**0.02, 0.07**	**0.05 (0.01)**	**0.02, 0.07**
Rash Impulsiveness	0.02 (0.05)	-0.09, 0.12			-0.01 (0.07)	-0.14, 0.13	-0.03 (0.11)	-0.25, 0.19
Session Number × Rash Impulsiveness	**0.03 (0.01)**	**0.003, 0.05**			0.02 (0.02)	-0.02, 0.05	0.02 (0.03)	-0.03, 0.07
Craving			0.01 (0.01)	-0.001, 0.03	0.02 (0.01)	-0.001, 0.031	0.01 (0.01)	-0.02, 0.04
Session Number × Craving			**0.01 (0.003)**	**0.01, 0.02**	**0.01 (0.003)**	**0.01, 0.01**	**0.01 (0.004)**	**0.001, 0.02**
Craving × Rash Impulsiveness							0.001 (0.002)	-0.004, 0.01
Session Number × Craving × Rash Impulsiveness							0.001 (0.001)	-0.001, 0.001
Random Effects	*σ2*		*σ2*		*σ2*		*σ2*	
Patient (Intercept)	3.59		4.23		4.31		4.33	

Note: Boldface indicates $p < 0.05$ as 95% confidence intervals do not include zero. All parameters are unstandardised on a log-likelihood scale.

Discussion

This is the first study to investigate the relationship between rash impulsiveness and craving in the prediction of response to treatment for alcohol dependence. Higher rash impulsiveness was predictive of more frequent craving over treatment, which was associated with greater risk of lapse. The indirect effect of impulsivity via its effect on craving was found to be significant, supporting the hypothesised mediation. The moderation hypothesis that higher rash impulsiveness would increase risk of lapse in response to craving frequency, was not supported.

This study replicated previous research finding a positive association between craving and rash impulsiveness among AUD patients [11,65]. Consistent with previous studies, higher craving [15,20,66] and impulsivity [11,34] were independently predictive of poorer treatment outcomes. Craving was found to diminish the unique effect attributed to rash impulsiveness when included within the same model. This supports the present findings that craving mediates rash impulsiveness as the final path to lapse. One explanation for this mediational process is that patients high in rash impulsiveness have an impaired cognitive ability to inhibit craving cognitions [67,68]. A cognitive model of desire, Elaborated Intrusion (EI) Theory, provides one theoretical framework by which this process may occur [16,69]. EI theory suggests that intrusive desire-related cognitions demand elaboration upon entering conscious awareness. Elaboration includes planning and appraisal of substance related behaviours and is self-reinforcing as cognitions oriented toward craving relief provide fleeting moments of pleasure. An individual's capacity to intervene early within this cycle, via distraction or reorientation is considered crucial to restricting the intensity of the craving experience. As patients with high rash impulsiveness are more likely to have difficulties on tasks requiring cognitive inhibition [70], they may be more vulnerable to elaboration of craving cognitions, resulting in more frequent and intense bouts of craving.

The hypothesis that patients higher in rash impulsiveness would be at greater risk of lapse in response to craving was not supported, suggesting inhibition of alcohol approach behaviours during craving is a significant challenge for patients regardless of trait impulsivity.

While craving frequency was found to diminish over the treatment period, the relative risk of lapse in response to craving increased as sessions progressed (Figure 2). This pattern may be due to persistent demands on craving inhibition, involving executive processes such as appraisal and reappraisal of proximal and distal expectations of alcohol consumption [16,71]. Reappraisal may lead to fluctuations in motivation for abstinence and drinking refusal self-efficacy [31]. For example, patients whose experience of craving causes more distress than anticipated may develop stronger positive expectations of the effects of alcohol on tension reduction, motivating use via negative reinforcement contingencies which undermine self-efficacy. As drinking refusal self-efficacy has been found to mediate the association between rash impulsiveness and hazardous drinking among AUD patients [31], future research should consider whether craving mediates rash impulsiveness in the prediction of drinking refusal self-efficacy.

An important feature of this study was its control of common covariates. However, as covariate hypotheses were not developed a-priori, effects identified should be interpreted modestly and within the context of past research. Younger patients were initially found to be subject to more frequent cravings, supporting findings from an actively drinking alcohol dependent sample [57]. However, this effect become non-significant when impulsivity was included in the analysis. It may be that younger patients have higher levels of impulsiveness which predisposes them to craving [72,73]. Future research may examine whether impulsivity mediates the effect of age on craving. Finally, women reported significantly more frequent craving than men. Few studies have considered gender with respect to alcohol craving,

though females have been demonstrated to experience stronger cravings for cocaine [74] and food [75]. Affective, endocrine, and neurobiological differences between males and females have been recognised as potential mechanisms contributing to differences in craving [76–78]. Future research may explore in detail gender differences in alcohol craving, and whether craving mediates the relationship between impulsivity and lapse similarly for women and men.

This study has some limitations. As rash impulsiveness was only measured at time one, the direction of effect between impulsivity and craving could not be tested statistically. The direction of mediation was inferred from theory proposing impulsivity is a relatively stable trait [23] and experimental research demonstrating that impulsivity predicts strength of craving [41–43]. However, without frequent assessment of both impulsivity and craving this study cannot confirm directionality. Another limitation is the craving measure used reflects past-week craving frequency, which does not capture phasic cycles in craving strength. Rash impulsiveness may be differentially related to strength and frequency of craving. For example, impulsive patients may have more difficulty resisting episodes of strong craving than persistent low levels of craving. Measures of rash impulsiveness also correlate with reward drive [22], which has been shown to predict craving (Kambouropoulos & Staiger, 2001; 2004; 2009). Controlling for patient reward drive in future studies would clarify the unique role of rash impulsiveness in craving. Reliance upon self-report is another limitation, restricting insight into the nonconscious features of impulsivity and craving discussed within the proposed theoretical processes. Assessment of drinking behaviours was also reliant upon self-report introducing potential memory bias and deception. Additional biological markers of alcohol use may be beneficial to corroborate self-report, though voluntary enrolment in treatment, and breath estimated BAL at the beginning of each session was expected to minimise deception [79].

Frequent assessment of craving, alcohol expectancies, motivation, and drinking-refusal self-efficacy is required to better understand the temporal relationships between these constructs in relation to treatment response [31,80]. These findings support frequent assessment of craving in patients with AUD to inform lapse risk and treatment approach [81]. Future research may also consider including craving as a marker of treatment response within adaptive algorithms for personalised interventions [7,81,82]. Patients with persistent craving are likely to benefit from greater emphasis on coping strategies, craving psychoeducation, or adjunctive pharmacotherapy [83–85].

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References

1. Cunningham, J. a. & McCambridge, J. Is alcohol dependence best viewed as a chronic relapsing disorder? *Addiction* **107**, 6–12 (2012).
2. Connor, J. P., Haber, P. S. & Hall, W. D. Alcohol use disorders. *Lancet* **387**, 988–998 (2016).
3. UKATT Research Team. Effectiveness of treatment for alcohol problems: findings of the randomised UK alcohol treatment trial (UKATT). *Bmj* **331**, 541 (2005).
4. Project MATCH Research Group. Matching patients with alcohol disorders to treatments: Clinical implications from Project MATCH. *J. Ment. Heal.* (1998).
5. Longabaugh, R. & Magill, M. Recent Advances in Behavioral Addiction Treatments: Focusing on Mechanisms of Change. *Curr. Psychiatry Rep.* **13**, 382–389 (2011).
6. Norcross, J. C. & Wampold, B. E. What works for whom: Tailoring psychotherapy to the person. *J. Clin. Psychol.* **67**, 127–132 (2011).
7. Kranzler, H. R. & McKay, J. R. Personalized treatment of alcohol dependence. *Curr. Psychiatry Rep.* **14**, 486–493 (2012).
8. Coates, J. M., Gullo, M. J., Feeney, G. F. X., Young, R. M. & Connor, J. P. A Randomized Trial of Personalized Cognitive-Behavior Therapy for Alcohol Use Disorder in a Public Health Clinic. *Front. Psychiatry* **9**, 1–12 (2018).
9. Adamson, S. J., Sellman, J. D. & Frampton, C. M. a. Patient predictors of alcohol treatment outcome: A systematic review. *J. Subst. Abuse Treat.* **36**, 75–86 (2009).
10. Magill, M. & Longabaugh, R. Efficacy combined with specified ingredients: A new direction for empirically supported addiction treatment. *Addiction* **108**, 874–881 (2013).
11. Evren, C., Durkaya, M., Evren, B., Dalbudak, E. & Cetin, R. Relationship of relapse with impulsivity, novelty seeking and craving in male alcohol-dependent inpatients. *Drug Alcohol Rev.* **31**, 81–90 (2012).

12. Kambouropoulos, N. & Staiger, P. K. ‘Cue reward salience’ predicts craving in response to alcohol cues. *Pers. Individ. Dif.* **46**, 78–82 (2009).

13. Kambouropoulos, N. & Staiger, P. K. The influence of sensitivity to reward on reactivity to alcohol-related cues. *Addiction* **96**, 1175–1185 (2001).

14. Kambouropoulos, N. & Staiger, P. K. Reactivity to alcohol-related cues: Relationship among cue type, motivational processes, and personality. *Psychol. Addict. Behav.* **18**, 275–283 (2004).

15. Bottlender, M. & Soyka, M. Impact of craving on alcohol relapse during, and 12 months following, outpatient treatment. *Alcohol Alcohol.* **39**, 357–361 (2004).

16. Kavanagh, D. J., Andrade, J. & May, J. Imaginary relish and exquisite torture: The elaborated intrusion theory of desire. *Psychol. Rev.* **112**, 446–467 (2005).

17. Sayette, M. A. *et al.* The measurement of drug craving. *Addiction* **95**, 189–210 (2000).

18. Monti, P. M., Rohsenow, D. J. & Hutchison, K. E. Toward bridging the gap between biological, psychobiological and psychosocial models of alcohol craving. *Addiction* **95 Suppl 2**, 229–236 (2000).

19. Hasin, D. S. *et al.* DSM-5 criteria for substance use disorders: Recommendations and rationale. *Am. J. Psychiatry* **170**, 834–851 (2013).

20. Flannery, B. A., Poole, S. A., Gallop, R. J. & Volpicelli, J. R. Alcohol craving predicts drinking during treatment: an analysis of three assessment instruments. *J. Stud. Alcohol* **64**, 120–126 (2003).

21. Pavlick, M., Hoffmann, E. & Rosenberg, H. A nationwide survey of American alcohol and drug craving assessment and treatment practices. *Addict. Res. Theory* **17**, 591–600 (2009).

22. Gullo, M. J., Loxton, N. J. & Dawe, S. Impulsivity: four ways five factors are not basic to addiction. *Addict. Behav.* **39**, 1547–56 (2014).

23. Dawe, S., Gullo, M. J. & Loxton, N. J. Reward drive and rash impulsiveness as dimensions of impulsivity: Implications for substance misuse. *Addict. Behav.* **29**, 1389–1405 (2004).

24. Boog, M., Goudriaan, A. E., Van De Wetering, B. J. M., Deuss, H. & Franken, I. H. A. The concepts of rash impulsiveness and reward sensitivity in substance use disorders. *Eur. Addict. Res.* **19**, 261–268 (2013).

25. Stautz, K., Dinc, L. & Cooper, A. J. Combining Trait Models of Impulsivity to Improve Explanation of Substance Use Behaviour. *Eur. J. Pers.* **31**, 118–132 (2017).

26. Whiteside, S. P. & Lynam, D. R. The Five Factor Model and impulsivity: using a structural model of personality to understand impulsivity. *Pers. Individ. Dif.* **30**, 669–689 (2001).

27. Zuckerman, M., Kuhlman, D. M., Joireman, J., Teta, P. & Kraft, M. A Comparison of Three Structural Models for Personality: The Big Three, the Big Five, and the Alternative Five. *J. Pers. Soc. Psychol.* **65**, 757–768 (1993).

28. Patton, J. H., Stanford, M. S. & Barratt, E. S. Factor structure of the barratt impulsiveness scale. *J. Clin. Psychol.* **51**, 768–774 (1995).

29. Gullo, M. J. *et al.* A laboratory model of impulsivity and alcohol use in late adolescence. *Behav. Res. Ther.* **97**, 52–63 (2017).

30. George, S. M., Connor, J. P., Gullo, M. J. & Young, R. M. A Prospective Study of Personality Features Predictive of Early Adolescent Alcohol Misuse. *Pers. Individ. Dif.* **49**, 204–209 (2010).

31. Gullo, M. J., Dawe, S., Kambouropoulos, N., Staiger, P. K. & Jackson, C. J. Alcohol expectancies and drinking refusal self-efficacy mediate the association of impulsivity with alcohol misuse. *Alcohol. Clin. Exp. Res.* **34**, 1386–99 (2010).

32. Urošević, S. *et al.* Effects of reward sensitivity and regional brain volumes on

substance use initiation in adolescence. *Soc. Cogn. Affect. Neurosci.* **10**, 106–113 (2015).

33. Sher, K. J., Bartholow, B. D. & Wood, M. D. Personality and substance use disorders: A prospective study. *J. Consult. Clin. Psychol.* **68**, 818–829 (2000).

34. Charney, D. a., Zikos, E. & Gill, K. J. Early recovery from alcohol dependence: Factors that promote or impede abstinence. *J. Subst. Abuse Treat.* **38**, 42–50 (2010).

35. Müller, S. E., Weijers, H. G., Böning, J. & Wiesbeck, G. a. Personality traits predict treatment outcome in alcohol-dependent patients. *Neuropsychobiology* **57**, 159–164 (2008).

36. Goldstein, R. Z. & Volkow, N. D. Drug addiction and its underlying neurobiological basis: Neuroimaging evidence for the involvement of the frontal cortex. *Am. J. Psychiatry* **159**, 1642–1652 (2002).

37. Jentsch, J. D. & Taylor, J. R. Impulsivity resulting from frontostriatal dysfunction in drug abuse: Implications for the control of behavior by reward-related stimuli. *Psychopharmacology (Berl).* **146**, 373–390 (1999).

38. Koob, G. F. & Volkow, N. D. Neurocircuitry of addiction. *Neuropsychopharmacology* **35**, 217–238 (2010).

39. Swick, D., Ashley, V. & Turken, U. Are the neural correlates of stopping and not going identical? Quantitative meta-analysis of two response inhibition tasks. *Neuroimage* **56**, 1655–1665 (2011).

40. Whelan, R. *et al.* Adolescent impulsivity phenotypes characterized by distinct brain networks. *Nat. Neurosci.* **15**, 920–927 (2012).

41. Doran, N., Spring, B. & McChargue, D. Effect of impulsivity on craving and behavioral reactivity to smoking cues. *Psychopharmacology (Berl).* **194**, 279–288 (2007).

42. Yarmush, D. E., Manchery, L., Luehring-Jones, P. & Erblich, J. Gender and Impulsivity: Effects on Cue-Induced Alcohol Craving. *Alcohol. Clin. Exp. Res.* **40**, 1052–1057 (2016).

43. Papachristou, H., Nederkoorn, C., Havermans, R., Van Der Horst, M. & Jansen, A. Can't stop the craving: The effect of impulsivity on cue-elicited craving for alcohol in heavy and light social drinkers. *Psychopharmacology (Berl).* **219**, 511–518 (2012).

44. Stockwell, T., Murphy, D. & Hodgson, R. The severity of alcohol dependence questionnaire: its use, reliability and validity. *Br. J. Addict.* **78**, 145–155 (1983).

45. Statham, D. J. *et al.* Measuring alcohol craving: Development of the Alcohol Craving Experience questionnaire. *Addiction* **106**, 1230–1238 (2011).

46. Coates, J. M. *et al.* The Mini Alcohol Craving Experience Questionnaire: Development and Clinical Application. *Alcohol. Clin. Exp. Res.* **41**, 156–164 (2017).

47. May, J. *et al.* The Craving Experience Questionnaire: A brief, theory-based measure of consummatory desire and craving. *Addiction* **109**, 728–35 (2014).

48. Dickman, S. J. Functional and dysfunctional impulsivity: personality and cognitive correlates. *J. Pers. Soc. Psychol.* **58**, 95–102 (1990).

49. Franken, I. H. A. & Muris, P. Gray's impulsivity dimension: A distinction between Reward Sensitivity versus Rash impulsiveness. *Pers. Individ. Dif.* **40**, 1337–1347 (2006).

50. Claes, L., Vertommen, H. & Braspenning, N. Psychometric properties of the Dickman Impulsivity Inventory. *Pers. Individ. Dif.* **29**, 27–35 (2000).

51. Sobell, L. C. & Sobell, M. B. Timeline Follow-Back. in *Measuring Alcohol Consumption* (eds. Litten, R. Z. & Allen, J.) 41–72 (Humana Press, 1992). doi:10.1007/978-1-4612-0357-5_3

52. Tasca, G. a & Gallop, R. Multilevel modeling of longitudinal data for psychotherapy

researchers: I. The basics. *Psychother. Res.* **19**, 429–437 (2009).

53. Gallop, R. & Tasca, G. a. Multilevel modeling of longitudinal data for psychotherapy researchers: II. The complexities. *Psychother. Res.* **19**, 438–452 (2009).

54. Hedeker, D. & Gibbons, R. D. Application of random-effects pattern-mixture models for missing data in longitudinal studies. *Psychol. Methods* **2**, 64–78 (1997).

55. Bates, D., Mächler, M., Bolker, B. M. & Walker, S. C. Fitting linear mixed-effects models using lme4. *J. Stat. Softw.* **67**, 1–48 (2015).

56. Jonas, D. E. *et al.* Pharmacotherapy for Adults With Alcohol Use Disorders in Outpatient Settings. *Jama* **311**, 1889 (2014).

57. Chakravorty, S. *et al.* Covariates of craving in actively drinking alcoholics. *Am. J. Addict.* **19**, 450–457 (2010).

58. Witkiewitz, K. *et al.* Temporal Stability of Heavy Drinking Days and Drinking Reductions Among Heavy Drinkers in the COMBINE Study. *Alcohol. Clin. Exp. Res.* **41**, 1054–1062 (2017).

59. Field, A. P. & Wilcox, R. R. Robust statistical methods: A primer for clinical psychology and experimental psychopathology researchers. *Behav. Res. Ther.* **98**, 19–38 (2016).

60. Koller, M. **robustlmm** : An *R* Package for Robust Estimation of Linear Mixed-Effects Models. *J. Stat. Softw.* **75**, (2016).

61. MacKinnon, D. P., Lockwood, C. M., Hoffman, J. M., West, S. G. & Sheets, V. A comparison of methods to test mediation and other intervening variable effects. *Psychol. Methods* **7**, 83–104 (2002).

62. MacKinnon, D. P., Fritz, M. S., Williams, J. & Lockwood, C. M. Distribution of the product confidence limits for the indirect effect: Program PRODCLIN. *Behav. Res. Methods* **39**, 384–389 (2007).

63. Tofighi, D. & MacKinnon, D. P. RMediation: An R package for mediation analysis confidence intervals. *Behav. Res. Methods* **43**, 692–700 (2011).

64. Mackinnon, D. P. & Dwyer, J. H. Estimating Mediated Effects in Prevention Studies. *Eval. Rev.* **17**, 144–158 (1993).

65. Joos, L. *et al.* The relationship between impulsivity and craving in alcohol dependent patients. *Psychopharmacology (Berl).* **226**, 273–283 (2013).

66. Law, B. *et al.* Craving Mediates Stress in Predicting Lapse During Alcohol Dependence Treatment. *Alcohol. Clin. Exp. Res.* **40**, 1058–1064 (2016).

67. Verdejo-García, A. *et al.* Effect of craving induction on inhibitory control in opiate dependence. *Psychopharmacology (Berl).* **219**, 519–526 (2012).

68. Naqvi, N. H. *et al.* Cognitive Regulation of Craving in Alcohol-Dependent and Social Drinkers. *Alcohol. Clin. Exp. Res.* **39**, 343–349 (2015).

69. May, J., Kavanagh, D. J. & Andrade, J. The Elaborated Intrusion Theory of desire: A 10-year retrospective and implications for addiction treatments. *Addict. Behav.* **44**, 29–34 (2015).

70. Bari, A. & Robbins, T. W. Inhibition and impulsivity: Behavioral and neural basis of response control. *Prog. Neurobiol.* **108**, 44–79 (2013).

71. Bandura, A. A sociocognitive analysis of substance abuse: An agentic perspective. *Psychol. Sci.* **10**, 214–217 (1999).

72. Eysenck, S. B. G., Pearson, P. R., Easting, G. & Allsopp, J. F. Age norms for impulsiveness, venturesomeness and empathy in adults. *Pers. Individ. Dif.* **6**, 613–619 (1985).

73. Quinn, P. D. & Harden, K. P. Differential changes in impulsivity and sensation seeking and the escalation of substance use from adolescence to early adulthood. *Dev. Psychopathol.* **25**, 223–239 (2013).

74. Elman, I., Karlsgodt, K. H. & Gastfriend, D. R. Gender differences in cocaine craving among non-treatment-seeking individuals with cocaine dependence. *Am. J. Drug Alcohol Abuse* **27**, 193–202 (2001).

75. Cepeda-Benito, A., Fernandez, M. C. & Moreno, S. Relationship of gender and eating disorder symptoms to reported cravings for food: Construct validation of state and trait craving questionnaires in Spanish. *Appetite* **40**, 47–54 (2003).

76. Kraus, T. *et al.* Leptin is associated with craving in females with alcoholism. *Addict. Biol.* **9**, 213–219 (2004).

77. Zilberman, M. L., Tavares, H. & El-Guebaly, N. Relationship between craving and personality in treatment-seeking women with substance-related disorders. *BMC Psychiatry* **3**, 1 (2003).

78. Kiefer, F., Jahn, H. & Wiedemann, K. A neuroendocrinological hypothesis on gender effects of naltrexone in relapse prevention treatment: Letter to the editor. *Pharmacopsychiatry* **38**, 184–186 (2005).

79. Bertholet, N., Winter, M. R., Cheng, D. M., Samet, J. H. & Saitz, R. How accurate are blood (or breath) tests for identifying self-reported heavy drinking among people with alcohol dependence? *Alcohol Alcohol.* **49**, 423–429 (2014).

80. Robinson, N., Kavanagh, D., Connor, J., May, J. & Andrade, J. Assessment of motivation to control alcohol use: The motivational thought frequency and state motivation scales for alcohol control. *Addict. Behav.* **59**, 1–6 (2016).

81. Tiffany, S. T., Friedman, L., Greenfield, S. F., Hasin, D. S. & Jackson, R. Beyond drug use: a systematic consideration of other outcomes in evaluations of treatments for substance use disorders. *Addiction* **107**, 709–718 (2011).

82. Nahum-Shani, I. *et al.* A SMART data analysis method for constructing adaptive treatment strategies for substance use disorders. *Addiction* **112**, 901–909 (2017).

83. Leggio, L. Understanding and treating alcohol craving and dependence: Recent pharmacological and neuroendocrinological findings. *Alcohol Alcohol.* **44**, 341–352 (2009).

84. Marlatt, G. A. & Witkiewitz, K. Relapse prevention for alcohol and drug problems. in *Relapse Prevention for Alcohol and Drug Problems* (eds. Marlatt, G. A. & Donovan, D.) 1–44 (Guilford Press, 2005).

85. Witkiewitz, K. *et al.* Mindfulness-based treatment to prevent addictive behavior relapse: Theoretical models and hypothesized mechanisms of change. *Subst. Use Misuse* **49**, 513–24 (2014).