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Impulsivity Moderates Subjective Responses to Alcohol in Alcohol-Dependent Individuals

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Abstract

Aims: Studies of social drinkers indicate that subjective response (SR) to alcohol and impulsivity are risk factors for the development of alcohol use disorder which may be related. It is unclear, however, whether there are significant relationships between SR and impulsivity among individuals with alcohol dependence. Using data from an intravenous (IV) alcohol challenge study, the present study is the first to explore the relationship between impulsivity and SR during alcohol administration among alcohol-dependent individuals.

Methods: Non-treatment-seeking, alcohol-dependent individuals (N = 42) completed the Delay Discounting Task to measure impulsivity and then completed two counterbalanced, placebo-controlled IV alcohol administration sessions, which included assessments of SR at breath alcohol concentration (BrAC) levels of 0.00, 0.02, 0.04 and 0.06 g/dl.

Results: Analyses revealed that more impulsive participants experienced higher subjective stimulation and positive mood in response to rising BrACs as compared to less impulsive individuals. More impulsive participants also experienced increased sedation over time regardless of condition (i.e. alcohol vs. saline).

Conclusion: These findings suggest that among alcohol-dependent individuals, impulsivity is positively associated with the hedonic effects of alcohol as compared to placebo. High impulsivity may characterize a subset of alcohol-dependent individuals who drink to experience the rewarding effects of alcohol.

INTRODUCTION

Subjective response (SR) to alcohol, which refers to one's subjective experiences of the pharmacological effects of alcohol, and impulsivity, a personality trait defined by a failure to delay rewards and to control thoughts and behaviors, are two well-established predictors of problematic drinking (Dick *et al.*, 2010; Ray *et al.*, 2016). There are two predominant views of SR as a risk factor for alcohol use disorder (AUD). Building on the well-established familial nature of alcohol dependence (AD; Verhulst *et al.*, 2014), Schuckit and colleagues (i.e. Schuckit, 1994b) developed the low level of response model, which posits that blunted SR represents an AUD risk factor due to the need to consume more alcohol to achieve comparable levels of subjective intoxication. Longitudinal studies have shown that family history positive individuals exhibit a low response to the intoxicating effects of alcohol as compared to family history negative participants (Schuckit, 1994a). Furthermore, independent of family history, low responders were over four times as likely to develop AD at a 10-year follow-up than high responders (Schuckit, 1994b). Other findings are more closely aligned with the differentiator model (Newlin and Thomson, 1990), which proposes a 2D model of SR where the predominant response domain differs based on the limb of intoxication. Specifically, stimulation is more prevalent along the ascending limb

and sedation more prevalent along the descending limb. The differentiator model further posits that at-risk drinkers experience enhanced stimulatory responses along rising blood alcohol concentration (BAC) and blunted sedation as BAC falls. Recent studies involving the differentiator model have focused primarily on drinking history and SR domain with less emphasis on limb of intoxication. King *et al.* (2016) reported that, among heavy social drinkers, individuals who experienced high stimulation and low sedation at peak breath alcohol concentration (BrAC) reported more binge drinking and AUD symptoms at both 2- and 6-year follow-ups and that these response patterns were fairly stable.

The vast majority of SR research thus far has focused on social drinkers, leaving a relative void in literature pertaining to SR in individuals with AD. Drobes *et al.* (2004) found that participants with AD experienced greater subjective stimulation than social drinkers in the hour following consumption of a gender-adjusted dose of alcohol (0.40 g/kg for males and 0.34 g/kg for females). King *et al.* (2016) examined SR in participants with low (M = 0.9, SD = 0.2), intermediate (M = 3.2, SD = 0.2) and high (M = 6.4, SD = 0.6) AUD symptoms at baseline and at 5–6 years follow-up. Individuals with moderate and high AUD symptoms experienced greater subjective stimulation, wanting and liking during a follow-up session, as compared to the low AUD group. Taken together, these studies suggest a positive correlation between alcohol use severity and reward-motivated drinking. By contrast, Bujarski *et al.* (2015) reported greater stimulation in light-to-moderate drinkers and in those with AD than in heavy drinkers, and no group differences in sedation. However, stimulation was more strongly associated with alcohol craving among non-dependent heavy drinkers as compared to subjects with AD. We propose that examining associations between impulsivity and SR may clarify these differences.

The Delay Discounting Task (DDT; Kirby *et al.*, 1999) is a well-validated behavioral measure of impulsive choice, which assesses an individual's preference for smaller immediate rewards versus larger delayed rewards as a function of the length of the delay and the magnitude of the monetary difference between rewards. Studies comparing the DDT to various self-report measures of impulsivity have observed null to moderate (r's = 0.39–0.50) associations (Madden *et al.*, 1997; Vuchinich and Simpson, 1998; Lane *et al.*, 2003), suggesting that impulsivity may not be a single trait, but rather several inter-related traits that may confer independent or joint risk on AUD. To that end, as compared to other behavioral and self-report measures, the DDT appears to be a stronger correlate of alcohol and substance use disorders (Courtney *et al.*, 2012).

Studies of the relationship between impulsivity and SR in social drinkers have produced mixed results. An early investigation of drinkers without AD found that self-reported impulsivity was not associated with self-reported energy/vigor and friendliness during alcohol administration (Nagoshi *et al.*, 1991). However, impulsivity was positively correlated with sedation in males along falling BAC. Erblich and Earleywine (2003) identified a positive relationship between behavioral under-control (i.e. impulsive sensation seeking) and subjective stimulation on the ascending limb of the BAC curve in college students who did not report drinking problems. A recent investigation of social drinkers reported a positive association between response inhibition failure and sedation along rising BrAC and a negative relationship between response inhibition failure and stimulation as BrAC fell though there was no relationship between self-reported impulsivity and SR (Shannon *et al.*, 2011). Two studies of undergraduate social drinkers did not observe associations between self-reported impulsivity and SR (Rose and Grunsell, 2008; Magrys *et al.*, 2013). Considered together, the aforementioned studies suggest that relationships between impulsivity and SR in social drinkers are poorly understood and contingent upon study design and measurement tools.

Leeman *et al.* (2014) were the first to examine impulsivity and SR in social drinkers at precise alcohol concentrations in a highly controlled environment. They achieved this by using an intravenous (IV) alcohol clamping method, which reduces some sources of variability in absorption rate and facilitates the maintenance of target BrACs enabling experimenters to better control alcohol exposure to the brain. The IV alcohol clamping method enabled Leeman *et al.* (2014) to test SR at low (0.04 g/dl) and high (0.10 g/dl) BrACs while minimizing sources of pharmacokinetic variability and responses to alcohol-related cues. More impulsive individuals were more responsive to the stimulant and less responsive to the sedative effects of both alcohol doses. No study to date has explored the relationship between impulsivity and SR in individuals with AD.

Studies have highlighted the influence of the A118G single-nucleotide polymorphism (SNP) of the mu-opioid receptor (*OPRM1*) on SR in heavy drinking participants. While evidence linking this SNP to AD is mixed (Arias *et al.*, 2006), several studies found that G-allele carriers experience the rewarding subjective effects of alcohol more strongly than do A-allele homozygotes (Ray and Hutchison, 2007; Ray *et al.*, 2013). This SR pattern was replicated in individuals with AD in the primary analysis of the present data, which oversampled for G-allele carriers. Given the prospective genotyping in this data set, *OPRM1* genotype was accounted for in the analyses for the present study.

The current investigation is a secondary analysis of an alcohol challenge study that aims to expand upon studies of SR and impulsivity. Specifically, this study is the first to investigate the moderating effects of impulsivity on SR in participants with AD. To achieve this aim, a well-validated behavioral indicator of impulsivity, the DDT and a placebo-controlled, ascending limb, IV alcohol administration paradigm were employed in a well-characterized sample of participants with AD. We hypothesized that impulsivity would be positively associated with the stimulant and hedonic subjective effects of alcohol and negatively associated with sedative effects along rising BrAC.

MATERIALS AND METHODS

Participants

Participants were non-treatment-seeking alcohol-dependent individuals (N = 42) recruited from the Los Angeles area. Inclusion criteria were the following: (a) between 21 and 65 years old, (b) met DSM-IV criteria for current (i.e. past month) AD and (c) consumed a minimum of 48 standard drinks in the month preceding the screening visit. Participants were excluded if they: (a) were currently receiving treatment for alcohol problems or planned on seeking treatment in the near future, (b) abstained from alcohol for 21 days prior to screening, (c) met diagnostic criteria for lifetime bipolar or any psychotic disorder and (d) reported clinically significant withdrawal symptoms as indicated by a Clinical Institute Withdrawal Assessment for Alcohol-Revised (CIWA-AR) score ≥10.

Procedures

During the screening visit participants completed interviews, questionnaires and the DDT to assess for inclusion and exclusion criteria and to measure individual differences. Participants also submitted a

saliva sample for genetic analysis. Of the 295 participants who completed the screening visit, 43 individuals were randomized for participation in experimental sessions. Prospective genotyping for the A118G SNP of the *OPRM1* gene accounted for most of the attrition from screening and allele frequencies were in agreement with Hardy–Weinberg equilibrium ($\chi^2(1) = 0.425$, $P = 0.514$) (Ray *et al.*, 2013). A physical examination was conducted to ensure that participants were healthy enough to receive alcohol.

Individual differences measures

Measures collected at screening and used to determine eligibility included: (a) the 30-day Timeline Follow back interview (Sobell and Sobell, 1981) to assess frequency and quantity of alcohol consumption, (b) the Structured Clinical Interview for DSM-IV (First *et al.*, 1995) to assess alcohol and substance use, mood and psychotic disorders and (c) the CIWA-AR (Sullivan *et al.*, 1989) which measured the presence and severity of alcohol withdrawal symptoms. The Alcohol Dependence Scale (ADS; Skinner and Allen, 1982), Drinkers Inventory of Consequences (DrInC-2 R; Miller *et al.*, 1995) and Penn Alcohol Craving Scale (PACS; Flannery *et al.*, 1999) were also administered on the screening visit to assess severity of alcohol-related problems. The first question of the Smoking History Questionnaire (Brown *et al.*, 2002) was administered to assess smoking status. Participants reported whether they had smoked <50 cigarettes, between 50 and 100 cigarettes and >100 cigarettes in their lifetime. Responses were collapsed so that only individuals who reported smoking >100 cigarettes were considered regular smokers. Table 1 provides a description of sample demographics, smoking status and alcohol use variables.

The DDT was administered during the screening visit to assess trait impulsivity (Kirby *et al.*, 1999). Participants were presented with 27 hypothetical scenarios containing a smaller immediate reward (Option A) and a delayed larger reward (Option B) and asked to respond to rewards as if they were real. For example, in one scenario, participants were asked if they preferred $27 today or $50 in 21 days. Reward values were derived from a previously validated measure of discounting (Kirby *et al.*, 1999) and ranged from $11 to $85 with delays from 7 to 186 days. From these hypothetical choice data, hyperbolic discounting rate *k*-scores were calculated to reflect the degree to which participants were willing to delay rewards with higher *k*-scores representing greater delay discounting rate.

Table 1. Sample demographics

Variable	Mean (SD)
Sex (% female)	26.2%
Race (% Caucasian)	69.0%
Age	29.1 (9.5)
Education	14.6 (3.4)
Smoking status (% smokers)[a]	61.9%
DSM-IV AD symptoms	4.8 (1.5)
ADS score	42.4 (5.5)
DrInc-2 R score	51.1 (24.8)
PACS score	20.1 (6.2)
CIWA-AR score	5.6 (4.4)
Binge drinking days (past 30 days)[b]	14.9 (7.8)
Number of drinking days (past 30 days)	19.3 (7.6)
Drinks per drinking day (past 30 days)	7.1 (2.9)

[a]Participants were considered smokers if they reported smoking 100+ lifetime cigarettes.

[b]A binge drinking day was considered 5+ drinks in a day for males and 4+ drinks in a day for females.

Alcohol administration procedures and measures

IV alcohol administration was used to control for pharmacokinetic variability between individuals and to control for alcohol-related cues (Ramchandani *et al.*, 2009). Participants completed two infusion sessions, one alcohol infusion and one saline control infusion in a single-blinded, randomized, counterbalanced and crossover design. There was a 1- to 2-week washout period between infusions with an average separation of 10.6 days. Participants registered a BrAC of 0.00 prior to experimental testing and regular smokers were permitted to smoke before alcohol administration. A nomogram which accounts for participants' sex and body mass was used to intravenously administer alcohol (Ray and Hutchison, 2007). Participants received a 5% EtOH solution at a rate of 0.126-ml/min × weight, in kilograms, for females and 0.166-ml/min × weight for males. Participants were titrated to BrACs of 0.02, 0.04 and 0.06 g/dl whereupon infusion rates were reduced by half to maintain stable BrAC while testing. Testing lasted an average of 5 min at each target BrAC during which time participants completed alcohol administration measures. Participants were released from the laboratory when their BrAC dropped to 0.02 g/dl (or a BrAC = 0.00 g/dl if driving). Nursing supervision was available during the entire protocol and at discharge.

Measures administered at target BrACs included (a) The Biphasic Alcohol Effects Scale (BAES), a 14-item questionnaire scored on an 11-point Likert scale that captures participants' subjective experiences of stimulation and sedation (Martin *et al.*, 1994). (b) The Profile of Mood States (POMS) is a 40-item questionnaire that characterizes mood across four dimensions: negative mood, positive mood, tension and vigor (McNair *et al.*, 1971). Both BAES and POMS have been validated in alcohol challenge studies (Ray *et al.*, 2013).

Data analysis plan

Repeated-measures analysis of covariance (ANCOVA) was conducted using *SPSS* version 23. ANCOVA models consisted of Impulsivity (DDT *k*-score), a continuous between-subjects covariate, Condition, a two-level within-subjects factor (alcohol vs. saline, coded 0 and 1), Time, a four-level within-subjects factor (0 at baseline, 1 at BrAC = 0.02 g/dl or 18 min, 2 at BrAC = 0.04 g/dl or 43 min and 3 at BrAC = 0.06 g/dl or 75 min) and their interactions. Dependent variables included Stimulation and Sedation as measured by the BAES and Positive Mood, Negative Mood, Tension and Vigor as measured by the POMS, each tested in a separate model. *OPRM1* genotype was included as a covariate because it was associated with SR in the parent study (Ray *et al.*, 2013). Consideration was given to age, sex, monthly drinks (total drinks in the past 30 days), ethnicity (Caucasian vs. non-Caucasian), smoking status (smoker vs. non-smoker) as potential control variables, but their respective inclusion in the final model did not influence the results presented in Table 2. *Post hoc* analysis was conducted by testing Impulsivity × Time interactions at each level of Condition as well as Impulsivity × Condition interactions at each level of Time.

RESULTS

Demographics

Participants were predominantly males (73.8%) between ages 21 and 51 ($M = 29.14$, SD = 9.48). The sample was also ethnically

diverse (Caucasian 69.0%; African American 11.9%; Asian American 9.5%; Latino 9.5%).

Impulsivity and subjective stimulation and sedation

First, we tested whether impulsivity moderated the stimulating effects of alcohol over and above the effects *OPRM1* genotype. We observed a significant Impulsivity × Condition × Time interaction on subjective Stimulation (F (3, 114) = 2.99, P = 0.03) such that impulsive individuals reported greater alcohol-induced stimulation across rising BrAC, as compared to less impulsive individuals and as compared to placebo (Fig. 1). We also found a significant Impulsivity × Time interaction (F (3, 114) = 3.13, P = 0.03) wherein more impulsive participants experienced greater Stimulation over the course of the infusion. There was no main effect of Impulsivity on Stimulation (F (1, 38) = 0.19, P = 0.69).

We also examined whether impulsivity moderated the sedative effects of alcohol while controlling for *OPRM1* genotype. We identified a significant Impulsivity × Time interaction (F (3, 114) = 7.59, P = 0.0001) such that highly impulsive individuals experienced increased Sedation across Condition over Time (Fig. 2). There was not a significant main effect of Impulsivity on subjective Sedation (F (1, 38) = 0.69, P = 0.41) nor were the Impulsivity × Condition (F (3, 114) = 0.02, P = 0.89) or Impulsivity × Condition × Time (F (3, 114) = 0.17, P = 0.92) interactions significant.

Impulsivity and mood

Over and above the effects of *OPRM1* genotype, we found a significant Impulsivity × Condition × Time interaction on Positive Mood (F (3, 114) = 2.64, P = 0.05), suggesting that more impulsive participants in the alcohol condition experienced greater Positive Mood along rising BrAC, as compared to less impulsive individuals and as compared to the placebo condition (Fig. 3). There was no main effect of Impulsivity on Positive Mood (F (1, 38) = 1.17, P = 0.29). Impulsivity × Condition (F (3, 114) = 0.76, P = 0.39) and Impulsivity × Time (F (3, 114) = 1.38, P = 0.25) interactions were not significant.

There were no significant main or interaction effects of Impulsivity on Negative Mood, Tension or Vigor accounting for *OPRM1* genotype. Notably, the Impulsivity × Condition × Time interaction on Vigor (F (3, 114) = 2.31, P = 0.08) approached significance wherein more impulsive participants reported marginally greater Vigor across rising BrAC in the alcohol condition, as compared to the placebo. See Table 2 for all main effects and interactions.

Post hoc analysis

Post hoc testing was conducted by testing Impulsivity × Condition interactions at each level of Time and Impulsivity × Time interactions at each level of Condition, each controlling for *OPRM1* genotype. Impulsivity × Condition interactions were not significant

Table 2. *F*-statistics and *P*-values for main and interaction effects

	Stimulation		Sedation		Positive Mood		Negative Mood		Tension		Vigor	
	F	*P*	*F*	*P*	*F*	*P*	*F*	*P*	*F*	*P*	*F*	*P*
OPRM1 genotype	3.50	0.07	0.32	0.57	1.17	0.29	0.08	0.77	0.17	0.68	2.36	0.13
Time	0.38	0.77	1.50	0.22	0.28	0.84	7.69	0.05	4.69	<0.01	2.04	0.11
Condition	3.70	0.08	4.25	0.05	4.22	0.05	0.20	0.66	2.27	0.10	1.44	0.24
Impulsivity	0.19	0.69	0.69	0.41	1.17	0.29	0.67	0.42	0.62	0.44	1.17	0.29
Time × Condition	0.53	0.66	0.27	0.85	0.58	0.63	1.52	0.21	0.61	0.61	0.81	0.45
Time × Impulsivity	3.13	0.03	7.59	<0.01	1.38	0.25	0.73	0.54	0.66	0.58	0.69	0.56
Condition × Impulsivity	0.07	0.79	0.02	0.89	0.76	0.39	0.90	0.35	0.25	0.62	0.13	0.72
Time × Condition × Impulsivity	2.99	0.03	0.17	0.92	2.64	0.05	0.09	0.96	0.45	0.72	2.31	0.08

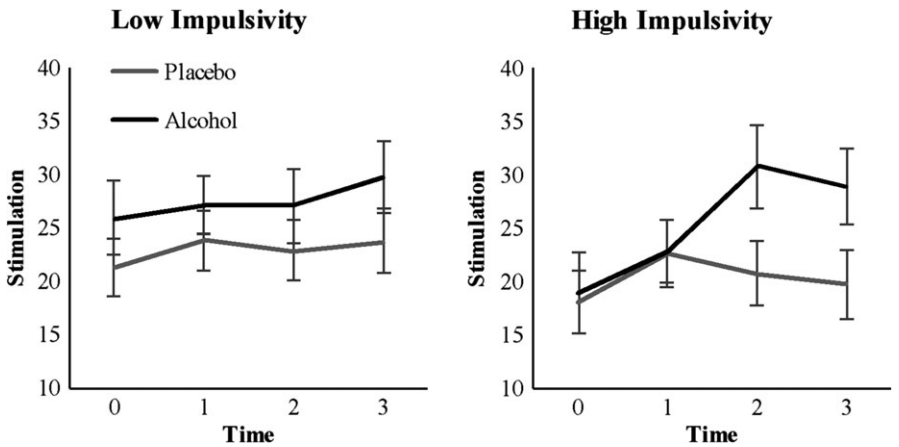

Fig. 1. Adjusted means for subjective Stimulation as a function of Time (Assessment Time or BrAC = 0.00, 0.02, 0.04, 0.06 g/dl), for Alcohol and Placebo conditions, for individuals with high and low Impulsivity (based on a median split of DDT *k*-scores for visual presentation only). Impulsivity was analyzed as a continuous variable, but is presented graphically as a median split. Error bars represent standard error of the mean.

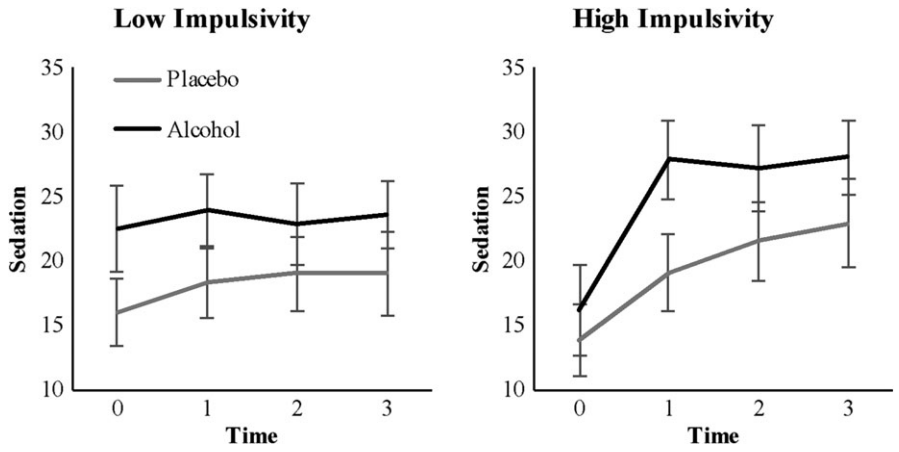

Fig. 2. Adjusted means for subjective Sedation as a function of Time (Assessment Time or BrAC = 0.00, 0.02, 0.04, 0.06 g/dl), for Alcohol and Placebo conditions, for individuals with high and low Impulsivity (based on a median split of DDT *k*-scores for visual presentation only). Impulsivity was analyzed as a continuous variable, but is presented graphically as a median split. Error bars represent standard error of the mean.

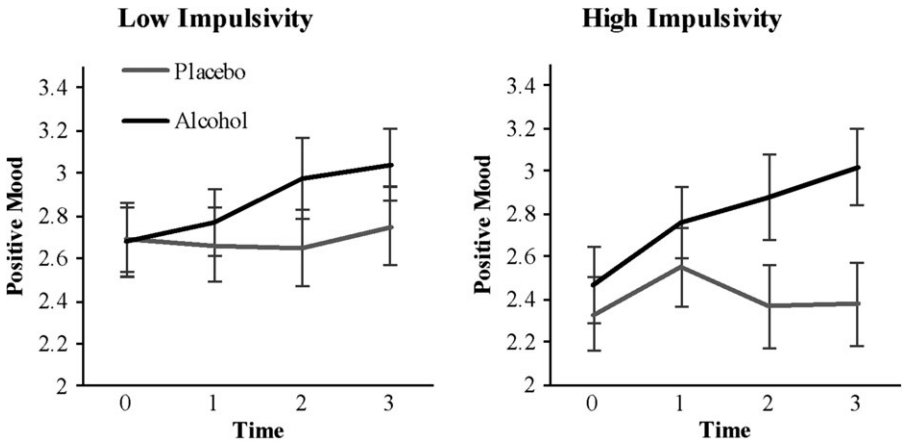

Fig. 3. Adjusted means for Positive Mood as a function of Time (Assessment Time or BrAC = 0.00, 0.02, 0.04, 0.06 g/dl), for Alcohol and Placebo conditions, for individuals with high and low Impulsivity (based on a median split of DDT *k*-scores for visual presentation only). Impulsivity was analyzed as a continuous variable, but is presented graphically as a median split. Error bars represent standard error of the mean.

(all P's > 0.17) for all outcome variables at each time point. However, there was a significant Impulsivity × Time interaction on Stimulation for participants in the alcohol (F (3, 114) = 3.80, P = 0.01), but not the placebo (F (3, 114) = 0.27, P = 0.84) condition. For Positive Mood, there was an Impulsivity × Time interaction for participants in the alcohol (F (3, 114) = 2.64, P = 0.05), but not placebo (F (3, 120) = 0.32, P = 0.81) condition. Taken together, these findings were consistent with the three-way interactions reported above.

DISCUSSION

This secondary data analysis of an existing alcohol administration study in non-treatment-seeking individuals with AD (Ray *et al.*, 2013) sought to elucidate the relationship between impulsivity and SR using highly controlled IV alcohol administration and a behavioral measure of impulsivity, the DDT. Results revealed that more impulsive participants experienced more subjective stimulation during alcohol infusion than less impulsive participants and as compared to the placebo condition. Additionally, greater impulsivity was associated with increases in positive mood over the course of rising BrAC and as compared to the placebo. Our findings extend the work of Leeman *et al.* (2014) by using a behavioral measure of impulsivity to demonstrate the association between impulsivity and SR in a sample of participants with AD. Furthermore, our results indicate that highly impulsive individuals with AD experience substantial increases in stimulation and hedonic reward during alcohol administration, suggesting that their alcohol consumption produces rewarding effects. By comparison, low impulsive individuals with AD may be less sensitive to the hedonic effects of alcohol, suggesting that alternative factors may influence the drinking behavior of these individuals.

Whereas Leeman *et al.* (2014) administered a self-report measure of impulsivity, the Barratt Impulsiveness Scale (Patton *et al.*, 1995), we used the DDT, a behavioral measure of impulsivity that may be less vulnerable to self-report bias. Given the mixed evidence regarding associations between self-report and behavioral measures of impulsivity, the high level of consistency between these data and those reported by Leeman *et al.* (2014) suggests that the association between impulsivity and SR is generalizable and robust to protocol changes (i.e. from self-report to behavioral measure of impulsivity).

Interestingly, our findings revealed that in highly impulsive individuals, sedation increased over time regardless of condition (alcohol vs. placebo). Since alcohol, as compared to saline, did not cause significant increases in sedation it is possible that participants simply became more sedated as the experiment proceeded, and that this waning was more evidenced among more impulsive individuals. Additionally, this study did not assess sedation on the descending limb of BrAC when these effects are thought to be preponderant (Newlin and Thomson, 1990). Finally, we measured only the negative elements of sedation (i.e. down, slow thoughts, sluggish) even though some individuals may experience sedation as a positive state. The recently developed Subjective Effects of Alcohol Scale (Morean *et al.*, 2013) has the potential to elucidate the relationship between impulsivity and sedation by capturing positively (i.e. calm, relaxed, secure) and negatively (i.e. dizzy, wobbly, woozy) valenced sedation items, which were not available in the present study.

Study strengths include the IV alcohol procedure which allowed us to control for individual differences in alcohol metabolism that can affect SR. Oral alcohol administration paradigms are unable to account for inter-individual differences in physiological functions such as gastric emptying, hepatic function and blood volume, that create significant variability in the time course of BrAC (Ramchandani *et al.*, 2009). Friel *et al.* (1995) administered alcohol orally (0.51 g/kg for males and 0.43 g/kg for females) to social drinkers and recorded BrAC at 8 time points post-drink. They reported between-subject BrAC variations ranging from 39% at 14 min to 14% at 125 min. Our IV alcohol infusion method ensures that participants reach equivalent BrACs at each time point. Moreover, IV as compared to oral alcohol administration is not tied to ordinary alcohol cues—taste, smell, touch and appearance—which may increase craving and impact mood (Jones *et al.*, 2013).

There are several limitations of the present study. While the IV alcohol technique offers a significant degree of experimental control, it lacks external validity as compared to oral alcohol administration studies. In this sample, *OPRM1* G-allele carriers experienced increased alcohol-induced stimulation, positive mood and vigor in comparison to A-allele homozygotes (Ray *et al.*, 2013). Therefore, we implemented statistical controls to account for potential biasing of our results.

CONCLUSION

This study is the first to investigate the relationship between impulsivity and SR in participants with AD. Our findings indicate that among individuals with AD, higher impulsivity was associated with greater stimulant and positive hedonic effects of alcohol along rising BrAC. While it is well established that high-risk social drinkers have impulsive tendencies (Verdejo-García *et al.*, 2008), our findings suggest that high impulsivity may characterize individuals with AD who drink for positive reinforcement. Future studies should explore individual differences that may explain the drinking behavior of comparatively less impulsive individuals with AD and seek to clarify associations between impulsivity and the sedative effects of alcohol across the progression of alcohol use and alcohol-related problems.

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CONFLICT OF INTEREST STATEMENT

None of the authors have any other conflicts of interest to disclose.

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