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A Prospective Comparison of How the Level of Response to Alcohol and Impulsivity Relate to Future DSM-IV Alcohol Problems in the COGA Youth Panel


Background: Alcohol problems reflect both environmental and genetic characteristics that often operate through endophenotypes like low levels of response (low LRs) to alcohol and higher impulsivity. Relationships of these preexisting characteristics to alcohol problems have been studied, but few analyses have included both low LR and impulsivity in the same model.

Methods: We extracted prospective data from 1,028 participants in the Prospective Youth Sample of the Collaborative Study on the Genetics of Alcoholism (COGA). At Time 1 (age 18), these drinking but non-alcohol-dependent males and females completed the Barratt Impulsivity Scale and the Self-Report of the Effects of Alcohol questionnaire regarding drinks required for effects the first 5 times of drinking (SRE5-LR). Two years later, they reported perceived drinking patterns of peers (PEER), their own alcohol expectancies (EXPECT), and their drinking to cope with stress (COPE). Subsequently, at Time 3, participants reported numbers of up to 11 DSM-IV alcohol criterion items experienced in the 2 years since Time 2 (ALC PROBS). Data were analyzed using structural equation modeling (SEM).

Results: In the SEM, Baseline SRE5-LR and impulsivity were weakly related and did not interact in predicting later ALC PROBS. LR was directly linked to Time 3 ALC PROBS and to PEER, but had no direct path to EXPECT, with partial mediation to ALC PROBS through PEER to EXPECT and via COPE. Impulsivity did not relate directly to ALC PROBS or PEER, but was directly related to EXPECT and COPE, with effects on ALC PROBS also operating through EXPECT and COPE.

Conclusions: Low LRs and impulsivity related to Time 3 ALC PROBS through somewhat different paths. Education- and counseling-based approaches to mitigate future alcohol problems may benefit from emphasizing different potential mediators of adverse alcohol outcomes for youth with low LRs versus those with high impulsivity or both characteristics.

Key Words: Levels of Response to Alcohol, Impulsivity, Alcohol Problems, Structural Equation Models.
a reflection of the long-standing interest by some COGA investigators in AUD risks related to how a person responds to alcohol (Dick et al., 2013; Schuckit et al., 2001; Sher et al., 2005; Wardell et al., 2015).

The low LR to alcohol indicates that higher doses of alcohol are needed to produce effects; that is, that drinkers have lower sensitivities to alcohol per drink. One of the several measures of a person’s reaction to alcohol (e.g., King et al., 2016; Newlin and Renton, 2010), LR, has been extensively evaluated as a predictor of future heavy drinking and alcohol-related problems (e.g., Quinn and Fromme, 2011; Ray et al., 2010; Wardell et al., 2015). While women have higher LRs (i.e., are more sensitive per drink) (Eng et al., 2005), within groups of women a lower LR relates to a higher risk of alcohol problems (Eng et al., 2005). A person’s LR tends to increase with age, but within older individuals, lower LRs still relate to higher AUD risks (Schuckit and Smith, 2004). Also, despite LR differences across some ethnic groups, within ethnicities a lower LR relates to higher alcohol problem risks (Ehlers et al., 1999; Wall et al., 1999).

LR was originally measured through alcohol challenges (e.g., Heath et al., 1999; King et al., 2016; Schuckit and Gold, 1988; Volavka et al., 1996), but these cannot be performed in individuals below the age of consent and are expensive and time-consuming. Thus, our group developed the Self-Report of the Effects of Alcohol (SRE) questionnaire, a retrospective measure of the number of standard drinks required across 4 potential effects in 3 time frames, including the approximate first 5 times of consuming alcohol (SRE5-LR), a period when acquired tolerance is unlikely to have developed (Ray et al., 2010; Schuckit, 2009b). SRE-based LRs are genetically influenced (Schuckit et al., 2001) and predict later heavy drinking and alcohol-related problems in drinking individuals as young as age 13, even after controlling for baseline alcohol intake and other characteristics (e.g., Chung and Martin, 2009; Schuckit et al., 2007, 2008). Alcohol challenge-based LR values and SRE results overlap approximately 0.60 in predicting future adverse alcohol-related outcomes (Schuckit et al., 2009b).

The second endophenotype of interest, decreased inhibitory control, includes impulsivity and other externalizing characteristics that contribute to acting without appropriate forethought (Depue and Collins, 1999; Dick et al., 2013; Kaiser et al., 2016; Wardell et al., 2015). Like low LR, aspects of diminished inhibitory control relate to both genes and environment, can differ across sexes, and are likely to change with age and stage of development (Dick et al., 2013; Meyers et al., 2014; Ohannessian and Hesselbrock, 2008).

Impulsivity is one of the most intensely studied components of diminished inhibitory control where high impulsivity can be observed early in life and relates to multiple adverse outcomes, including AUDs and other substance use disorders (SUDs) (Kendler et al., 2003; Meyers et al., 2014; Salvatore et al., 2015; Sher et al., 2005; Wardell et al., 2015). Gene-by-environment interactions have been identified for this concept, including how peer substance use patterns moderate the impact on heavy drinking of genes contributing to impulsivity (e.g., Salvatore et al., 2015).

Because endophenotypes like the low LR and impulsivity explain only part of the risk of alcohol problems, our group has used structural equation models (SEMs) to evaluate environmental and attitudinal characteristics that might partially mediate how low LR and impulsivity relate to later alcohol problems. SEM-based studies indicated that low LR related to adverse alcohol outcomes both directly and through partial mediation by associating with heavy-drinking peers, developing exaggerated expectancies of the positive effects of alcohol, and using alcohol to cope with stress (e.g., Schuckit et al., 2009a, 2010, 2011). Similar models have been evaluated regarding how aspects of impaired impulse control relate to heavy drinking and alcohol problems might be partially mediated by substance using peers, poor coping skills, positive alcohol expectancies, and drinking to cope (e.g., Jacob et al., 2009; Jessor and Jessor, 1977; Sher, 1991; Tarter et al., 1999; Zucker et al., 1995). Our group has reported that the impact of impulse control-related characteristics on excessive drinking and related problems was partially mediated by positive alcohol expectancies and drinking to cope, but found less consistent evidence of partial mediation by peer heavy drinking (Schuckit and Smith, 2006).

To date, few studies have included both LR and impulsivity in the same prospective model to evaluate how these endophenotypes operate when considered together. We published one such evaluation of men, most of whom were college graduates, but the sample was modest in size (N = 393) and the model was structured such that some potential mediators were measured at the same time as the outcome (Schuckit and Smith, 2006). However, in that model, the family history of AUDs related to both a low LR and an externalizing construct that reflected higher levels of impulsivity and sensation seeking, and there was only a weak relationship between that externalizing variable and LR. That SEM demonstrated potential mediation of the relationship of both LR and the externalizing variable to adverse alcohol outcomes through positive alcohol expectancies and drinking to cote.

The current analyses extended our work to a more socioeconomically heterogeneous and larger sample of adolescents and young adults, individuals who by virtue of their age are at risk of heavy drinking and alcohol problems. We used 3 stages of data gathering, each of which was separated from the next by approximately 2 years. Based on the existing literature, the analyses tested 4 hypotheses: (i) both a baseline lower LR and higher Barratt Impulsivity scores will predict a greater number of later alcohol problems, even after considering family history of AUDs and age at baseline, sex, and ethnicity; (ii) LR and impulsivity will be only weakly related to each other and will not interact in predicting later alcohol problems; (iii) LR and impulsivity will each demonstrate both direct and partially mediated relationships to later alcohol problems; and (iv) both SRE5-LR and impulsivity will
increment over the other in hierarchical regression analyses such that consideration of the 2 Baseline endophenotypes better predicts future alcohol problems than either predictor alone.

**MATERIALS AND METHODS**

**Subjects**

The original COGA subjects were recruited beginning in 1990 at 6 data gathering centers following approval by each site’s Human Subjects’ Protections Committee. These subjects (i) had been patients with alcohol dependence in alcohol and drug treatment programs who had multiple first-degree relatives who met criteria for the same disorder or (ii) were comparison subjects from various community samples (Bucholz et al., 1994; Hesselbrock et al., 1999). In 2009, the protocol shifted to 12- to 21-year-old relatives of the original subjects for whom at least 1 parent had been interviewed in the original study. The resulting members of the COGA Prospective Youth Sample have been followed every 2 years. As of December 2016, the youth sample included 3,791 individuals, 1,355 of whom were age 12 to 26 and had completed the SRE, and the Barratt Impulsivity questionnaire. Of these, 117 were excluded because they had already developed alcohol dependence as defined in the DSM-IV criteria (American Psychiatric Association, 1994). Of the remainder, 1,028 had Baseline evaluations (the time the SRE was completed) and 1 (n = 174) or 2 (n = 854) of the subsequent follow-ups. Almost half (49.4%) were nieces or nephews of original COGA probands, 20.9% were offspring, 14.1% were grandchildren, 2.5% were siblings, 0.6% were cousins, and for the remaining 12.5%, the relationship to original subjects had not been recorded.

**Baseline Assessments**

Baseline and follow-up data were gathered using the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA) standardized interview. This instrument has sensitivities and specificities for most diagnoses that range from 75 to 90%, with positive and negative predictive values and retest reliabilities in a similar range (Bucholz et al., 1994; Hesselbrock et al., 1999). Histories of AUDs in a parent were based on interviews with mothers and fathers of these subjects, using imputation for parents who had not been interviewed. Additional details about the prospective study can be found elsewhere (Bucholz et al., 2017).

The retrospective SRE questionnaire regarding the approximate first 5 times of consuming alcohol was used to determine Baseline SRE5-LR values. SREs record numbers of drinks required for up to 4 effects actually experienced, including feeling any effect, slurring speech, unsteady gaits, and unintended falling asleep (Schuckit et al., 1997, 2005). Time 2 retest reliabilities regarding categorizing an individual as a low responder of <0.70, and the 4.5-year test–retest reliabilities of 0.72 (Ray et al., 2010; Schuckit et al., 1997, 2005).

Baseline impulsivity used total scores from adolescent (age 18) and adult (age 18) Barratt Impulsivity Scale forms (Stanford et al., 2009). This instrument scores 30 items from 1 (rarely or never) to 4 (usually) regarding statements like “I plan carefully,” “I do things without thinking,” “I am self-controlled,” and “I act on impulse.” The Barratt was selected because the questions were relevant to COGA’s electrophysiological measures, and most other scales are more time-consuming and/or have a focus on hostility or aggression that were not central to the goals of these analyses (Hollander et al., 2000). The Barratt has Cronbach’s alpha = 0.83 and 1-month retest reliabilities of 0.83 (Stanford et al., 2009), with values for the adolescent and adult versions combined using z-scores for each of the 2 forms.

**Time 2 Assessments**

Peer drinking obtained at the 2-year follow-up used items from the Important People and Activities Scale (Longabaugh et al., 2001) regarding the participant’s perception of the drinking status of up to 4 close peers on a 5-point scale ranging from abstainer to heavy drinker along with an scale from 0 (not at all) to 7 (daily) drinking, and their maximum drinks on a 5 point scale from 0 (does not drink) to 4 (≥10 drinks per occasion).

Alcohol expectancies were generated from the adolescent (age 18) and adult (≥18) forms of the Alcohol Expectancy Questionnaire (AEQ) that records the person’s beliefs about how alcohol affects people (Goldman, 2002). The adolescent version uses true/false scoring, while the adult form rates items from 1 (disagree strongly) to 5 (agree strongly). Scores were extracted for AEQ subscales we have found to be most closely related to alcohol problems (Schuckit et al., 2009a,b, 2011), including Global expectancies (e.g., “drinking makes the future look brighter”), Social Behavioral/Assertiveness expectancies (e.g., “a few drinks make it easier to talk to people”), and expected Relaxation effects of alcohol (e.g., “alcohol decreases muscle tension”). Adolescent and adult results were combined using z-score values.

Drinking alcohol to cope used the 6 items from a modified Drinking to Cope Scale that asks whether a person actually uses alcohol for various effects (Carver et al., 1989; Cooper et al., 1995; Park and Leverson, 2002). These included drinking to forget worries, cheer up, relax, decrease feeling anxious or sad, mitigate boredom, or to feel more confident, each scored from 1 (almost never) to 4 (almost always).

**Time 3 Alcohol Problems**

The SSAGA interview was repeated at Time 3, and the number of 11 DSM-IV alcohol abuse and dependence criterion items that occurred during the 2-year interval since Time 2 was recorded. This outcome is referred to as “alcohol problems” in the Results and Discussion sections of this article.

**Statistical Analyses**

After addressing missing data using a maximum likelihood procedure, logarithmic, square root, or inverse reflected transformations were performed as needed to correct for skew. Relationships among variables gathered at Times 1, 2, and 3 were evaluated using Pearson product–moment correlations.

The hypothesized SEM model was developed and evaluated via AMOS (Arbuckle, 2014) software using maximum likelihood estimations. To optimize potential clinical implications of how LR and impulsivity operate, these 2 predictors are manifest variables rather than latent constructs. Time 2 potential mediators of the effects of LR and impulsivity and Time 3 outcomes were represented as latent variables and evaluated with confirmatory factor analyses. The resulting measurement model for latent variables was incorporated within the final full SEM after dropping components that were not significant. Two potential latent variables did not have subscales (e.g., the Drinking to Cope Scale and the number of DSM-IV AUD criteria endorsed), so 3 “parcels” were created as indicators for each variable by placing the items for that measure into 3 a priori groups (Little et al., 2002). Within the SEM, direct associations and indirect statistical mediation were evaluated using Mplus, version 7 (Muthén and Muthén, 2012) based on bootstrapping with 1,000 resamples with results presented as 95% confidence intervals (mediation was present if the intervals did not cross zero). Good fit criteria for the measurement model and the SEM included (i) comparative fit index (CFI) ≥ 0.90; (ii) nonnormal fit index (NNFI) close to 1.0; (iii) root mean square error of approximation (RMSEA) ≤ 0.05; and (iv) standardized root mean squared residual
RESULTS

Table 1 describes the characteristics of the 1,028 COGA Youth Panel participants across Time 1 (Baseline), Time 2 (2 years after baseline), and Time 3 (2 years after Time 2). At Baseline, these drinking but non-alcohol-dependent subjects were on average 18 years old, their mean SRE5-LR score was 3.5, and their mean adolescent and adult Barratt Impulsivity scores were 73 and 64, respectively. At Time 2, participants reported peers who were perceived to be between light and moderate drinkers and consumed alcohol about 1.2 days per week, with a maximum quantity of 4.1 standard drinks (10 to 12 g ethanol) per occasion.

Figure 1 presents the hypothesized model, which is based on a Social Information Processing Model (e.g., Dodge et al., 2003). As explained in more detail elsewhere (Schuckit et al., 2004), the model focuses on how alcohol-related experiences are processed by an individual regarding their vulnerability to peer pressure, especially in adolescence and young adulthood; how a low LR and heavier peer drinking are likely to create an expectancy that heavy drinking is normal and desirable; and how a low LR, observation of the acute effects of alcohol in peers, and expectancies of the benefits of heavy drinking encourage using alcohol to deal with life stresses.

The key elements of Fig. 1 focus on how Baseline SRE5-LR and impulsivity (IMPULSE) relate to each other and to Time 3 alcohol problems (ALC PROBS). In the model, manifest variables (e.g., age) are rectangles and latent variables (i.e., factors generated within the measurement model) are circles. Based on prior studies, we hypothesized that Time 1 higher SRE5-LR scores (i.e., lower LRs per drink) and higher impulsivity will each relate to higher Time 3 alcohol problems, but will only weakly relate to each other. The model further proposes that SRE5-LR will also relate directly or indirectly to all 3 Time 2 measures, which in turn will relate directly to ALC PROBS, and indirectly to ALC PROBS through drinking to cope (COPE). To evaluate whether SRE5-LR and impulsivity operate similarly within the SEM, relationships similar to those for SRE5-LR are proposed for impulsivity in Fig. 1. These key relationships among SRE5-LR, impulsivity, Time 2 variables, and ALC PROBS are indicated in bold in Fig. 1. Sex, age, ethnicity, and AUD histories in one or both parents are used as covariates to determine whether the key relationships in bold operate even after considering these additional characteristics.

Step 1 in testing the hypothesized model evaluated Pearson product–moment correlations among the manifest and latent variables, as shown in Table 2. Here, higher scores on the SRE5-LR (indicating more drinks were needed for effects, or lower LRs per drink) and impulsivity correlated significantly with ALC PROBS at 0.22 and 0.19, respectively, and to each other at a significant 0.14. Although not shown, the SRE5-LR by impulsivity interaction term predicting ALC PROBS was not significant (r = 0.004, p = 0.91).

### Table 1. Values for Variables at Time 1 (Baseline), Time 2 (Intermediate Time), and Time 3 (Outcome) for 1,028 COGA Youth Panel Participants (Mean and Standard Deviations or %)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time 1 (Baseline)</td>
<td></td>
</tr>
<tr>
<td>Sex (% female)</td>
<td>51.9</td>
</tr>
<tr>
<td>Age</td>
<td>18.7 (2.28)</td>
</tr>
<tr>
<td>Ethnicity (% EA)</td>
<td>65.1</td>
</tr>
<tr>
<td>SRE5-LR</td>
<td>3.5 (1.84)</td>
</tr>
<tr>
<td>1 or both parents' lifetime AUD (%)</td>
<td>65.3</td>
</tr>
<tr>
<td>Barratt Impulsivity Scores</td>
<td></td>
</tr>
<tr>
<td>Adolescent</td>
<td>72.8 (11.37)</td>
</tr>
<tr>
<td>Adult</td>
<td>63.7 (10.20)</td>
</tr>
<tr>
<td>Time 2 (2-year follow-up at age 21.2 [2.55])</td>
<td></td>
</tr>
<tr>
<td>Peer Drinking Scores for PEER</td>
<td></td>
</tr>
<tr>
<td>Status</td>
<td>3.3 (0.66)</td>
</tr>
<tr>
<td>Frequency d/wk</td>
<td>1.2 (1.22)</td>
</tr>
<tr>
<td>Maximum drinks/occasion</td>
<td>4.1 (2.81)</td>
</tr>
<tr>
<td>AEQ Scores for EXPECT</td>
<td></td>
</tr>
<tr>
<td>Global Adolescent</td>
<td>7.7 (3.37)</td>
</tr>
<tr>
<td>Adult</td>
<td>56.6 (18.57)</td>
</tr>
<tr>
<td>Social Behavior Adolescent</td>
<td>8.8 (3.34)</td>
</tr>
<tr>
<td>Adult</td>
<td>30.6 (10.06)</td>
</tr>
<tr>
<td>Relaxation Adolescent</td>
<td>10.4 (2.38)</td>
</tr>
<tr>
<td>Adult</td>
<td>26.5 (8.26)</td>
</tr>
<tr>
<td>DTC Scores for COPE</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1.7 (0.53)</td>
</tr>
<tr>
<td>Parcel 1</td>
<td>1.4 (0.56)</td>
</tr>
<tr>
<td>Parcel 2</td>
<td>1.8 (0.64)</td>
</tr>
<tr>
<td>Parcel 3</td>
<td>1.8 (0.67)</td>
</tr>
<tr>
<td>Time 3 (4-year follow-up at age 23.5 [2.70])</td>
<td></td>
</tr>
<tr>
<td>Number of DSM-IV Alcohol problems for ALC PROBS</td>
<td></td>
</tr>
<tr>
<td>Total of 11</td>
<td>1.9 (1.99)</td>
</tr>
<tr>
<td>Parcel 1</td>
<td>0.1 (0.18)</td>
</tr>
<tr>
<td>Parcel 2</td>
<td>0.2 (0.23)</td>
</tr>
<tr>
<td>Parcel 3</td>
<td>0.2 (0.25)</td>
</tr>
</tbody>
</table>

EA = European ethnicity; SRE5-LR = Self-Report of the Effects of Alcohol questionnaire as assessment of the Level of Response to Alcohol; AUD = alcohol use disorder; PEER drinking status based on a 5-point scale ranging from 1 (abstainer) to 5 (heavy drinker) [3.3 indicates between light and moderate drinkers], and peer frequency based on an 8-point scale ranging from 0 (not at all) to 7 (daily) [converted to d/wk], and peer quantity reflects a maximum drinks score on a 5-point scale ranging from 0 (does not drink) to 4 (≥10 per occasion) [converted to # of drinks]; AEQ = the full Alcohol Expectancy Questionnaire adolescent (True/False) and adult subscale scores (1 = disagree strongly to 5 = agree strongly) for Global, Social Behavior, and Relaxation used to generate EXPECT with adolescent and adult values z-score and combined; DTC = Drinking to Cope scores (each item scaled from 1 = almost never to 4 = almost always) used to generate COPE; Number of DSM-IV Alcohol Problems is the number of 11 diagnostic items from the DSM-IV, used to generate ALC PROBS; PEER, EXPECT, COPE, and ALC PROBS are latent variables generated in Figs 2 and 3 as presented in the Methods; 2 of the potential latent variables, Drinking to Cope and number of DSM-IV AUD criteria items endorsed, did not have reliable subscales, and SEM latent variables are optimal if there are at least 3 items, so 3 groups of items from those scales were placed a priori in “parcels” as indicators for those variables.

(RMR) ≤ 0.08 (Hu and Bentler, 1998). Cohen effect sizes were used for ALC PROBS in the SEM and for hierarchical regression analyses to address Hypothesis 4, where 0.02 indicated small effects, 0.15 indicates medium effects, and 0.35 denotes a large effect (Cohen, 1992).
SRE5-LR scores correlated positively with PEER, EXPECT, and COPE, and impulsivity related positively to EXPECT and COPE, but not to PEER ($r = 0.06$, $p = 0.08$). All Time 2 variables correlated significantly with ALC PROBS. Table 2 also demonstrates how Baseline covariates related to each other and to additional characteristics in the model.

Figure 2 demonstrates how latent variables were created and shows significant relationships in the measurement model. The indices indicated good fit: $CFI = 0.98$, $NNFI = 0.97$, $RMSEA = 0.058$ (0.050 to 0.066), and Standardized RMR = 0.033. The 3 indicators for PEER loaded on the latent variable at 0.79 to 0.91; EXPECT indicators
within the measurement model, all 4 latent variables (PEER, EXPECT, COPE, and ALC PROBS) correlated positively with each other.

Figure 3 presents the SEM (32% of the variance of ALC PROBS explained, \( f^2 = 0.47 \), reporting significant beta weights for paths, correlations, and the \( R^2 \)'s for endogenous latent components. Fit statistics for the SEM were satisfactory, including CFI = 0.94, NNFI = 0.92, RMSEA = 0.063 (0.058 to 0.068), and Standardized RMR = 0.039. Relationships within the SEM included that SRE5-LR related to ALC PROBS both directly and potentially indirectly via a path through PEER drinking. Note that mediation is formally tested below. PEER then related directly to ALC PROBS, and potentially through EXPECT and COPE. EXPECT, potentially related to ALC PROBS indirectly through COPE. As described earlier, a SRE5-LR by impulsivity interaction term did not relate to ALC PROBS.

The apparent relationships of impulsivity to ALC PROBS were a bit different from how SRE5-LR operated in the SEM (mediation is tested below). Impulsivity had no direct path to ALC PROBS and did not relate significantly to PEER drinking in this model. Rather, impulsivity linked to ALC PROBS only indirectly, operating through a direct relationship with COPE and through a potential impulsivity to EXPECT to COPE pathway. The overlaps for impulsivity and SRE5-LR in the SEM appeared in how EXPECT and COPE related to ALC PROBS and how COPE linked to ALC PROBS. Note that in distinction from impulsivity, there were no direct links from SRE5-LR to COPE.

Several additional steps were taken to further evaluate the lack of a zero-order correlation between IMPULSE and PEER in Table 2 (where \( r = 0.06, p = 0.08 \) and the absence of a direct path between these 2 variables in Fig. 3. First, analyses were run separately for adolescents and adults rather than using the combined adolescent and adult sample z-score values in Table 2. This resulted in no significant
correlations between impulsivity and PEER. Next, while no Barratt subscale differences regarding relationships with PEER had been predicted, we looked separately at scores for nonplanning, motor, and cognitive subscales in adolescent and adult Barratt measures. The results for adults indicated significant correlations with PEER for motor ($r = 0.08$, $p = 0.04$) and cognitive ($r = 0.08$, $p = 0.03$) subscales, and in adolescents for the cognitive subscale ($r = 0.13$, $p = 0.05$). However, when we substituted a latent variable for the Barratt generated from the 3 Barrett subscales into the SEM in Fig. 3, the relationship of IMPULSE and PEER remained nonsignificant within the model (beta weight = 0.03, $p = 0.50$).

Next, the analyses formally tested mediation between Baseline SRE5-LR and ALC PROBS as well as impulsivity and ALC PROBS. Significant indirect paths (95% confidence intervals) included: (i) SRE5-LR to PEER to EXPECT to COPE to ALC PROBS (0.005 to 0.018); (ii) SRE5-LR to PEER to COPE to ALC PROBS (0.004 to 0.018); (iii) SRE5-LR to PEER to ALC PROBS (0.019 to 0.058); (iv) IMPULSE to EXPECT to COPE to ALC PROBS (0.018 to 0.058); and (v) IMPULSE to COPE to ALC PROBS (0.022 to 0.068).

The direct and indirect effects were evaluated further using standardized regression coefficients, as shown in Table 3. These data demonstrate that the indirect (or mediated) relationship of LR to ALC PROBS was mostly accounted for by LR-PEER-ALC PROBS, while the indirect relationship of Impulsivity to ALC PROBS was fairly equally divided between IMPULSE-COPE and IMPULSE-EXPECT-COPE-ALC PROBS.

Finally, to evaluate Hypothesis 4 outside the context of the SEM, we determined the relative performance of using Baseline SRE-5-LR alone to predict ALC PROBS, Baseline impulsivity alone as a predictor, and using both predictors together. In step 1 of a hierarchical regression analysis SRE5-LR was entered, producing an $R^2 = 0.083$ ($p < 0.001$, $f^2 = 0.09$) in predicting ALC PROBS; and in step 2, after adding impulsivity the change in $R^2 = 0.04$ ($p < 0.001$, $f^2 = 0.04$). Subsequently, in a separate hierarchical regression analysis, in step 1, impulsivity was entered first and yielded an $R^2 = 0.056$ ($p < 0.001$, $f^2 = 0.06$) in predicting ALC PROBS; then in step 2, SRE5-LR was entered and the change in $R^2 = 0.067$ ($p < 0.001$, $f^2 = 0.07$). When both SRE5-LR and impulsivity were entered simultaneously $R^2 = 0.122$ ($p < 0.001$, $f^2 = 0.139$). The results indicate that SRE5-LR and impulsivity contributed independently to alcohol problems.
The results in Table 2 supported Hypothesis 1 in that both Baseline SRE5-LR and impulsivity predicted a higher number of alcohol problems 4 years later. This finding is consistent with prior studies by our group (e.g., Schuckit and Smith, 2006; Schuckit et al., 2010, 2011) and was an important first step for evaluating Hypotheses 2 to 4. The documentation that many key variables correlated significantly with each other supports the importance of using SEM to test how these characteristics related over time when considered in the same prospective model.

Based on prior analyses (Schuckit and Smith, 2006), Hypothesis 2 predicted that SRE5-LR and impulsivity would correlate only weakly. The current findings indicated the 2 variables correlated at 0.14 and did not interact in predicting ALC PROBS in the SEM. The absence of a close relationship between the 2 key Baseline endophenotypes foreshadowed the differences in Fig. 3 regarding how SRE5-LR and impulsivity related to ALC PROBS.

Hypothesis 3 predicted that both SRE5-LR and impulsivity would have direct as well as partially mediated relationships with later alcohol problems. To determine whether the 2 key Baseline measures operated similarly in the SEM, we evaluated each using the same intermediate (Time 2) variables and similar hypothesized pathways to ALC PROBS in the hypothesized model. In Fig. 3, this approach revealed potentially important differences in the significant paths for SRE5-LR and impulsivity where, contrary to our prediction, only SRE5-LR related directly to ALC PROBS, and only the effect of LR was partially mediated by perceived peer drinking (PEER).

Thus, efforts to decrease the risk of later alcohol problems in individuals with low LRs to alcohol (e.g., Schuckit et al., 2016) might place special emphasis on the direct risk of alcohol problems from a low LR, even if individuals educate themselves about realistic expectancies of the effects of alcohol and avoid drinking to cope with stress. Although steps to modify the impact of expectancies and drinking to cope with stress appeared to be helpful in our recent prevention protocol (Schuckit et al., 2016), the results might have been even better if more emphasis had been placed on the direct vulnerability drinkers with low LRs carry when they drink, and the special importance of guarding against being influenced by heavy-drinking peers.

The enhanced risk of developing alcohol problems associated with impulsivity in Fig. 3, however, was not direct, but was mediated by direct paths to EXPECT and COPE that were not seen for SRE5-LR. These findings suggest that programs attempting to decrease alcohol problems in more impulsive individuals might emphasize different aspects of the SEM than might be true for LR. Successful approaches to preventing heavy drinking and associated problems in these individuals (see Conrod et al., 2013) might place special emphasis on overly positive alcohol expectancies and drinking to cope with stress, but less intense emphasis on the roles of peer drinking or direct pathways from impulsivity to alcohol problems.

Using alcohol to cope with stress (COPE) related closely to ALC PROBS in both Table 2 and Fig. 3, indicating this characteristic should be included in most efforts to prevent alcohol-related problems. This is especially important for impulsivity, because without a direct path to ALC PROBS and no direct path from EXPECT to ALC PROBS, much of the relationship between impulsivity and ALC PROBS operated either directly through COPE or through a possible EXPECT to COPE pathway.

The 0.62 beta weight between EXPECT and COPE is worth noting. EXPECT and COPE are not the same domains, with the former asking questions like “alcohol
makes people more relaxed and less tense” but COPE uses questions like “I use alcohol to relax.” Thus, EXPECT relates to beliefs about alcohol effects, while COPE relates to whether the participant actually uses alcohol for specific effects.

The results in Fig. 3 regarding LR are similar to those reported in earlier iterations of the COGA Youth Panel and in other populations (e.g., Schuckit and Smith, 2006; Schuckit et al., 2004, 2011). One exception is that while studies of adults generally show a direct path from LR to COPE, SEMs using younger subjects rarely show that direct link (e.g., Schuckit et al., 2009a, 2010, 2012). Perhaps the relationship of LR to COPE becomes stronger as drinkers get older and have had more experience with alcohol, or the differences might reflect age-related increases in social desirability biases where older heavy drinkers see drinking to cope as a more acceptable explanation for their drinking behaviors. Another result worthy of comment in Fig. 3 is the absence of a consistently significant relationship of IMPULSE to PEER, even when adolescent and adult Barratt scales were evaluated separately or when Fig. 3 was re-evaluated using a latent construct for IMPULSE generated from the 3 subscales of that measure.

Hypothesis 4 predicted that both SRE5-LR and impulsivity would each contribute to the prediction of later ALC PROBS. Consistent with our prior report (Schuckit and Smith, 2006), the current series of hierarchical regression analyses indicated that both the low LR to alcohol and impulsivity contributed to the prediction of alcohol problems in subjects in the COGA Youth Panel.

As with all studies, it is important to recognize the limitations of the current work. First, most participants in the Youth Panel came from families recruited because of multiple family members with AUDs, and the generalizability to other samples needs to be determined. However, at least regarding the LR measure, the current SEM results are generally similar to analyses reported from the San Diego Prospective Study as well as the Avon Longitudinal Study of Parents and Children (Schuckit and Smith, 2006; Schuckit et al., 2011). Second, SEM analyses evaluate the potential validity of a specific hypothesized model, but do not demonstrate whether that model is superior to other models. Third, the analyses were based on evaluating mediation by 3 Time 2 characteristics often used in our work (i.e., PEER, EXPECT, and COPE), and further study is required to evaluate additional possible mediators as well as moderators. Fourth, for reasons described in the Methods, only 1 externalizing measure, the Barratt, was available for use in these analyses, and it is important to evaluate additional impulsivity measures and other externalizing characteristics in future work. Similarly, DSM-IV was used for alcohol problems, and the fact that 10 of the 11 criterion items are the same in DSM-IV and DSM-5 makes it likely similar results would be seen for DSM-5, but this needs to be directly tested (Hasin et al., 2013). Next, all Baseline and follow-up information involved self-reports without corroboration. Finally, the PEER latent variable was based on the participants’ perception of drinking in close friends, and different results might be observed if those peers had been directly interviewed. Similarly, while our group considered other approaches (e.g., a longitudinal change model), we felt that the potential clinical implications of our work were best served by the SEM in Fig. 3, and to optimize clarity of the results in Fig. 3, the analyses presented here did not test for reciprocal influences.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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