Insular Risk Processing Predicts Alcohol Use Via Externalizing Pathway in Male Adolescents

JACOB ELDER, B.A.,[a,b,*] ALEXIS BRIEANT, M.S.,[a] NINA LAUHARATANAHIRUN, PH.D.,[a,c,d] BROOKS KING-CASAS, PH.D.,[a,e] & JUNGMEEN KIM-SPOON, PH.D.[a]

[a]*Department of Psychology, Virginia Tech, Blacksburg, Virginia*
[b]*Department of Psychology, University of California, Riverside, Riverside, California*
[c]*United States Army Research Laboratory, Human Resources and Engineering Directorate, Aberdeen Proving Ground, Maryland*
[d]*Annenberg School for Communication, University of Pennsylvania, Philadelphia, Pennsylvania*
[e]*Fralin Biomedical Research Institute, Roanoke, Virginia*

ABSTRACT. Objective: Male adolescents exhibit greater impulsivity and externalizing symptomatology relative to female adolescents. Furthermore, externalizing symptomatology has been associated with greater alcohol use and differential anterior insula functioning. The current longitudinal study on adolescents examined whether activity in the anterior insula, when processing uncertain outcomes and representing risk, is directly associated with gender differences in later adolescent alcohol use frequency, as well as indirectly through externalizing symptomatology. **Method:** Using functional magnetic resonance imaging, we examined whether gender moderated these associations in a sample of 161 adolescents (53% male) with repeated annual measurements over 3 years. We monitored responding of a region implicated in risk processing during an economic lottery choice task involving uncertain outcomes. Self-reported externalizing symptomatology and alcohol use frequency were collected at all time points. **Results:** Results indicated that there was a significant indirect effect of anterior insula processing during the task at Time 1 on alcohol use at Time 3 through externalizing symptomatology at Time 2 for male, but not female, adolescents. Externalizing symptomatology predicted alcohol use for both male and female adolescents. **Conclusions:** The findings suggest gender differences in vulnerability to later alcohol use, specifically in terms of how a neurobiological susceptibility to risk insensitivity may disproportionately influence male adolescents' externalizing symptomatology. Male adolescents who do not effectively integrate risk-related signals are likely to engage in externalizing behaviors, which in turn are related to later alcohol use. Findings also suggest differential roles of risk-related brain function that contribute to gendered pathways to adolescent health-risk behaviors. (*J. Stud. Alcohol Drugs, 80,* 602–613, 2019)

ADOLESCENCE IS often associated with the emergence of various psychological disorders and risk factors for maladjustment (Avenevoli et al., 2015; Paus et al., 2008). Adolescence is also known as an important developmental period during which brain development and problem behaviors contribute to the development of substance use behaviors (Kim-Spoon et al., 2017b). Despite clear gender differences in the development of certain psychopathology outcomes, such as higher prevalence of externalizing symptomatology and substance use among adult males (Kramer et al., 2008), developmental pathways that explain why males exhibit greater vulnerability are not fully understood. We examined gender differences[1] in the developmental pathways through which neural recruitment of a region implicated in risk processing may contribute to the development of externalizing symptomatology and alcohol use.

Male and female adolescents exhibit relatively equivalent rates of alcohol abuse and dependence (Center for Behavioral Health Statistics and Quality, 2017; Cotto et al., 2010), although some research has suggested that male adolescents engage in higher rates of alcohol use than female adolescents (Flory et al., 2004). However, male adolescents experiment more frequently with alcohol (Kuntsche & Müller, 2012) and binge drink more often (Chartier et al., 2010). Meanwhile, the best predictor of substance use among adult populations is being male (Mahalik et al., 2015). Adult males, compared with females, drink alcohol more often, drink greater amounts, and have a higher likelihood of engaging in binge drinking (Becker et al., 2012; Courtenay, 2000;

[1]It has been suggested that gender enculturation and environmental (e.g. sociocultural) variables can alter brain function (Eliot, 2011). We draw on previous research findings investigating both gender and sex differences, as the terms are sometimes used interchangeably and there is limited neuroimaging research on strictly psychological gender roles. However, we note that gender rather than biological sex may better reflect the differences we examine here, as both biological and sociocultural factors contribute to differences in variables such as brain development and substance use (Becker et al., 2016). Furthermore, gender rather than sex is associated with differences in the functional lateralization of emotion processing (Bourne & Maxwell, 2010) and brain volume (Belfi et al., 2014).

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*Jacob Elder was at the Department of Psychology at Virginia Tech at the time the research was conducted. He is now at the Department of Psychology, University of California, Riverside, 900 University Ave., Riverside, CA 92521. Correspondence may be sent to him at that address or via email at: jacob.elder@email.ucr.edu.

Pinkhasov et al., 2010). Furthermore, longitudinal research from early adolescence to late adolescence has found that males exhibit patterns of greater and increasing substance use behaviors relative to females (Johnston et al., 2014; Mahalik et al., 2013). Adult men exhibit higher rates of alcohol dependence at a 2.3:1 ratio relative to women (Grant et al., 2004). Altogether, the research suggests that there are not consistently gender disparate rates of alcohol consumption in adolescence. However, given males' greater likelihood of transitioning from casual use to dependence (Lopez-Quintero et al., 2011) and their higher rates of dependence in adulthood (Grant et al., 2004), it is important to understand what features of male adolescence lead to an acceleration of alcohol use in adulthood. Research has demonstrated gender differences in adolescent vulnerability to alcohol use such that internalizing symptomatology predicts alcohol use among females and externalizing symptomatology predicts alcohol use among males (Jun et al., 2015).

Gender differences have also been demonstrated in the prevalence of externalizing disorders and symptomatology. Males show a greater incidence of externalizing disorders such as conduct disorder and attention-deficit/hyperactivity disorder (Barkley, 2006; Compton et al., 2000, 2007; Moffitt et al., 2001) as well as greater externalizing symptomatology (Kramer et al., 2008; Stinson et al., 2005). Research has also demonstrated that males' externalizing symptoms increase from a modest gender gap in adolescence to a large gap by age 24 (Hicks, 2007). This may further contribute to the widening observed gender differences in adult alcohol use.

The Triadic Model (Ernst et al., 2006) may partially explain gender differences in adolescent vulnerability to alcohol use. It describes vulnerability to risk taking in adolescence as a consequence of developmental imbalances between approach systems (underlying goal seeking in response to reward) and avoidance systems (underlying withdrawal from aversive cues). Specifically, the model proposes that adolescence is a heightened period for risk taking because avoidance systems are not capable of properly inhibiting approach systems (Ernst, 2014; Somerville & Casey, 2010). Hammerslag and Gulley (2016) proposed that sensation seeking and impulsivity predict substance use to a greater extent among male adolescents than female adolescents via neurodevelopmental imbalances in the maturation and remodeling of approach and avoidance systems. This is supported by literature suggesting that approach- (i.e., striatum), regulatory- (i.e., dorsolateral prefrontal cortex), and avoidance-related structures (i.e., insula) develop at different rates and exhibit heterogeneous and sexually dimorphic patterns of growth and maturation across time (Hammerslag & Gulley, 2016; see also Raznahan et al., 2014; Zuo et al., 2010).

Consistent with evidence of sexually dimorphic patterns of brain development and vulnerability, female adolescents display less impulsivity relative to males (Cross et al., 2011; Kuhn, 2015; Shulman et al., 2015), and these variables have been associated with alcohol consumption and alcohol-related problems (Ayer et al., 2011; Hittner & Swickert, 2006; Zuckerman & Kuhlman, 2000). Relatedly, impulsivity is considered a core subcomponent of externalizing symptomatology (Martel et al., 2017), and research has established that externalizing symptomatology also has a substantial impact on the early initiation of drinking, heavy drinking, and alcohol problems (Englund et al., 2008; King & Chassin, 2007; Maggs et al., 2008; Merline et al., 2008; Sartor et al., 2007), and predicts later alcohol use (Steele et al., 1995). Related literature describes gender differences in neurodevelopmental vulnerability to substance use disorders, highlighting an externalizing pathway for male adolescents and an internalizing pathway for female adolescents, via dissociable neural mechanisms (Dir & Hulvershorn, 2019; Heitzeg et al., 2018).

The Triadic Model (Ernst, 2014) theorizes that the anterior insula (aINS) may be involved in avoidance-motivated behaviors and influences decisions by amplifying the perceived cost of delay. The aINS signals to individuals the significance of a stimulus or decision (Lamm & Singer, 2010; Singer et al., 2009) and is heavily involved in the anticipation of uncertain outcomes (Critchley et al., 2001), as well as the representation and processing of risk in adults (Huettel et al., 2006; Mohr et al., 2010; Preuschoff et al., 2008) and adolescents (van Duijvenvoorde et al., 2015). Research has established that altered functional interactions of the aINS with prefrontal networks can result in elevated substance use (Cisler et al., 2013). Adolescent health-risk behaviors may emerge when avoidance-related regions that are involved in risk processing are poorly regulated (Kim-Spoon et al., 2017a; Maciejewski et al., 2018). Relatedly, evidence of a relationship between externalizing symptomatology and the aINS has been demonstrated. aINS network coherence was negatively associated with externalizing symptomatology domains, such as general disinhibition, in a community sample of adults (Abram et al., 2015). Research has also found that adult participants with borderline personality disorder—which is conceptualized as a distress and externalizing disorder (Eaton et al., 2011)—displayed reduced aINS activity in an economic exchange task, potentially exhibiting an insensitivity to social information for decision-making (King-Casas et al., 2008). In addition, externalizing adolescent males' aINS responses did not distinguish between reputation types, suggesting an insensitivity to integrating social information that can inform approach or avoidance decisions (Sharp et al., 2011).

In the current longitudinal study, we sought to examine the role of the aINS in adolescent vulnerability to alcohol use, with an emphasis on gender differences. We tested a developmental cascade model (Masten & Cicchetti, 2010), hypothesizing that the longitudinal association between aINS responding during decision-making for uncertain outcomes and adolescent alcohol use would be mediated via external-

izing symptomatology. We further tested whether the associations among aINS activity, externalizing symptomatology, and alcohol use differ between male and female adolescents.

Method

Participants

The current sample included 167 adolescents (52% males) who were 13 or 14 years old at Time 1 (M = 14.13, SD = 0.54), 14 or 15 years old at Time 2 (M = 15.05, SD = 0.55), and 15 or 16 years old at Time 3 (M = 16.08, SD = .55), with approximately 1 year in between each time point. Adolescents were primarily from the Appalachian and rural regions of the southeastern United States and identified predominantly as White (79%), 11% African American, and 10% other. Median household income was between $35,000 and $49,000. The protocol was in accordance with the university's institutional review board standards.

At Time 1, 157 families participated. At Time 2, 10 families were added for a final sample of 167. However, 24 families did not participate at all possible time points for reasons including ineligibility for tasks (n = 2), declined participation (n = 17), and lost contact (n = 5) during the follow-up assessments. We performed attrition analyses using a general linear model (GLM) univariate procedure to determine whether there were systematic predictors of missing data. Results indicated that the rate of participation (indexed by the proportion of years participated to years invited to participate) was not significantly predicted by demographic variables (p = .86 for age, p = .49 for income, p = .05 for sex, p = .20 for race, contrasted as White vs. non-White). Four participants were excluded from analyses because they identified as transgender or gender nonbinary and two additional participants were missing data on all study variables, yielding a final sample of 161 adolescents.

Procedures

Participants were recruited from the community via flyers, recruitment letters, and e-mail. Individuals were ineligible for the study if they had a history of head injury resulting in loss of consciousness for more than 10 minutes, claustrophobia, orthodontia impairing image acquisition, or contraindications to functional magnetic resonance imaging. Data collection occurred at university offices in which adolescents first agreed to participation via written assent, while parents provided written consent. The adolescents were then administered the protocol by trained research assistants.

Measures

Substance use. Adolescents reported the typical frequency of alcohol use (Wills et al., 2008) by indicating what was most true of their alcohol use (i.e., beer, wine, hard liquor, or mixed drinks) at Times 1, 2, and 3 using a 6-point scale (1 = *never used,* 2 = *tried once or twice,* 3 = *used three to five times,* 4 = *usually use a few times a month,* 5 = *usually use a few times a week,* 6 = *usually use every day*).

Externalizing symptomatology. At Times 1 and 2, adolescents' levels of externalizing symptomatology were assessed with the Youth Self-Report (YSR; Achenbach & Rescorla, 2001), a 112-item questionnaire that assesses behavior problems in youth ages 11 to 17. Behaviors were rated on a 3-point scale ranging from 0 = *not true* to 2 = *very true. T* scores from the externalizing symptomatology scale were used. The YSR has shown strong psychometric properties for externalizing symptomatology (α = .90; Achenbach & Rescorla, 2001) and demonstrates reliability in the current sample (α = .84).

Insular risk processing. At Time 1, adolescents chose between pairs of uncertain gambles in an economic lottery choice task containing high or low monetary outcomes with specific probabilities (Holt & Laury, 2002) while their blood-oxygen-level–dependent (BOLD) response was monitored using functional magnetic resonance imaging (Figures 1A & 1B). Probabilities associated with potential monetary outcomes were represented with 10-slice pie charts to maximize comprehension of numerical information for participants. Monetary outcomes and probabilities varied across trials. The associated risk for each gamble was measured using a coefficient of variation (CV),[2] a scale-free metric calculated by dividing the standard deviation by expected value (Lauharatanahirun et al., 2018).

[2]Coefficient of variation (CV) was used to calculate the level of risk associated with each option, with higher values of CV corresponding to increased levels of risk. CV for each option represents the ratio of the standard deviation of potential outcomes associated with an option to the expected value (EV) of that option:

$$EV = P_{high} \times V_{high} + P_{low} \times V_{low} \quad (1)$$

$$CV = \frac{\sqrt{P_{high}(V_{high} - EV)^2 + P_{low}(V_{low} - EV)^2}}{EV} \quad (2)$$

P_{high} and P_{low} is the probability of the high and low outcome, respectively, V_{high} and V_{low} is the high and low monetary outcome. Using a behavioral economics approach to study risk and risk-related processes during decision-making, standard deviation is a measure of risk for a specific gamble option and is represented by the numerator of the CV equation. The denominator is the expected value or the average expected payout of the gamble. Given that individuals often examine outcome variability (i.e., risk) relative to the average outcome, previous research has shown that CV (compared to standard deviation or variance alone) is a better metric for explaining risky decisions (Bach et al., 2017; Weber et al., 2004). Because probabilities were the same for both gambles in a given trial, the difference between low and high monetary amounts differentiated the level of risk between options. That is, the option with the smaller difference in values (e.g., $1.88−$1.50 = $0.38; Figure 1) indicated relatively low risk compared with the option with the larger difference in values (e.g., $3.61−$0.09 = $3.52; Figure 1).

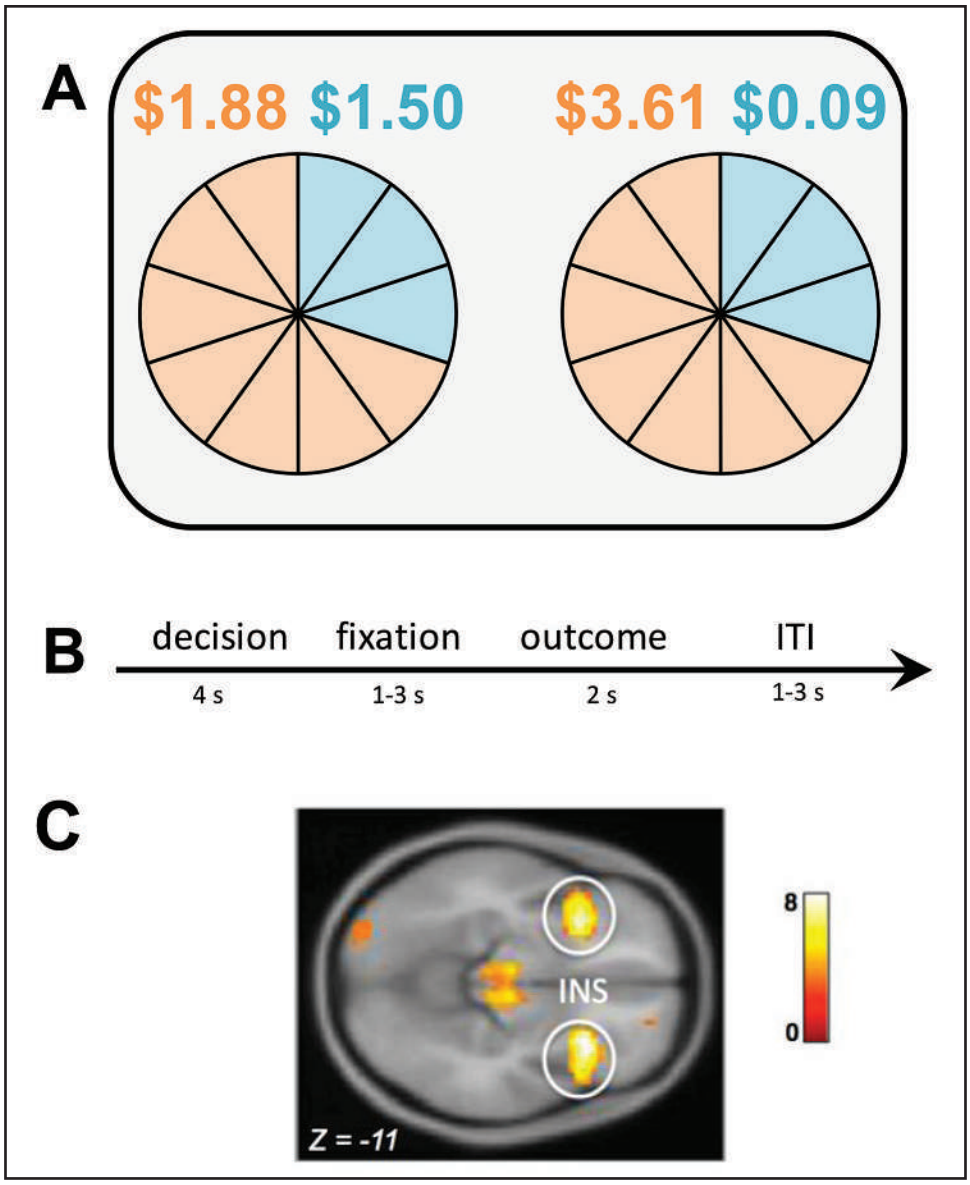

FIGURE 1. (A) In the lottery choice task, adolescents were asked to choose between pairs of uncertain gambles. For each gamble, there was a high and low monetary outcome, each associated with a specific probability. The associations between outcomes and probabilities were represented with corresponding colors (orange or blue). (B) Each trial consisted of a decision phase, a fixation phase, an outcome phase, and an inter-trial-interval (ITI). (C) During the decision phase of the economic lottery choice task, adolescents exhibited increased BOLD responses in the bilateral anterior insular cortex to chosen gambles that were of higher relative to lower levels of risk (i.e., coefficient of variation; CV) at Time 1, $t(145) = 7.22$, p(FWE correction) < .05). Figure adapted from Maciejewski et al. (2018). Used with permission.

Within each pair of gambles, one option was always riskier (higher variance) than the other (lower variance). Adolescents were compensated based on the actual results from four randomly selected trials in order to incentivize performance in the task (Smith, 1976). Participants were instructed that each trial was independent from all other trials and was equally likely to be selected for compensation. The task consisted of 72 trials and it took participants approximately 30 minutes to complete.

Imaging acquisition and analysis. Functional images were acquired using a 3.0T Tim Trio (Siemens, Erlangen, Germany) with the following parameters: echo-planar imaging, gradient recalled echo; repetition time (TR) = 2 seconds; echo time (TE) = 30 ms; flip angle = 90°; 34 axial slices, 4.0 mm slice thickness, 220 × 220 mm field of view (FOV), 64 × 64 grid, and hyperangulated slices acquired at 30 degrees from the anterior commissure posterior commissure line. The structural scan was acquired using a high-resolution magne-

tization prepared rapid acquisition gradient echo sequence (TR = 1,200 ms, TE = 2.66 ms, FoV = 245 × 245 mm, 1 mm slice thickness, 192 slices with spatial resolution of 1 × 1 × 1 mm). Data were processed and analyzed using SPM8 (Statistical Parametric Mapping; Welcome Department of Imaging Neuroscience, London, UK). Functional images were corrected for head motion using a six-parameter rigid-body transformation, realigned, and normalized to template space before smoothing. Images were then realigned and normalized to the Montreal Neurological Institute template using parameters derived from a segmented anatomical image co-registered to the mean echo-planar imaging (EPI) image and were spatially smoothed using an 8-mm full width at half-maximum Gaussian kernel.

At the subject level of the general linear model (GLM), the decision and outcome events of the task were modeled with durations of 4 and 2 seconds, respectively. A parametric regressor of decision-phase activity equivalent to the CV for chosen gambles and a parametric regressor indicating whether subjects received high or low monetary outcomes during the outcome phase were included in the model. At the group level of the GLM, whole-brain analysis was conducted to determine how CV for chosen gambles modulated BOLD responses during the decision phase (see the Appendix at the end of the article). Given the consistent and robust results implicating the aINS as a key region involved in risk processing (Mohr et al., 2010), we hypothesized that BOLD responses in the bilateral aINS would be adjusted by the level of CV. To test a priori hypotheses, region-of-interest analyses were performed using SPM8. Eigenvariate values were extracted for the left and right insular cortex using a 6 mm sphere around the peak voxel coordinates for each region (left: x = -30, y = 17, z = -14; right: x = 30, y = 20, z = -11). Figure 1C illustrates activation in the bilateral aINS during the lottery choice task for Time 1. We created an average insular risk-processing score using bilateral insular eigenvariate values, with higher scores indicating higher BOLD responses in the aINS.

Plan of analysis

For all study variables, descriptive statistics were examined to determine the normality of distributions and outliers. Skewness and kurtosis were examined for all variable distributions and acceptable levels were less than 3 and 10, respectively (Kline, 2005). Outliers were identified as values ≥ 3 *SD* from the mean. In these cases (n = 3), values were Winsorized to retain statistical power and attenuate bias resulting from elimination. Multivariate GLM analyses indicated no significant effects of demographic variables at Time 1 on alcohol use outcomes at Time 3 (p = .09 for age, p = .54 for family income, p = .31 for race). The hypothesized models were tested via structural equation modeling (SEM) using Mplus (Muthén & Muthén, 1998–2017). Overall model fit indices were determined by chi-square value, degrees of freedom, corresponding p value, root mean square error of approximation (RMSEA), and confirmatory fit index (CFI). RMSEA values less than .05 were considered a close fit whereas values less than .08 were considered a reasonable fit (Browne & Cudeck, 1993), and CFI values of greater than .90 were considered an acceptable fit whereas values greater than .95 were considered an excellent fit (Bentler, 1990). Full-information maximum likelihood (FIML) estimation procedure (Arbuckle, 1996) was used for missing data because FIML estimates are superior to those obtained with listwise deletion or other ad hoc methods (Schafer & Graham, 2002). To test significance levels of mediated effects, asymptotic and resampling strategies were used with bootstrapping, with 10,000 iterations with bias-corrected bootstrap estimations of the 95% confidence interval (CI; Preacher & Hayes, 2008).

Results

Table 1 presents descriptive statistics and correlations for all model variables. Mean comparisons between males and females on study variables indicated that the two groups were not significantly different on alcohol use, $t(141)$ = -0.25, p = .80; externalizing symptomatology, $t(144)$ = 1.36, p = .18; or insula activation, $t(136)$ = 0.71, p = .48. At Time 1, 32% of adolescents reported having used alcohol at least once or twice. The prevalence of alcohol use in the current sample appeared to reflect typical rates in a community sample of adolescents, with 48% of adolescents indicating they had never used alcohol, 22% had tried once or twice, 22% had used three to five times, and 8% usually used a few times a month. Thus, we log transformed the outcome variable using log base 10 to correct for nonnormality in the distribution.

To test group differences between males and females with respect to the patterns of associations among the study variables, the sample was divided by gender. To test the statistical significance of the difference between the male and female groups, we used two-group SEM. We first fit a model testing the primary hypothesized paths (aINS activity Time 1 → externalizing symptoms Time 2 → alcohol use Time 3) while accounting for the effects of earlier externalizing symptoms at Time 1 and earlier alcohol use at Times 1 and 2 (Figure 2A). These variables demonstrated relatively strong stability (autoregressive effects) over time (b* = 0.61 for externalizing symptoms, and b* = 0.62–0.64 for alcohol use). The full model demonstrated acceptable fit, $\chi^2(10)$ = 12.38, p = .26, RMSEA = 0.05, CFI = .99. Lower aINS activity at Time 1 significantly predicted higher levels of externalizing symptomatology at Time 2 for males (b = -2.40, SE = 0.86, p = .005) but not females (b = 0.61, SE = 0.95, p = .523). In turn, externalizing symptomatology at Time 2 predicted

Table 1. Descriptive statistics and correlations for main study variables by gender

Variable	1.	2.	3.	4.	5.	*M* (*SD*)	Range
Male							
1. Insula activation Time 1						0.07 (0.88)	-1.94–2.38
2. Externalizing symptomatology Time 1	-.07					50.10 (9.31)	29.00–71.00
3. Externalizing symptomatology Time 2	-.25*	.65**				50.35 (8.72)	29.00–71.00
4. Alcohol use Time 1	-.12	.51**	.38**			1.45 (0.73)	1.00–4.00
5. Alcohol use Time 2	.01	.38**	.46**	.66**		1.61 (0.94)	1.00–4.00
6. Alcohol use Time 3	-.06	.42**	.48**	.60**	.71**	1.88 (1.01)	1.00–4.00
Female							
1. Insula activation Time 1						-0.03 (0.80)	-1.94–2.63
2. Externalizing symptomatology Time 1	.06					48.66 (9.19)	29.00–71.00
3. Externalizing symptomatology Time 2	.11	.75**				48.30 (9.39)	29.00–70.00
4. Alcohol use Time 1	-.03	.36**	.36**			1.32 (0.53)	1.00–3.00
5. Alcohol use Time 2	-.07	.34**	.48**	.55**		1.49 (0.73)	1.00–4.00
6. Alcohol use Time 3	.12	.21	.38**	.42**	.64**	1.92 (1.03)	1.00–4.00

Notes: Superscripts indicate significance of mean differences on the given variable between males and females. Raw alcohol use scores are presented for descriptive statistics rather than the log-transformed values included in the final model.
*$p < .05$; **$p < .01$.

higher alcohol use frequency at Time 3 for males ($b = 0.005$, $SE = 0.002$, $p = .040$) but not females ($b = 0.002$, $SE = 0.003$, $p = .447$). We then tested the specific indirect effect of aINS activation on alcohol use via externalizing symptoms. The results indicated a significant indirect effect for males ($b = -0.01$, $SE = 0.02$, 95% CI [-0.030, 0.00]; $\beta = -.05$) but not for females ($b = -0.004$, $SE = 0.01$, 95% CI [-0.006, 0.011]; $\beta = -.05$).

Focusing on our primary hypothesized effects, we trimmed the autoregressive effects for externalizing symptoms and alcohol use, as well as the direct path between aINS activation at Time 1 and alcohol use at Time 3, because this effect was nonsignificant across both groups. According to the chi-square difference test, trimming these paths did not significantly degrade model fit ($\Delta\chi^2 = 11.57$, $\Delta df = 8$, $p = .171$); thus, the trimmed model was chosen as the final, more parsimonious model. This final model demonstrated excellent fit, $\chi^2(2) = 0.81$, $p = .669$, RMSEA = 0.00, CFI = 1.00. In the final model, lower aINS activity at Time 1 significantly predicted higher levels of externalizing symptomatology at Time 2 for males ($b = -2.55$, $SE = 1.22$, $p = .036$) but not females ($b = 1.39$, $SE = 1.53$, $p = .365$). In turn, externalizing symptomatology at Time 2 predicted higher alcohol use frequency at Time 3 for both males ($b = 0.01$, $SE = 0.002$, $p < .001$) and females ($b = 0.01$, $SE = 0.003$, $p < .001$). Standardized estimates are presented in Figure 2B. We further tested the significance of the indirect effect of aINS activity at Time 1 on alcohol use at Time 3 via externalizing symptomatology. Results indicated a significant indirect effect for males ($b = -0.03$, $SE = 0.02$, 95% CI [-0.062, -0.001]; $\beta = -.12$) but not for females ($b = 0.01$, $SE = 0.02$, 95% CI [-0.013, 0.050]; $\beta = .05$). We then tested nested model comparisons via two-group SEM to determine whether the effect of aINS activation on externalizing symptomatology was significantly different between males and females. Results from the chi-square difference test indicated that constraining this path to be equal between males and females significantly degraded model fit ($\Delta\chi^2 = 3.85$, $\Delta df = 1$, $p = .049$), indicating that the strength of the effect of aINS activation on externalizing symptomatology was significantly stronger for males relative to females.

As supplementary analyses, we tested whether behavioral performance on the task similarly predicted later alcohol use via externalizing symptomatology. Insular activation was significantly correlated with the proportion of risky selections during the task ($r = -.40$, $p < .001$). Although the model demonstrated acceptable fit, $\chi^2(2) = 2.57$, $p = .277$, RMSEA = 0.06, CFI = 1.00, task behavior did not significantly predict externalizing symptomatology for males ($b = 0.72$, $SE = 1.63$, $p = .66$) or females ($b = 0.44$, $SE = 1.25$, $p = .73$). Thus, we were able to detect significant pathways to alcohol use on a neurobiological, but not behavioral, level.

Discussion

Existing literature suggests gender differences in externalizing symptomatology (Kramer et al., 2008) and alcohol use (Becker et al., 2012), as well as in neurobiological development throughout adolescence (Sisk & Foster, 2004). The current longitudinal study sought to investigate potential gender differences in neurobiological vulnerability to adolescent alcohol use. Specifically, we aimed to illustrate the processes through which gender differences in later alcohol use emerge via externalizing symptomatology as well as aINS processing. Our findings demonstrated that for males, decreased aINS activity was associated with higher externalizing symptomatology, which in turn was related to greater alcohol use frequency. Meanwhile, for females, aINS activity did not significantly predict externalizing symptomatology, although externalizing symptomatology was associated with later alcohol use. Furthermore, the indirect effect of aINS activity on alcohol use frequency was significant for males but not for females.

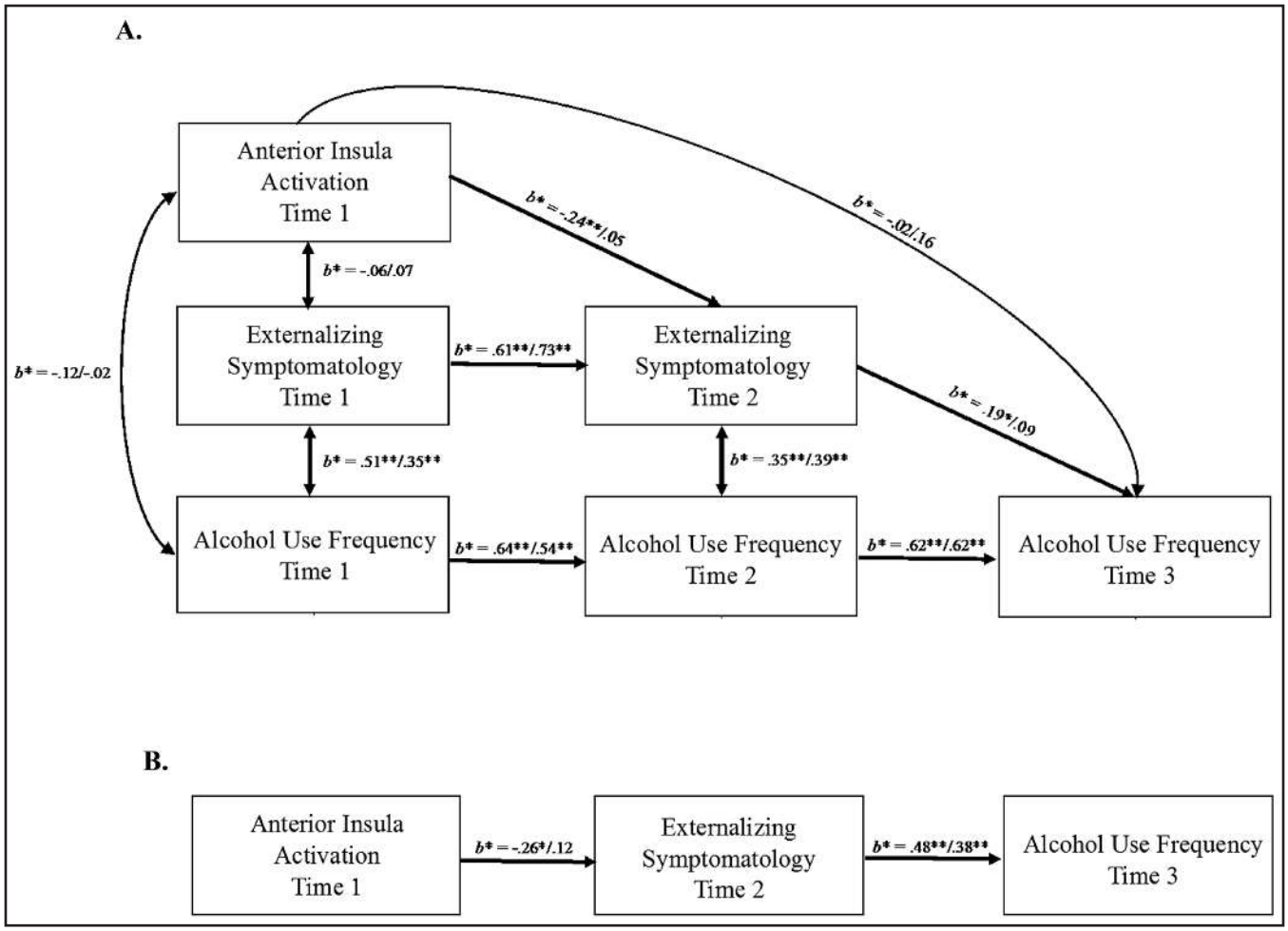

FIGURE 2. Standardized estimates for the effect of bilateral anterior insula activation on alcohol use via externalizing symptomatology in adolescents. (A) Full model including autoregressive effects of alcohol use and externalizing symptomatology. (B) Final trimmed model. *Note:* Standardized parameter estimates are listed for males/females.
*$p < .05$; **$p < .01$.

The Triadic Model (Ernst et al., 2006) posits that there are neurodevelopmental imbalances in the maturation and remodeling of different brain regions that contribute to differences in the regulation of reward- and risk-seeking behaviors, manifesting in adolescent vulnerability to risk-taking behaviors such as alcohol use. The model centers on functional relationships at the interface of avoidance and approach modules. Consistent with this model, there have been recent advances in understanding neurodevelopment in regions hypothesized to play a role in avoidance and risk processing, such as the aINS, and how it relates to adolescent health-risk behaviors (Kim-Spoon et al., 2017a; Lauharatanahirun et al., 2018; Maciejewski et al., 2018). The current findings provide preliminary evidence that aINS functioning may contribute differentially to the development of risk-taking behaviors between male and female adolescents.

There is evidence that the aINS operates as a risk-processing mechanism (Mohr et al., 2010). Risk may be represented and processed in the aINS due to the region's crucial role in mapping internal bodily states (Craig, 2002, 2009; Critchley, 2005), interpreting aversive bodily states and emotions (Quartz, 2009), anticipating and processing rewards (Beck et al., 2009), and evaluating whether to avoid a decision via the attribution of emotional significance to events (Burke & Tobler, 2011; Singer et al., 2009). Our results indicated that among male adolescents, but not female adolescents, reduced aINS response is associated with greater externalizing symptomatology. That is, a reduced sensitivity to risk is more likely to manifest in greater externalizing symptomatology among male adolescents than female adolescents. Consistent with previous work demonstrating that externalizing symptomatology predicts alcohol use regardless of gender (Englund et al., 2008), both male and female adolescents' externalizing symptomatology was associated with alcohol use. Importantly, male adolescents

were more vulnerable to alcohol use as a result of decreased risk processing than females. As such, our findings illuminate the processes through which the aINS contributes to alcohol use in males during adolescence.

A possible explanation for these findings may be gender differences in lateralization of functional connectivity between the aINS and regions underlying cognitive control and somatosensory input. Research regarding hemispheric lateralization of aINS functional connectivity describes age-related decreases in males, but not females, between the aINS and superior frontal gyrus (Kann et al., 2016), which is within the dorsolateral prefrontal cortex, a region implicated in age-related changes in cognitive control (Langner et al., 2015; Zhu et al., 2014). Meanwhile, adult females, but not adult males, showed right-lateralized connectivity to the thalamus (Kann et al., 2016), which encodes nociceptive stimulus intensity and directs sensory information to the aINS (Friedman et al., 1986). Male adolescents may be less sensitive to interoceptive and somatosensory salience signals, which aligns with other studies demonstrating gender differences in pain (Fillingim & Maixner, 1995) and emotional sensitivity (Kring & Gordon, 1998).

Gender differences in lateralization of aINS functional connectivity are also consistent with the Triadic Model's suggestion that dysregulation of approach- and avoidance-systems contribute to health-risk behaviors (Ernst, 2014). Among men, but not women, novelty seeking was positively correlated with left-lateralized connectivity in the aINS to the putamen and pallidum (Kann et al., 2016), which are within and receive input from the striatum, respectively. Given that the striatum and insula are connected anatomically (Chikama et al., 1997) and both regions have been implicated in reward predictions (Beck et al., 2009), this suggests a potential mechanism underlying gender differences in pathways of vulnerability to alcohol use. Related to the current research, these gender differences in affective processing due to gender-differentiated functional lateralization of somatosensory input detection and cognitive control may then manifest in age- and gender-related differences in insular risk processing. Indeed, other literature supports this with findings that women tend to engage more recruitment of the insula when involved in the same level of risk as men (Lee et al., 2009). Male adolescents who do not effectively integrate risk-related signals may be particularly susceptible to later externalizing symptomatology and alcohol use via comparatively less processing and regulation of salience signals in the aINS.

Last, our data suggest that behavioral performance of risky decision-making is not predictive of externalizing symptomatology. This finding appears to be consistent with the observation that neural response sensitivity can capture individual differences in neurobiological vulnerability, whereas laboratory-based behavioral performance is relatively limited in representing real-life behaviors (Richards et al., 2013). Thus, the findings highlight the advantage of studying brain–behavior associations: identifying neurobiological vulnerability may provide a powerful tool for determining adolescents susceptible to substance use, in order to enact preventative measures.

Findings should be considered in the context of study limitations. First, there were relatively low levels of alcohol use because of our use of a community sample. Second, research has been mixed on how much biological (e.g., genetic, hormonal) and environmental (e.g., sociocultural, economic) factors differentially contribute to gender differences in externalizing symptomatology, as well as to early alcohol use and problems (Hicks et al., 2007; Meyers et al., 2014; Rose et al., 2004), and to what extent environmental variables (e.g., gender enculturation) may affect gender differences in brain development and substance use (Becker et al., 2016; Eliot, 2011). The differing degree of biological compared with environmental contributions to gender differences in brain development, externalizing symptomatology, and substance use should be investigated in future research. Hormones have been demonstrated to play a significant role in gender differences in behavior (Juraska et al., 2013); thus, the contribution of sex hormones to differential pathways to alcohol use warrants further investigation. Additionally, although the scope of this study was to investigate the pathway involving externalizing symptomatology through which male adolescents are vulnerable to alcohol use, female-specific pathways of vulnerability to substance use, such as internalizing symptomatology (Dir & Hulvershorn, 2019; Hammerslag & Gulley, 2016; Heitzeg et al., 2018), should be investigated.

The current findings may inform prevention efforts to protect adolescents who are most vulnerable to initiating and progressing alcohol use and, thus, later dependence problems. By identifying how males and females are differentially vulnerable to early alcohol use via different pathways, specialized and effective prevention efforts can be developed to mitigate adverse long-term outcomes. The current findings clarify the role of the aINS in risk processing and alcohol use, highlighting the crucial role of neurobiological susceptibility in the development of alcohol use behaviors.

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Appendix overleaf

Appendix. List of regions associated with increasing coefficient of variation (CV) during the Time 1 Decision phase: Parametric regressor of CV for chosen options

Cluster no.	Region	Size	Peak MNI coordinates			*T*
			x	y	z	
1	Right insular cortex	605	30	20	-11	8.24
	Right insular cortex		45	17	-2	7.27
2	Right anterior cingulate cortex	1,798	3	35	22	8.14
	Right anterior cingulate cortex		6	41	4	6.25
	Right pallidum		12	2	-5	5.91
3	Left insular cortex	430	-30	17	-14	7.79
	Left insular cortex		-39	17	-5	7.65
4	Right middle cingulate cortex	111	3	-16	34	4.84
5	Left middle occipital lobe	93	-36	-94	1	4.14
	Left middle occipital lobe		-27	-97	-8	4.08
6	Right middle occipital lobe	45	24	-100	1	4.09
	Right inferior occipital gyrus		36	-88	-8	3.59
7	Right precentral gyrus	8	42	5	31	3.54
8	Right superior orbitofrontal cortex	5	21	56	-8	3.43

Notes: Size refers to the number of voxels in the cluster. At the subject level, decision and outcome events were included with a duration of 4 and 2 seconds, respectively. In addition, a parametric regressor of CV-modulated decision-phase activity and a parametric regressor of outcome phase activity representing whether the subject received the high or low outcome was included in the subject model. All activations reported here survive whole-brain family-wise error multiple comparisons correction at a threshold of $p < .05$. MNI = Montreal Neurological Institute; no. = number. Adapted from Maciejewski et al. (2018). Used with permission.