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# Binge and high-intensity drinking—Associations with intravenous alcohol self-administration and underlying risk factors

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## Abstract

Some styles of alcohol consumption are riskier than others. How the level and rate of alcohol exposure contribute to the increased risk of alcohol use disorder is unclear, but likely depends on the alcohol concentration time course. We hypothesized that the brain is sensitive to the alcohol concentration rate of change and that people at greater risk would self-administer faster. We developed a novel intravenous alcohol self-administration paradigm to allow participants direct and reproducible control over how quickly their breath alcohol concentration changes. We used drinking intensity and the density of biological family history of alcohol dependence as proxies for risk. Thirty-five alcohol drinking participants aged 21–28 years provided analytical data from a single, intravenous alcohol self-administration session using our computer-assisted alcohol infusion system rate control paradigm. A shorter time to reach 80 mg/dl was associated with increasing multiples of the binge drinking definition ( $p = 0.004$ ), which was in turn related to higher density of family history of alcoholism (FHD,  $p = 0.04$ ). Rate-dependent changes in subjective response (intoxication and stimulation) were also associated with FHD (each  $p = 0.001$ ). Subsequently,

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given the limited sample size and FHD range, associations between multiples of the binge drinking definition and FHD were replicated and extended in analyses of the Collaborative Study on the Genetics of Alcoholism database. The rate control paradigm models binge and high-intensity drinking in the laboratory and provides a novel way to examine the relationship between the pharmacokinetics and pharmacodynamics of alcohol and potentially the risk for the development of alcohol use disorders.

#### KEYWORDS

alcohol self-administration, ascending limb, binge drinking, high-intensity drinking, subjective response

## 1 | INTRODUCTION

Binge drinking is common<sup>1</sup> and associated with significant health risks (e.g., previous studies<sup>2-5</sup>). The impact on risk of how one consumes alcohol (how quickly and how high an alcohol concentration is achieved) is inherent in the definition of binge and high-intensity drinking. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) explicitly recognizes binge (“... a pattern of drinking that brings blood alcohol concentration (BAC) levels to [80 mg/dL]”) as one pattern of risky drinking, typically occurring after four or five drinks for women and men—in about 2 h.<sup>6</sup> Breath alcohol concentration (BrAC) indexes the arterial concentration (as in Lindberg et al.<sup>7</sup>), to which the brain is exposed.<sup>8</sup> Unfortunately, many individuals consume more than four or five alcohol drinks on an occasion. This pattern, termed high-intensity drinking,<sup>9</sup> is associated with an elevated risk of developing an alcohol use disorder (AUD).<sup>10-13</sup> Binge and high-intensity drinking are also clearly influenced by genetic risk; existing and novel risk loci were associated with typical maximum alcohol consumption in the Million Veteran project,<sup>14</sup> with ~50% of the sample consuming *at least* four or five drinks on an occasion.

Several AUD risk models have been proposed based on the subjective response to alcohol, each derived using oral alcohol challenges and suggesting a relationship between alcohol pharmacokinetics and pharmacodynamics. The two models with the most support are the low level of response model and the differentiator model. The low level of response model is based on the finding that males with a positive family history of AUD (FHP) reported lesser subjective responses to an alcohol challenge than those without family history (family history negative, FHN).<sup>15</sup> The differentiator model posits that FHP individuals are more sensitive to the rewarding effects on the ascending limb (period of increasing BrAC), and more tolerant to the sedating effects on the descending limb (when BrAC is decreasing), compared with FHN controls.<sup>16</sup> Ingestion of alcohol, however, results in substantial variation in peak BrAC and latency to peak BrAC, limiting experimental control over how quickly alcohol exposures change (e.g., Norberg et al.<sup>17</sup> and Ramchandani et al.<sup>18</sup>). Consequently, most research has focused on the response to alcohol on the ascending versus descending limbs. Nonetheless, interest in the effects of rate of change of BrAC, per se, has existed for some time.<sup>19-21</sup>

Intravenous (IV) alcohol administration techniques document a relationship between the alcohol concentration time course and its effects, including the role of rate of change of brain exposure. The alcohol clamp comprises a linear rise to a target BrAC, which is then maintained for hours, thus eliminating rate of change as a contributing factor to measurements obtained during the clamp. Outcomes include subjective and physiological responses to both the investigator-defined initial positive rate of change of BrAC (initial response to alcohol) and changes in the response during maintenance of a steady BrAC (acute tolerance). The clamp paradigm has successfully examined family history of AUD,<sup>22-24</sup> genetic association of acute tolerance,<sup>25</sup> recent drinking history,<sup>24</sup> and other indicators of risk.<sup>26</sup> Conversely, using a paradigm where specific rates of BrAC ascent and descent were prescribed, we reported increased perceptions of “high” and “intoxicated” measured at the same BrAC and elapsed time on the ascending versus descending limb in moderate drinkers, and the reverse of that pattern in light drinkers.<sup>27</sup> Thus, the precise exposure control provided by IV alcohol administration techniques supports a relationship between positive and negative rates of change of BrAC and response to alcohol, drinking history, and other AUD risk factors. Taken together, the observations across the oral and IV alcohol challenge literature invited a study of how the steepness of self-controlled positive rates of change in BrAC relate to the subjective response to alcohol, family history, recent drinking history and risk for AUD.

Alcohol self-administration paradigms are increasingly common in human studies and suggest the importance of examining how quickly people consume alcohol, the relationship between how quickly BrAC changes and subjective response or other risk factors. Using oral alcohol self-administration techniques, investigators have primarily investigated the temporal dynamics of a drinking episode. Outcomes of interest have largely been limited to total volume of alcohol consumed, frequency or speed of consumption, and latency to start or finish a drink.<sup>28-33</sup> These studies provided minimal examination of alcohol concentration temporal dynamics beyond peak, ascending versus descending limb, or overall differences (for example, previous studies<sup>30,34</sup>), likely secondary to the aforementioned variability in alcohol exposure even after a standard “drink” and challenges collecting frequent alcohol concentration measures after oral consumption. Using an IV alcohol paradigm, Stangl et al. reported that those who self-infused more rewards in the first 30 min of the lab study reported

drinking more heavily in the past month and reported a greater rewarding subjective response compared with participants who infused less during the same interval.<sup>35</sup> Recently, the time to achieve a binge level exposure of 80 mg/dl was associated with AUD risk,<sup>36</sup> genetic risk,<sup>37</sup> and high-risk drinking.<sup>38</sup> In these studies, each IV alcohol reward is identical. Thus, participants only achieved *indirect* control of the overall rate of BrAC change through selection of *when* alcohol was delivered. Further, the rate of change associated with each reward was identical and thus may have been too rapid or too slow for an individual participant for whom the rate of change influences, if not determines, reward. Recently, investigators employed ecological momentary assessment and estimated blood alcohol concentrations to examine alcohol consumption in the community. Noting the limitations of the methodology, they reported that, within drinking episodes, “faster consumption” (determined as greater rates of change in *estimated* blood alcohol concentration) was associated with decreased negative affect and increased positive affect.<sup>39</sup> Consequently, while the alcohol self-administration literature consistently identifies a role for drinking rate and the resultant alcohol pharmacokinetics in multiple outcome measures, no study has yet to provide participants direct and reproducible control over their alcohol exposure time course.

We developed a novel IV alcohol self-administration paradigm to assess preference for high *rates of change* of BrAC as a potential underlying risk factor for AUD. By allowing participants to directly control how quickly their BrAC changed for each reward interval, we

tested the primary hypothesis that their self-administered alcohol exposure profile is associated with recent binge and high-intensity drinking. In addition, we explored the underlying reasons including the role of subjective sensitivity to rate of change of alcohol exposure and family history density of AUD amongst other AUD-related risk. Then, based our results implicating family history density of AUD and recent binge and high-intensity drinking, we tested whether the interview-based associations found in our laboratory study replicated in a much larger sample population from the Collaborative Study on the Genetics of Alcoholism (COGA) (Appendix A).

## 2 | METHODS

See Supporting Information for expanded details.

### 2.1 | Laboratory participants

A total of 37 participants, 18 men and 19 women aged 21–27, completed the study. All were healthy, non-treatment seeking, and at-risk alcohol-consuming participants comprising 29 and 4 European and African ancestry respectively, with the remainder being of mixed, other, or unknown ancestry (Laboratory Session; Table 1A). All participants were heavy drinkers ( $\geq 7/14$  drinks per week or  $\geq 3/4$  drinks on one occasion for women and men, respectively<sup>6</sup>). The study was

**TABLE 1** Demographic analysis by drinking intensity group

	Low	Moderate	High	Extreme	p value
A: Laboratory sample: Drinking intensity group					
Number	2	11	14	8	
Age	-	22.9 (0.53)	23.4 (0.57)	23.0 (0.63)	0.83
Gender (%F)	-	73%	43%	50%	0.32
FHD	-	0.06 (0.03)	0.09 (0.03)	0.18 (0.04)	0.04
Craving (PACS)	-	6.1 (1.0)	8.7 (1.0)	7.1 (1.6)	0.39
SRE-total	-	5.92 (0.58)	6.81 (0.92)	7.46 (0.62)	0.28
AUDIT	-	8.0 (0.66)	11.1 (0.8)	8.8 (1.49)	0.39
Maxdrinks	-	6.2 (0.42)	10.7 (0.44)	15.9 (0.72)	0.004
DD/W	-	2.6 (0.2)	2.8 (0.27)	3.2 (0.55)	0.50
D/DD	-	3.5 (0.26)	5.5 (0.62)	5.5 (0.83)	0.03
B: COGA sample: Drinking intensity group					
Number	45	74	119	406	
Age	24.4 (0.36)	24.4 (0.27)	22.3 (0.21)	24.8 (0.11)	0.033
Gender (%F)	62.2%	70.3%	61.5%	38.9%	<0.0001
FHD	0.23 (0.03)	0.27 (0.03)	0.30 (0.02)	0.35 (0.01)	<0.0001
Maxdrinks	3.1 (0.18)	6.4 (0.12)	10.3 (0.15)	24.1 (0.56)	<0.0001

Note: Due to small number ( $n = 2$ ), participants with membership the low drinking intensity group of the laboratory sample were excluded from all group-based analyses. Data show mean (standard error) or percent. Maxdrinks, DD/W, and D/DD: maximum number of drinks in a 24-h period, drinking days per week, and drinks per drinking day, respectively, over timeline followback interval. The italics were to emphasize statistically significant results.

Abbreviations: AUDIT: Alcohol Use Disorders Identification Test; FHD, family history density of biological relatives with an AUD; PACS, Penn Alcohol Craving Scale.

approved by the Indiana University School of Medicine Institutional Review Board. NIAAA guidelines for administering alcohol in human studies were followed. Participants were interviewed, providing demographic and medical information, a recent 35-day drinking (timeline follow-back<sup>40,41</sup>), an evaluation of antecubital vein access and vital signs, a blood sample for liver function testing, and a urine sample for drug use and pregnancy-testing. As tobacco use is also highly prevalent in heavier drinkers,  $N = 8$  recent smokers were included.

## 2.2 | Alcohol self-administration sessions

Each participant undertook one IV alcohol self-administration session. Participants were instructed to avoid consuming alcohol after 4 PM on the previous day and to not eat anything after midnight. Each was admitted to the outpatient section of the Indiana Clinical Research Center at Indiana University Hospital at approximately 8 AM; all participants had a zero BrAC and females had a negative urine pregnancy test. Smokers were offered nicotine replacement during the session (none accepted). A standardized breakfast was provided, followed by antecubital IV catheter placement in the non-dominant arm. In response to the participant's experimental choices, the required infusion rate profile was calculated in real time, utilizing an individualized physiologically based pharmacokinetic model<sup>42</sup> and the computer-assisted alcohol infusion system (CAIS<sup>43-45</sup>). BrAC was measured frequently throughout the experiment. The safety limit, above which alcohol self-administration was suspended, was 150 mg/dl. Participants were not informed of their BrAC at any time.

Rate selection and subjective response assessments were repeated in 3 min epochs (Figure 1). Three min was determined to be the minimum interval over which the participant could experience the effects of the selected rate of BrAC based upon pharmacokinetic modelling of brain alcohol concentration and consistent with work by Gomez et al.<sup>8</sup> A visual display allowed the participant to choose the next rate of BrAC change by turning a dial. Participants were instructed that the experimental objective was to determine how much they enjoyed various alcohol exposure rates and that they

would be able to increase, decrease, or keep their BrAC the same as they desired. They were encouraged to make decisions with minimal delay, during which their BrAC was held constant. The maximum ascending rate in each epoch was 5 mg/dl per min or whatever lesser rate would achieve a BrAC within 5 mg/dl of the safety limit. The maximum available descent rate was initially  $-5$  mg/dl per min, reducing with equilibration of alcohol in the total body water,<sup>46-49</sup> and subsequently limited by the participant's alcohol elimination rate. The display was dynamically updated to present the current range of available choices.

Participants documented their current subjective perceptions over approximately 20 s at the end of each epoch, using a visual comparison to their preceding selection (Figure 1), consistent with our prior work.<sup>25,50,51</sup> The following subjective response questions were used, adapted from the Subjective High Assessment Scale<sup>52</sup> as implemented by Schuckit et al.,<sup>15,53-55</sup> the Brief Biphasic Alcohol Effects Scale,<sup>56</sup> and the Subjective Effects of Alcohol Scale.<sup>57</sup>

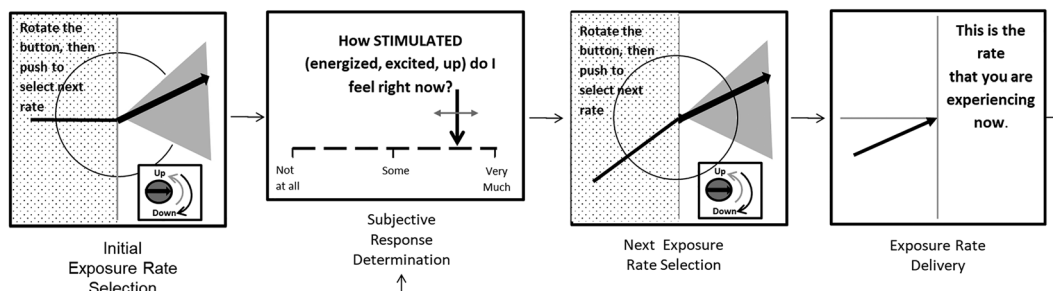
- How much am I feeling the effects of the drug right now? (INTOXICATED).
- How STIMULATED (energized, excited, up) do I feel right now?
- How ANXIOUS (tense, jittery, nervous) do I feel right now?
- How RELAXED (carefree, mellow, loose) do I feel right now?
- How SEDATED (slow thoughts, sluggish, difficulty concentrating) do I feel right now?

After the session, participants were transferred to a private room until the later of 5 PM or their BrAC fell below 20 mg/dl. We compensated participants \$25 in cash at the time of the interview and \$125 at release.

### 2.2.1 | Laboratory measures

#### *Time to reach BrAC of 80 mg/dl*

The elapsed time (minutes) at which the participant reached a BrAC of 80 mg/dl was employed as the primary outcome, as in our prior



**FIGURE 1** Exposure rate selection and subjective response determination sequence. The task began with an initial exposure rate selection, with the display indicating no past rate of change (baseline). During each 3 min epoch, beginning at 2.5 min, a set of subjective responses were collected over approximately 20 s after which time the next exposure rate selection prompt was displayed, indicating the prior selection in the left hand (shaded) portion of the display. The choice and subjective response sequence was repeated throughout the experiment. The next exposure rate was then selected by rotation of the response button (Griffin Technologies Powermate<sup>®</sup>, depiction inset) to a position within the available range depicted in grey. The arrow position followed the button rotation in real time, and the rate chosen is confirmed by a single button press.

work.<sup>36–38</sup> Two participants did not self-administer alcohol and post-session debriefing identified intentional manipulation to achieve an earlier discharge time in one case and, in the other, a significant recent stressor which would have precluded their involvement had it been reported at the screening interview. These individuals were excluded from all analyses.

#### *Subjective response to alcohol*

Operationalizing our prior work for repeated assessment,<sup>58</sup> subjective response to alcohol as a function of time was modelled as a linear combination of the current alcohol concentration, the preceding rate of change in alcohol concentration, and the cumulative exposure to alcohol at that time across all measured time points, using Matlab (Mathworks, Natick MA). The coefficient relating the rate of change in alcohol concentration to subjective response served as the analytical variable.

### 2.2.2 | Interview-based measures

Family history of AUD module of the SSAGA,<sup>59</sup> the Alcohol Use Disorders Identification Test (AUDIT<sup>60</sup>), Penn Alcohol Craving Scale (PACS<sup>61</sup>), and the retrospective Self-Reported Effects of Alcohol (SRE<sup>62</sup>) were collected. For safety and procedure-related purposes, the Clinical Institute Withdrawal Assessment for Alcohol<sup>63</sup> and the Center for Epidemiologic Studies Depression Scale<sup>64</sup> were completed.

#### *Drinking intensity*

Laboratory sample drinking intensity (DI) was characterized by the self-reported maximum number of drinks in a 24 h period (Maxdrinks) during the 35 day timeline follow-back interval, divided by four or five drinks for women and men respectively, a strategy comparable to that adopted in the epidemiological literature<sup>9,12,13</sup> and labelled as low-risk if  $DI < 1$  ( $N = 2$ ), moderate-risk if  $1 \leq DI < 2$  ( $N = 11$ ), high-risk if  $2 \leq DI < 3$  ( $N = 14$ ), and extreme-risk if  $DI \geq 3$  ( $N = 8$ ). Given sample size concerns, the low-risk group was excluded from all group-based analyses, leaving a final analytical sample of 33 subjects. In the subsequent study, DI groups were created in COGA using the lifetime Maxdrinks variable. DI group demographic characteristics by sample are in Table 1A,B, with additional COGA sample data presented in Table S1B.

#### *Family history density*

A family history density (FHD) score<sup>65</sup> was calculated for each participant in both samples. FHD scores were based on degree of biological relatedness, in which parents and full-siblings with a lifetime history of DSM-IV alcohol dependence contributed 0.5 for each person, each dependent grandparent or sibling of parents contributed 0.25, and non-affected biological relatives contributed zero. We calculated FHD as the sum of weights divided by the number of counted relatives. A detailed description of Materials and Methods is provided in Supporting Information.

### 2.2.3 | Statistical analyses

#### *Time to reach 80 mg/dl*

Survival analyses used a Cox proportional hazards model to test if the time at which drinkers reached 80 mg/dl differed as a function of DI. The Akaike information criteria (AIC) was utilized to evaluate fit. Nicotine and gender were tested and included if significant ( $p < 0.05$ ). FHD was tested in a separate model to avoid any confounds between FHD and DI group. To verify that our primary result was not a function of the DI group definition process, subsequent analyses examined the relationship between Maxdrinks and time to reach 80 mg/dl.

#### *Subjective response*

The individual contribution of FHD and DI group to the subjective response was evaluated using separate analyses of variance (ANOVA) model for FHD and for DI group. We included FHD, AUDIT, and the FHD\*AUDIT interaction in each ANOVA model to account for the potential effect of high AUDIT scores in those with higher FHD.

#### *Drinking intensity groups*

An ANOVA model was used to examine the characteristics of the three DI groups for age, FHD, craving (PACS), and AUDIT (Table 1A) by using DI group as a predictor variable. Tukey-corrected pairwise comparisons were used to identify how the groups differed. A chi-square test was used to test whether gender and nicotine use was associated with the DI groups.

#### *Family history density*

To utilize risk information inherent in the DI group variable, an ordinal logistic regression model was employed to examine the hypothesis that FHD predicts DI group. The Score Test was employed to test the equal proportional odds assumption. ANOVA models were subsequently used to assess if FHD predicted the alcohol-related interview variables PACS/DAQ, SRE-total, and AUDIT/SC scores. Age and gender were excluded from the models because they were not significant.

Pearson correlation coefficients were estimated to aid in interpretation of associations between quantitative variables, when applicable. Odds ratios (OR) and 95% confidence intervals (CI) are reported when appropriate. An adjusted  $\alpha = 0.01$  was used to correct for the five subjective responses analysed in the same model. An  $\alpha = 0.05$  was employed for all other analyses. All analyses were completed using SAS v9.4.

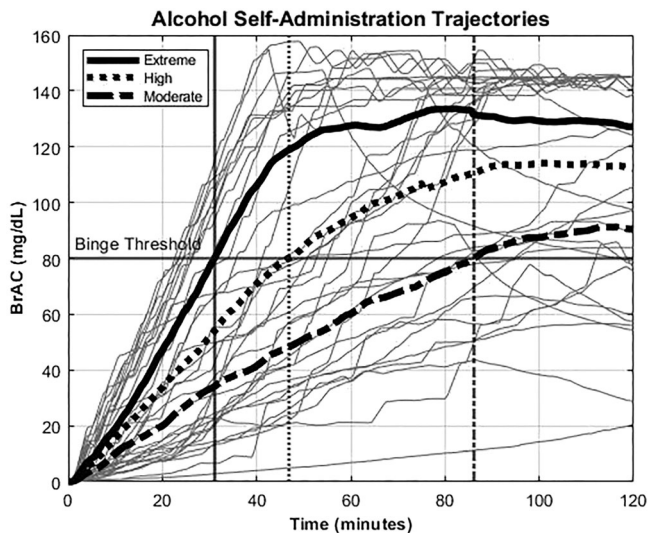
## 3 | RESULTS

### 3.1 | Demographics

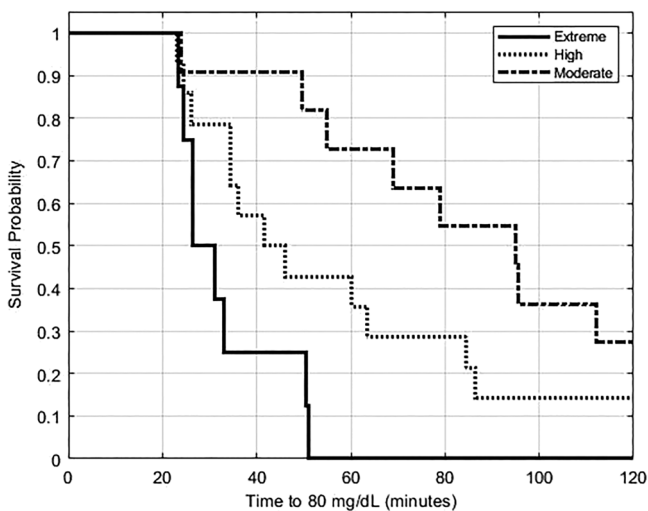
The (mean; standard deviation) age of participants in the laboratory sample was (23.1; 1.9) years and (24.8; 2.3) in the COGA sample. The laboratory sample reported (12.7; 6.0) drinks per week. There were slightly more women than men in both samples (laboratory sample = 55%, COGA sample = 51%).

### 3.2 | Alcohol self-administration

Many laboratory participants reached the safety limit of 150 mg/dl. DI group significantly predicted the time until a participant reached binge drinking BrAC threshold (80 mg/dl; overall  $p = 0.004$ , AIC = 153.7) with five participants not reaching 80 mg/dl (Figures 2 and 3). The extreme-risk DI group reached a BrAC of 80 mg/faster (mean 33.3 min) than the high-risk DI group (mean 57.2 min); hazard ratio = 3.33, 95% CI = [1.22, 9.09],  $p = 0.02$ , and faster than the moderate-risk DI group (mean 85.4 min); hazard ratio = 7.14, 95% CI = [2.22, 21.74],  $p = 0.01$ ; There was an emerging trend in the



**FIGURE 2** Alcohol self-administration trajectories. Individual BrAC time courses and average time course for the DI groups are displayed. Mean times to reach 80 mg/dl are noted by vertical lines.



**FIGURE 3** Survival analysis of time to a binge alcohol exposure of 80 mg/dl. Kaplan-Meier curves show that drinking intensity group significantly predicted the time until a subject reached binge drinking BrAC threshold ( $p = 0.004$ ). Five total participants did not reach 80 mg/dl, demarcated by the high and moderate group's survival probability remaining non-zero at 120 min.

difference in time between the high- and moderate-risk DI groups; hazard ratio = 2.13, 95% CI = [0.85, 5.26],  $p = 0.10$ . FHD, nicotine, and gender were not associated with time until binge level exposure occurred for the DI groups (all  $ps > 0.10$ ).

Individuals with higher Maxdrinks also reached 80 mg/dl levels more quickly ( $p = 0.004$ , hazard ratio = 2.21, AIC = 162.4).

### 3.3 | Rate-dependent subjective response

DI group did not predict any rate-dependence of subjective responses (all  $ps \geq 0.38$ ). FHD by itself predicted rate sensitivity (at  $p \leq 0.01$ ) for two of the five subjective responses to alcohol (Table 2).

#### 3.3.1 | Intoxication

Higher FHD was associated with lower rate-dependent intoxication effects ( $p = 0.001$ ). AUDIT score was not associated with intoxication, per se, ( $p = 0.09$ ), but individuals with both a high FHD and high AUDIT scores reported feeling significantly more intoxication as a function of rate of alcohol exposure (FHD\*AUDIT  $p = 0.003$ ).

#### 3.3.2 | Stimulation

Higher FHD was associated with lower rate-dependent stimulation ( $p = 0.01$ ). As with intoxication, AUDIT score was not associated with rate sensitivity of stimulation ( $p = 0.10$ ), although individuals with higher FHD and AUDIT scores reported moderately more stimulation (FHD\*AUDIT  $p = 0.05$ ).

#### 3.3.3 | Anxious

There was an association between both higher FHD and higher AUDIT scores and a greater alcohol rate-dependent anxiety ( $p = 0.04$  and  $p = 0.03$ , respectively); however, the significance did not survive correction. There was no significant interaction between AUDIT and FHD and anxiety ( $p = 0.09$ ).

#### 3.3.4 | Sedation and relaxation

No association between alcohol exposure rate and FHD, AUDIT, or their interaction was identified in the measure of Sedation or Relaxation (all  $ps > 0.2$ ).

### 3.4 | Drinking intensity group

Individuals in the high-risk DI group had higher AUDIT scores than those in the moderate-risk DI group ( $p = 0.04$ , Table 1A). Those in the

**TABLE 2** Beta and standard error of the general linear model rate of change of BrAC coefficients to each subjective response for the full analysis of variance model employing FHD, AUDIT, and FHD\*AUDIT

Subjective response	FHD	AUDIT	FHD*AUDIT
Intoxication	−57.2 (15.87) <b><i>p</i> = 0.001</b>	−0.49 (0.28) <i>p</i> = 0.088	5.66 (1.70) <b><i>p</i> = 0.003</b>
Stimulation	−42.58 (15.30) <b><i>p</i> = 0.001</b>	−0.45 (0.27) <i>p</i> = 0.103	3.40 (1.63) <i>p</i> = 0.047
Anxious	30.96 (14.18) <i>p</i> = 0.038	0.55 (0.25) <i>p</i> = 0.034	−2.68 (1.51) <i>p</i> = 0.088
Sedation	14.55 (22.22) <i>p</i> = 0.516	0.18 (0.38) <i>p</i> = 0.645	−0.44 (2.36) <i>p</i> = 0.855
Relaxation	18.69 (16.62) <i>p</i> = 0.271	0.35 (0.29) <i>p</i> = 0.240	−2.17 (1.78) <i>p</i> = 0.232

Note: The computation is shown for assessing FHD, AUDIT score, and the combination. Increasing biological family history of alcohol density was associated with less alcohol exposure rate-dependent sensitivity on the measures of intoxication, representing general drug effects, and on stimulation. Significant effects, based on an adjusted  $\alpha \leq 0.01$ , shown in bold; marginal effects italicized.

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; FHD, family history density of biological relatives with an alcohol use disorder.

extreme-risk DI group had higher FHD compared to those in the moderate-risk DI group ( $p = 0.036$ ). There were no pairwise differences between the groups for any other alcohol-related screening variable (all  $ps > 0.2$ ).

### 3.5 | Family history density

FHD predicted DI group ( $p = 0.02$ ; Score Test  $p = 0.40$ ), a finding that prompted subsequent testing for replication in the COGA sample, given the small laboratory sample size and limited FHD range.

#### 3.5.1 | COGA participants

The COGA sites began with recruitment of AUD probands from inpatient and outpatient treatment facilities and administered a poly-diagnostic interview, the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA),<sup>66,67</sup> and targeted families with a high density of first-degree relatives with alcohol dependence. Comparison families were recruited within the same communities.<sup>68</sup> To approximate the laboratory sample, COGA were included in analyses only if they were of European ancestry, between the ages of 21 and 28 at their most recent interview, and ever drank at least one full alcohol beverage. One person per extended family corresponding to the participant with the lowest identification number in the age range was retained. The final COGA sample contained  $N = 644$  individuals, with 65% having a parent with AUD. FHD was computed in the COGA sample<sup>58</sup> in the same way as the laboratory sample. See Supporting Information for more discussion of the COGA sample.

Higher FHD was associated with greater drinking intensity in the COGA sample ( $p = 0.0002$ ; Score Test  $p = 0.54$ , Figure S1).

Individuals with a higher FHD were 7.75 times more likely to be in the extreme-risk DI group compared with the other DI groups (based on unit of 0.25 in FHD calculation; 95% confidence interval (CI) = [1.45, 40.76]). FHD was not associated with any of the alcohol-related screening measures (all  $ps > 0.30$ ) in the laboratory sample.

## 4 | DISCUSSION

Rate control is the first human laboratory paradigm where participants had explicit, reproducible control over their *rate* of change of alcohol exposure. The results support our primary hypothesis—that people who report risky drinking self-administered alcohol to a binge level faster. This behaviour suggests that they may consume alcohol to raise their BrAC quickly versus simply achieving a higher level, potentially a pharmacodynamic mechanism underlying risky drinking. Clinically, this observation provides evidence of the importance of counselling people on not only how much and how often but also *how quickly* they drink, urging extra precaution for those with greater FHD. The results support FHD as a risk factor for elevated drinking intensity; it is also associated with subjective response, although in an indirect and complex manner. The findings also build upon previous studies that used retrospective evaluation of a free-access IV alcohol-self-administration paradigm to demonstrate that time to achieve binge levels during a drinking episode reflected risk factors for AUD such as gender, family history of AUD, impulsivity, and level of response.<sup>35,36,38</sup>

As a risk factor, FHD captures a combination of biological (genetic) and psychosocial/environmental factors. The genetics of alcohol consumption has garnered interest (e.g., previous studies<sup>69,70</sup>), yet binge and high-intensity phenotypes are relatively unexplored. Use of the AUDIT consumption subscale<sup>71</sup> has been



productive,<sup>72-74</sup> but this measure does not specifically capture the high-intensity drinking phenotype and may reflect non-problematic alcohol usage.<sup>74</sup> Further, some work suggests the prediction of clinical phenotypes based on AUDIT consumption-based polygenic risk scores may be sample-dependent.<sup>75</sup> Maxdrinks, which, at higher ranges, is more specific to Binge and High-Intensity Drinking, has proven a valuable phenotype in genetic studies.<sup>14,76,77</sup> Consequently, our laboratory finding of an association between FHD and drinking intensity group is congruent with the literature and significantly strengthened by replication in the much larger COGA sample. In fact, supplementary COGA analyses showed that drinking intensity accounted for more variability in the alcohol screening measures than FHD (See Supporting Information), highlighting the importance of collecting information on drinking patterns within and across events.

Our results suggesting that psychodynamic effects of alcohol may be exposure-rate dependent is not new, but remains relatively unexplored.<sup>19-21</sup> Studies using oral challenge techniques have been limited by the lack of control of the alcohol concentration trajectory. Under conditions in which participants could select their exposure rate, FHD, but not drinking intensity group, was associated with rate-dependent subjective response. Specifically, this negative relationship between FHD and the alcohol exposure-rate dependent term for both intoxication and stimulation, suggests that those with higher FHD perceive less of these effects for a given positive exposure rate. Such a person may have to drink faster if intoxication or stimulation is a goal, suggesting support for the low level of response model. Another possibility is that higher FHD is associated with greater, more rapid acute tolerance to intoxicating and stimulating effects.

Exposure-rate sensitivity should be applicable to the descending limb, but few participants in our study chose to reduce their alcohol exposures. Thus, extension of our results to the descending limb and directly comparing to the pre-existing subjective response models of risk is not advised.

Study limitations are primarily related to the small laboratory sample size, resulting in a limited range of FHD and diversity, and limited power to detect smaller effect sizes. Further, Maxdrinks was determined over the 35 day timeline follow-back interval in the laboratory sample compared with the lifetime assessment in the COGA dataset. However, variability in timeframe and drinking pattern assessment is also present in the larger literature,<sup>9,11-14</sup> and the optimal timeframe and metrics for assessing drinking intensity likely varies with the question of interest; potentially serving as either a state or trait risk factor. In the laboratory sample, however, the groups each consumed alcohol over a similar timescale—approximately 3 days per week, and across the entire sample, this was typically the weekend (Figure S2). Thus, the primary difference was the intensity of each event. In that context, our survival analysis results appear to be reflective of recent drinking intensity. Consequently, further study will be required to assess the potential impact of acute and/or chronic tolerance on our alcohol self-administration and subjective response measures, since each

theoretically contributes to ongoing rapid alcohol self-administration in the laboratory and the community. Alcohol is not administered intravenously in the community, and our protocol did not include the sensory and environmental cues participants routinely experience when ingesting alcohol. The absence of such cues may have contributed to lack of association between drinking intensity and the subjective responses. The difference in route of administration and environment may limit generalizability, but we chose a controlled lab environment to assess alcohol's pharmacological effect and to allow exquisite control of exposure rates (in contrast to consumption rates) which is not possible with ingestion. Our sessions also began in the morning to allow for monitoring after alcohol-self-administration, and while not a common time-of-day for alcohol consumption for many, the time course of exposures suggests this was not a significant impediment (Figure 2). Finally, we asked subjects how much they enjoyed controlling their rates of exposure. While this positive valence focus is appropriate for those in an early stage of their drinking career (or within the binge-intoxication stage of AUD development, summarized in Koob and Volkow<sup>78</sup>), the instructions may need to be tailored to future populations under study. Despite these limitations, the strengths of this study include obtaining multiple assessments per subject to estimate the pharmacokinetic-pharmacodynamic relationship, constraining the age ranges in the COGA sample to reduce differences between the samples, and replicating Laboratory interview-based results in the much larger COGA sample.

There are several potential uses of the rate control paradigm. Most importantly, these results support the need for studies aiming to change how quickly people drink, the desire for rapidly increasing alcohol exposures, and their underlying neurobiology. Rate control could serve as an endpoint in studies aimed to screen interventions for efficacy prior to larger clinical trials. For example, a reduction (if not elimination) in the time to achieve 80 mg/dl could be considered a successful outcome of intervention, whether it is counselling about the dangers of binge drinking, a repurposed compound, or neuromodulation of reward circuitry. Further, pairing targeted analyses with objectively determined degrees of intense drinking may be a way to identify specific genes (or combinations) underlying subjective response, although obtaining a sufficient sample size may be challenging. Exploration of other contributors to drinking intensity, such as impulsivity<sup>79</sup> and sex as well as sexual identity differences,<sup>80</sup> are also warranted. Further, we envision rate control as an objective tool to examine the role of acute and chronic tolerance on the Binge and High-Intensity Drinking phenotype.

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#### CONFLICT OF INTEREST

None of the authors has any financial or intellectual conflict of interest in this research.

#### AUTHOR CONTRIBUTIONS

MHP and SOC were responsible for study concept, design, and execution. MHP, JB, and LW performed statistical analyses. MHP, LW, JB, and SOC drafted the manuscript. AK oversaw day-to-day lab operations and provided review of the manuscript for important intellectual content. BS and VR provided insight into analytical strategy. UZ contributed to theoretical design and reviewed the manuscript. MS contributed to the subjective response interpretation. HJE, TF, and JN contributed to the genetic analysis and reviewed the manuscript for important intellectual content. GP, CK, and BP determined FHD in the COGA dataset. All authors critically reviewed content and approved the final version for publication.

#### INVITATIONS

Investigator interest in adapting the capabilities of the Computer-assisted Alcohol Infusion System to their own research is welcome and those interested should send an email to [mplaweck@iupui.edu](mailto:mplaweck@iupui.edu).

#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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