Sex differences in distributed error-related neural activation in binge drinking young adults

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Abstract

Detecting and responding to errors is central to goal-directed behavior and cognitive control, which are thought to be supported by a network of structures that includes the anterior cingulate cortex and anterior insula. Notable sex differences in the maturational timing of cognitive control neural systems create differential periods of vulnerability for psychiatric conditions, such as substance use disorders, between males and females. Here we examined sex differences in error-related activation across an array of distributed brain regions during a go/no-go task in a sample of binge drinking college students. Regions of interest previously linked to error-related activation, including the anterior cingulate cortex, insula, and frontoparietal structures, were selected in a term-based meta-analysis and individual differences in their activation were indexed using a multivariate summary measure. Males exhibited significantly higher levels of this multivariate summary measure than females. Males also reported significantly greater substance use; however, substance use did not significantly predict neural activation in a linear regression analysis. These findings suggest that males have more marked responses to errors across a network of regions linked to performance monitoring and cognitive control.

Keywords: sex differences, alcohol use, error, fMRI, principal component analysis

INTRODUCTION

Neural systems underlying cognitive control develop throughout adolescence and into emerging adulthood, as evidenced by electrophysiology (e.g., Tamnes et al., 2013) and functional magnetic resonance imaging (fMRI) studies (e.g., Taylor et al., 2007). There are notable sex differences in the maturational timing of these system (e.g., Giedd et al., 2012; Hammerslag & Gulley, 2016; Shulman et al., 2015), which may create divergent periods of risk for psychological disorders between males and females. For example, substance use and substance-related problems escalate at a greater rate in males than in females during emerging adulthood (Kuhn 2015; Palmer et al., 2009).

The ability to detect errors and subsequently implement corrective adjustments that prevent similar errors in the future is thought to be a key component of cognitive control that is essential for goal-directed behavior (Botvinick et al., 2004; Ridderinkhof et al., 2004; Yeung & Summerfield, 2012). As a result, there has been a wealth of research examining the neuroimaging correlates of error-related activation during tasks that are designed to demand cognitive control. Two commonly used behavioral choice tasks are the go/no-go and stop signal tasks. In both, participants respond to “go” stimuli, but must withhold their response when presented with less frequent “no-go” stimuli. Trials in which participants erroneously respond to “no-go” stimuli have been consistently linked to prominent activations in the anterior cingulate cortex (ACC) and bilateral anterior insula (Garavan et al., 2002; Menon et al., 2001; Stevens et al., 2009; Weigard et al., 2020). These results are consistent with theoretical models positing that the ACC and anterior insula are central nodes in a “salience network” that supports goal-directed behavior by monitoring task-relevant events (such as errors) and engaging cognitive control processes in response to them (Menon & Uddin, 2010; Seeley et al., 2007). Representative of

models of error monitoring's importance for goal-directed behavior, reduced salience network and prefrontal responses to errors during behavioral tasks have been linked to greater substance use and related externalizing behavior (Aharoni et al., 2013; Campanella et al., 2017) and have been found to prospectively predict substance use in longitudinal data (Heitzeg et al., 2014; Weigard et al., 2021). Taken together, this body of work suggests that neural responses to errors reflect the stability of brain systems involved in facilitating cognitive control and goal-directed behavior through the monitoring of errors and other task-relevant events. In turn, poorer integrity of these systems may be associated with greater risk of developing substance use and related externalizing psychopathology.

There are only a few fMRI studies that have investigated sex differences in error-related activation. In healthy participants, greater functional connectivity was reported in the ACC, right inferior frontal gyrus, thalamus, and amygdala in adolescent and adult females compared to males (Chung et al., 2020), with greater activation in the ACC and right thalamus in adult females compared to males (Li et al., 2009). In at-risk participants, adult females with a family history of alcohol use disorder showed greater activation in bilateral thalamus compared to family history positive males; no sex differences were found in family history negative participants (DeVito et al., 2013). Finally, adult female social drinkers had greater activation in bilateral thalamus, right middle/superior temporal cortex, and bilateral ACC compared to adult male social drinkers (Ide et al., 2018). Of these studies, three included both adults and emerging adults in the same sample, spanning ~18 to 40 years of age (DeVito et al., 2013; Ide et al., 2018; Li et al., 2009), while the fourth study was composed of participants between 12 and 25 years (Chung et al., 2020). Only Chung et al. (2020) tested for effects of age. These broad age ranges—in particular, those that span several neurodevelopmental stages—have left our

understanding of sex differences in brain function specific to certain developmental periods such as emerging adulthood equivocal.

Here we sought to characterize sex differences in the neural response to error commission in a sample of binge drinking college students aged 18–21 years, as this age range represents a period when important sex differences in behavior appear. To qualify for the study, participants had to meet criteria for binge drinking; most participants also had histories of other substance use. Measures of alcohol consumption, alcohol problems, cannabis use, illicit drug use, and a self-report measure of impulsivity were also collected. We replicated our previous methods by forming a multivariate summary measure (the first component from a principal component analysis) of error-related activation across an array of distributed brain regions associated with error monitoring and the salience network (Weigard et al., 2021). Based on prior research, we expected that females would have greater error-related neural activation, as indexed by this multivariate summary measure, compared to males.

METHODS

Participants and Procedure

Participants were 69 (34 female) individuals aged 18.1–20.8 years who were part of a neuroimaging study examining sex differences in college students who binge drink. To qualify for the study, individuals had to screen positive for hazardous drinking via an online screening (Alcohol Use Disorders Identification Test–Consumption; AUDIT-C), be enrolled in college, and be 18–21 years of age. Exclusionary criteria were: neurological, acute, uncorrected, or chronic medical illness; current use of centrally active medications; MRI contraindications such as metal implants, medical devices, pregnancy, or claustrophobia; current treatment for

schizophrenia or major depressive, anxiety, eating, post-traumatic stress, or bipolar disorders; left-handedness or ambidexterity. See Table 1 for race/ethnicity and other demographic information.

Participants were asked to abstain from alcohol, cannabis, and illicit substances for at least 48 hours prior to the scan session. Participants who were taking medication for ADHD were also asked to abstain for 48 hours prior to the scan session. Urine drug screens were conducted immediately before the scan; those who tested positive were rescheduled. Female participants also underwent urine pregnancy screens immediately before the scan to ensure they were safe to enter the MRI environment. All measures except the AUDIT-C were collected on the day of the fMRI scan. Participants provided written informed consent, and the study was approved by the University of Michigan Medical School Institutional Review Board.

Questionnaires

Alcohol

The AUDIT-C was collected during the initial screening phase and reported on the previous 30 days. The AUDIT-C consists of the first three items of the full-scale AUDIT (Bush et al., 1998) and assesses frequency of drinking, typical number of drinks consumed on a drinking day, and frequency of heavy drinking. Responses to each question are scored 0–4, yielding a maximum score of 12. To screen positive for hazardous drinking, females had to score ≥ 4 and males ≥ 5 . These sex-specific score differences reflect research illustrating that females have higher blood alcohol levels after drinking same amount of alcohol as males, even when controlling for body weight, suggesting higher risk at lower levels of alcohol use (Wechsler et al., 1995). The AUDIT-C was collected 3.48 ± 2.67 weeks prior to the fMRI scan.

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The Timeline Followback (TLFB) was used to obtain a retrospective estimate of daily drinking over the 30 days prior to the fMRI scan (Sobell & Sobell 1992; 1995). Participants used a calendar to provide estimates of their daily drinking (one 12 oz beer, 5 oz glass of wine, or 1.5 oz shot of liquor = 1 drink). From this we calculated the number of drinks consumed in the past 30 days (alcohol quantity).

The Rutgers Alcohol Problem Index (RAPI) was used to assess alcohol-related problems and consequences (White & Labouvie, 1989). Participants were asked the number of times they experienced each of 18 negative consequences (e.g., missing class, going to class drunk) because of drinking in the 30 days prior to their fMRI scan. After removing two items that had zero variance (items 5 [relatives avoided you] and 17 [felt physically or physiologically dependent on alcohol]), Cronbach's alpha was .72, indicating acceptable internal consistency.

Other substance use

A retrospective estimate of cannabis use over the 30 days prior to the fMRI scan was also estimated using the TLFB (Sobell & Sobell, 1996). Participants used a calendar to provide estimates of their daily cannabis use (entered as number of grams, where 1 joint = 0.5 grams). We tallied the number of individuals who reported cannabis use (yes/no) and also calculated grams consumed in the past 30 days (cannabis quantity). The Drug History Questionnaire (DHQ) was used to quantify illicit drug use (other than alcohol and cannabis; Sobell et al., 1995). The DHQ asks whether each of nine different drug classes was ever used, giving a value from 0 to 9 for each participant indicating the number of different drug types used in their lifetime. The Adult Self-Report (Achenbach & Rescorla, 2003) was used to determine the number of participants who reported any nicotine use in the 6 months prior to the fMRI scan.

Impulsivity

The Barratt Impulsivity Scale (BIS-11) was used to assess the behavioral construct of impulsiveness (Patton et al., 1995). Participants responded to 30 items describing how often they display certain impulsive or non-impulsive behaviors (e.g., I do things without thinking; I am self-controlled). Cronbach's alpha was .86, indicating good internal consistency.

Analysis plan for questionnaire data

Questionnaire data were analyzed using SPSS v27. Independent samples *t*-tests were used to test for significant differences between males and females on the following variables: age, the two TLFB variables (alcohol quantity, cannabis quantity), AUDIT-C, RAPI, illicit drug use, and BIS-11. Pearson chi-square tests were used to test for significant differences between males and females for number of individuals reporting any past 30-day cannabis use, past 6-month nicotine use, or lifetime illicit drug use. Pearson correlations were used to test for significant associations between BIS-11 scores and other variables—alcohol quantity, cannabis quantity, AUDIT-C, RAPI, and illicit drug use scores.

Stimuli and task

An event-related go/no-go task (e.g., Cope et al., 2020; Durston et al., 2002; Hardee et al., 2014; Heitzeg et al., 2014, 2010; Weigard et al., 2021) was used to assess brain activation during false alarms (i.e., pressing the button during a “no-go” stimulus). Participants were instructed to respond via button press to “go” stimuli (all letters except for “X”; 75% of stimuli) but withhold their response to “no-go” stimuli (letter “X”; 25% of stimuli). Stimulus duration was 500 ms, with a 3500 ms inter-stimulus interval consisting of a black screen with a white fixation cross. Participants completed five 3.5-minute runs of 49 trials each. In-scanner behavior was recorded during the task; rates of false alarms (pressing the button for “no-go” stimuli) and hits (pressing the button for “go” stimuli) were recorded. Reaction times to false alarms and hits, measured

from the beginning of stimulus presentation, were also recorded. All participants practiced the task outside the scanner prior to scanning to be familiar with the instructions.

fMRI data acquisition and processing

Whole-brain blood oxygen level-dependent (BOLD) functional images were acquired on a 3.0 T GE Signa scanner (Milwaukee, WI, USA) with an 8-channel Nova Medical surface coil array (Siemens, Munich, Germany) using T2*-weighted single-shot combined spiral in/out sequences (Glover & Law, 2001) with the following parameters: TR = 2000 ms; TE = 30 ms; flip angle = 90 degrees; field of view = 200 mm; 64 x 64 matrix; slice thickness = 4 mm; 29 slices. High-resolution anatomical T1 scans were also obtained for spatial normalization (three-dimensional spoiled gradient-recalled echo, TR = 12.3 ms, TE = 5.2 ms, field of view = 256 mm; 256 x 256 matrix; slice thickness = 1 mm). Foam padding around the head, along with instructions to participants on the importance of keeping still, were used to minimize motion.

fMRI data: preprocessing

An iterative algorithm was used to reconstruct functional images (Noll et al., 2005; Sutton et al., 2003). The data were further preprocessed using SPM12. Anatomical (T1-weighted) images were co-registered to functional data. T1-weighted images were then registered to Montreal Neurological Institute (MNI) space using the CAT12 Toolbox and DARTEL. This warp field was applied to the functional data to bring all participants into template space and smoothed with the 6 mm full-width half maximum Gaussian kernel. Motion was assessed based on the number of frames censored, with a framewise displacement threshold of 0.9 mm, using ICA-AROMA (Pruim et al., 2015). Removal of artifacts arising from head motion was performed on the smoothed functional time series using ICA-AROMA.

fMRI data: individual level

SPM12 was used to process images at the individual level with a general linear model. Go trials, correct rejections, and false alarms were modeled separately with the standard hemodynamic response (event duration 4000 ms from stimulus onset); 24 motion parameters were also modeled as nuisance variables (the original six translations and rotations plus their derivatives and quadratics). Images that represented the hemodynamic response associated with our contrast of interest, false alarm versus go stimuli, were computed for each participant.

fMRI data: group level

Regions of interest (ROIs) were obtained by conducting a term-based search in Neurosynth (Yarkoni et al., 2016) with the term “error.” The result is an “association test” statistical map that indicates whether activation in each voxel occurs more consistently in studies that mention the term “error” than in those that do not (neurosynth.org/faq). Clusters with <10 voxels were excluded from this map (14 clusters between 2 and 6 voxels as well as 32 single voxels). Eight clusters remained (minimum size = 28 voxels), and 8 mm radius spheres were centered on their peak coordinates (Figure 1). Clusters were found in midline ACC, left and right insula/inferior frontal gyrus, left and right striatum, left and right inferior parietal cortex, and right pre-supplementary motor area. See Table 2A for details including coordinates.

Mean parameter estimates were extracted from each ROI for the false alarm versus go contrast. These estimates were then entered into a principal components analysis (PCA) using the R package *FactoMineR* (Lê et al., 2008). Scores of the first component (PC1) from this PCA were used as our primary measure of error-related activation to harness the advantage of a multivariate network-based approach and because we anticipated that this component would display strong loadings from the ROIs closely associated with the salience network in previous literature (ACC and bilateral insula) (Seeley et al., 2007), similar to our own recent work in a

different sample (Weigard et al., 2021). PC1 values were entered into SPSS to test for sex differences as well as for associations with alcohol use, alcohol problems, other substance use, and self-reported impulsivity. Finally, a multiple linear regression was performed to determine the relative contributions of substance use and sex to PC1. Specifically, RAPI, alcohol quantity, cannabis quantity, and number of illicit drug types used were entered in the first step, and sex was entered in the second step.

Post-hoc whole-brain sensitivity analysis

To assess whether the PCA-based findings for sex differences were consistent with findings from a traditional mass univariate approach, a whole-brain search was conducted in SPM12 using an independent-samples *t*-test for the false alarm versus go contrast.

RESULTS

Sex differences in behavior and substance use

Males and females were not significantly different on age or in-scanner task behavior. See Table 1 for statistics as well as for reports on race/ethnicity.

There were significant differences between males and females on the AUDIT-C and alcohol quantity, where males reported using more alcohol than females. There was also a significant difference between males and females with respect to the number of participants who reported using cannabis in the past 30 days, cannabis quantity in the past 30 days, and the number of different lifetime illicit drug types used: More males used any cannabis, and males reported a greater quantity of cannabis and a greater number of lifetime illicit drug types. There were no significant differences on BIS-11 or RAPI scores. See Table 1 for results.

When examining the association between impulsivity and alcohol variables among the full sample (i.e., males and females combined), there was a significant positive association between BIS-11 and alcohol quantity ($r = .34, p = .005$) and RAPI scores ($r = .38, p < .001$). The association between BIS-11 and AUDIT-C scores was not significant. Each significant correlation was examined in each sex individually; females showed a significant positive association between BIS-11 and alcohol quantity ($r = .36, p = .046$), whereas males showed a significant positive association between BIS-11 and RAPI scores ($r = .54, p < .001$).

Error-related activation

Results from the PCA of error-related activation in our 8 ROIs are displayed in Table 2A. Five components were necessary to explain more than 90% of the variance, although the first component explained the majority (50.54%; Table 2B). Consistent with our prior work in an independent sample (Weigard et al., 2021), the first component had strong positive loadings from all regional activations that were entered into the PCA, but the main salience network structures displayed the most substantial loadings on this component: ACC (.79), right IFG/insula (.85), and left IFG/insula (.84). Therefore, this component (PC1) can be viewed as a multivariate summary measure of error-related activation that is primarily driven by activity in the salience network.

Sex differences in error-related activation

An independent samples t -test in SPSS revealed a significant sex difference in PC1, $t(67) = -2.94, p = .005, d = -0.71$, in which males had a higher mean component score (0.62 ± 2.13) than females (-0.78 ± 1.81). A post-hoc independent-samples t -test conducted on a whole-brain basis in SPM12 for the false alarms versus go contrast revealed males had greater activation than females at a cluster-level threshold of $p < .05$, corrected for family-wise error, in 2 clusters,

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centered on: 1) left thalamus, extending into right thalamus ($x = -8$, $y = -28$, $z = 4$; $p = .001$; $z = 4.58$; cluster size = 5622 voxels), and 2) left dorsolateral prefrontal cortex, extending into left ACC ($x = -10$, $y = 46$, $z = 18$; $p = .003$; $z = 3.30$; cluster size = 4439 voxels). A third cluster, centered on the right premotor/supplementary motor cortex, extending into the right insula and precentral gyrus ($x = 62$, $y = 2$, $z = 6$; $p = .052$; $z = 3.21$; cluster size = 2693 voxels) trended toward significance. There was no significant activation when interrogating a female > male contrast for false alarms versus go.

Correlations between error-related activation and impulsivity and substance-related measures

There were no significant correlations between PC1 and in-scanner behavior (hit rate, hit reaction time, false alarm rate, false alarm reaction time) or between PC1 and alcohol measures (AUDIT-C, alcohol quantity, RAPI), cannabis quantity, or BIS-11 score (all $ps > .105$). Each of these associations was also tested in males and females individually; there were no significant correlations between PC1 and these measures for males or females individually (all $ps > .146$). There was a significant positive correlation between PC1 and number of illicit drug types used ($r = .26$; $p = .033$); however, no significance was found when this association was tested separately in males ($p = .291$) and females ($p = .543$).

Linear regression predicting error-related activation

Alcohol problems, alcohol quantity, cannabis quantity, and number of illicit drug types used were entered in the first step of a multiple linear regression predicting PC1; sex was entered in the second step. The overall model was significant, $F(5,63) = 3.08$, $p = .015$, adjusted $R^2 = .20$. Sex was the only significant predictor of PC1, $t = 2.76$, $p = .007$. Cannabis quantity ($p = .095$) and number of illicit drug types ($p = .099$) both trended toward significance (all other $ps > .457$).

DISCUSSION

The goal of this study was to examine sex differences in error-related brain activation in binge-drinking college students. Following our previous work (Weigard et al., 2021), we used PCA to obtain a multivariate measure of error-related activation across brain regions previously linked to error monitoring. Consistent with our previous work, we found that the majority of the variance in error-related activation within this set of regions was explained by a single component that was most closely linked to salience network structures (ACC, bilateral insula). This suggests that individual differences in error-related activation across the ROIs are largely driven by the salience network. Males demonstrated significantly higher levels of this multivariate summary measure than females, suggesting that males tend to exhibit greater neural responses to errors across a broad network of regions linked to the monitoring of errors and other salient events.

Our hypothesis, based on the extant literature investigating sex differences in error-related activation that females would have a greater response compared to males, was not supported. Previous research examining sex differences in error-related activation report effects in regions reported here, specifically the ACC and right inferior frontal gyrus (Chung et al., 2020; DeVito et al., 2013; Ide et al., 2018; Li et al., 2009). However, the directionality of the findings in these studies was at odds with the current findings as they reported greater neural activation in females compared to males. This inconsistency may be due to several methodological differences, including sample variability (age range and other subject characteristics), paradigm (stop signal or go/no go) and our analytic approach that focuses on a multivariate composite measure of error-related activation rather than mass univariate analyses. Of these previous studies, only Chung et al. (2020) examined sex differences in error-related responsivity across regions and

networks as opposed to within discrete regions, similar to what was done here. Whereas we focused on the magnitude of task-related responses to errors, Chung and colleagues used independent component analysis to assess sex differences in the strength of functional connectivity within and between networks engaged in inhibition and error responsivity during the go/no-go task. Females generally had greater functional connectivity within and between networks engaged during the task, which included the ACC, right inferior frontal gyrus, right thalamus, and right amygdala. Yet, in an exception to this trend, males displayed greater connectivity than females between networks centered in bilateral posterior cingulate and left inferior parietal lobule. Combined with results of the current study, this work suggests that females may have a reduced magnitude of error-related activation relative to males, but possibly better integration of networks involved in failed inhibitory control. Similarly, an electrophysiology study examining error-related negativity (ERN), a negative deflection in the event-related potential that occurs 50–100 ms after an error (Falkenstein et al., 1991; Gehring et al., 1993), found that males had a greater ERN amplitude relative to females during a modified Eriksen flanker task (Larson et al., 2011). The researchers suggested that the increased ERN amplitude in males compared to females was due to a greater engagement of cognitive control regions, potentially to achieve behavioral performance levels that were similar to females, which is consistent with the behavioral findings in the current study.

A strength of the present study is its use of a multivariate approach that focused on individual difference dimensions that drive activation across an array of brain regions rather than the traditional mass-univariate approach that seeks to separately identify effects in discrete brain regions. This approach was motivated by recent findings demonstrating that variance in neuroimaging measures relevant to individual differences in cognitive and behavioral covariates

is unlikely to be selectively associated with discrete brain regions. Instead, it is typically represented across large, spatially distributed brain networks (Cohen et al., 2017; Sripada et al., 2019; Dubois et al., 2018; Zhao et al., 2021). However, a trade-off of such an approach is that inferences about which individual regions may be particularly relevant to a given effect are less precise. Nonetheless, the component loadings from the PCA suggest that key nodes in the salience network, the ACC and bilateral insula, are the strongest contributors to the summary measure of error-related activation, indicating that individuals with strong salience network responses to errors tend to activate other error-related ROIs (particularly in prefrontal and parietal cortices) to a greater degree than individuals with weaker salience network responses. As this summary measure is greater in males, it can be inferred that males tend to have greater salience network responses to errors and, as a result, may also show greater responses in other error-related regions.

The current study did not find any task performance differences between males and females. This agrees with the aforementioned studies (Chung et al., 2020; DeVito et al., Ide et al., 2019 Li et al., 2009) and also reflects findings across various task domains where no task performance differences are reported yet sex differences in neural activation are observed (e.g., Chen et al., 2007; Clements et al. 2006; Grabowski et al., 2003; Li et al., 2006; Shaywitz et al., 1995; Smith et al., 2014). This lack of performance differences is hypothesized to stem from males and females using distinct neurocognitive strategies to achieve the same task outcomes (De Vries et al., 2004). Along these lines, we propose two possibilities based on the current study's findings. A "resource-based" account suggests males require additional neural resources to accomplish the same level of performance (e.g., as proposed in Larson et al., 2011), while an "affective" account proposes males have a more pronounced affective response to errors, and error-related regions

activate to a greater extent than is necessary to make effective adjustments to performance.

Future work that specifically evaluates these accounts would help elucidate between these two theories.

While our findings may not generalize to populations that are free from substance use, alcohol and cannabis use in young adulthood is normative, especially among college students (Schulenberg et al., 2021). Here, male participants used more substances, as they had significantly higher binge-drinking scores, used greater quantities of alcohol and cannabis, and used a greater number of illicit drug types in their lifetime than females. This parallels evidence in the larger population showing that, despite a general convergence among males and females for drinking behaviors (Keyes et al., 2008), emerging-adult males still report significantly more frequent and heavier alcohol use than emerging-adult females (Schulenberg et al., 2021). Males also report significantly higher rates of cannabis use (including 30-day use) as well as lifetime use of any illicit drugs (other than cannabis), relative to females (Schulenberg et al., 2021). Linear regression analysis results suggest our findings are not due an imbalance between the sexes with respect to alcohol or other substance use but instead directly stem from sex differences in neural activation. Sex was the only significant predictor of PC1, even after accounting for alcohol, cannabis, and illicit drug use. Similarly, DeVito et al. (2013) also did not find an association between alcohol use and go/no-go fMRI task activation in participants who had a family history of alcohol use. Males reported drinking more than females, but there was no association between alcohol use and neural activation, leading the authors to hypothesize that their fMRI results were not due to sex differences in alcohol use. Given previous research linking error-related activation to prospective substance use (Heitzeg et al., 2014; Weigard et al., 2021), it is notable that no relations between error-related activation and substance use were identified

in the current cross-sectional sample. The lack of such associations may be due to methodological differences between this study and prior studies in their definition of substance use (e.g., focusing on a multi-substance composite) or the age ranges investigated. Furthermore, as relations between error-related activation and substance use appear to be moderate in size (e.g., standardized beta = -0.21, Weigard et al., 2021), the sample size in the current study may have not allowed for enough power to reliably detect such an association.

There are a few limitations to consider. First, findings may not generalize to populations free from substance use, although as noted previously, alcohol and cannabis use during young adulthood is normative (Schulenberg et al., 2021). Still, the results presented here are relevant for understanding sex differences in error-related neural activation in individuals with varying levels of substance use. Second, our results may not apply to other age groups, given the defined age range of our participants. The age range of the current study represents a time when neural regions underlying cognitive control are undergoing maturation (Giedd & Rapoport, 2010; Gogtay et al., 2004; Shaw et al., 2008; Toga et al., 2006) and when important sex differences in behavior begin to emerge. For example, sex differences in alcohol and substance use are modest during adolescence but increase substantially after the age of 18, when males drink more frequently and in larger quantities and have greater rates of cannabis use (Palmer et al., 2009).

In conclusion, findings from the current study reveal that males have significantly greater error-related neural activation across a broad network of regions that associated with error monitoring and other salient events. These results are relevant for the further characterization of sex differences in cognitive control, which may have implications for understanding those at risk for substance use or other cognitive control disorders. Furthermore, a better understanding of the

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neural correlates underlying sex differences in cognitive control may be informative for more targeted cognitive-based substance use interventions.

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Table 1. Demographic and summary statistics for total sample, males, and females

	Total sample (N=69)	Females (n=34)	Males (n=35)	<i>t</i> (<i>df</i>) or <i>X</i>²	<i>p</i>-value
Age at scan (yrs)	19.41 ±0.80	19.39 ±0.83	19.42 ±0.78	-.19 (67)	.851
<i>Race/Ethnicity (n Hispanic/Latinx)</i>					
Caucasian	51 (2)	26 (0)	25 (2)	na	.420 (.507) ^a
Asian	10 (0)	4 (0)	6 (0)	na	.519 ^a
Black/African American	2 (0)	1 (0)	1 (0)	na	.746 ^a
Two or more	5 (0)	2 (0)	3 (0)	na	.351 ^a
Other	1 (1)	1 (1)	0 (0)	na	.493 (.493) ^a
<i>In-scanner behavior</i>					
Hit rate %	98.08 ± 4.54	98.92 ±1.9	97.27 ±7.7	1.23 (38) ^b	.226 ^b
Hit RT (ms)	462.11 ±71.49	459.58 ±76.21	464.57 ±67.61	-.29 (67)	.775
False alarm rate %	14.12 ±10.28	13.92 ±9.89	14.29 ±10.79	-.15 (67)	.885
False alarm RT (ms)	415.45 ±96.51	416.76 ±122.64	414.18 ±63.47	.11 (67)	.913
<i>Substance use measures</i>					
AUDIT-C score	6.30 ±1.60	5.88 ±1.54	6.71 ±1.57	-2.18 (67)	.033
Alcohol quantity (drinks) in 30d	32.29 ±20.80	26.13 ±18.14	37.74 ±21.72	-2.34 (67)	.022
RAPI score	4.68 ±4.20	4.45 ±4.47	4.89 ±3.99	-.42 (67)	.676
Cannabis use in past 30d, <i>n</i> (%)	35 (50.7%)	13 (38.2%)	22 (62.9%)	4.18 ^c	.041^c
Cannabis quantity (grams) in 30d	1.58 ±3.71	.42 ±1.42	2.71 ±4.78	-2.71 (40) ^b	.010^b
Any nicotine use in 6 mos, <i>n</i> (%)	19 (27.5%)	7 (20.6%)	12 (34.3%)	1.62 ^c	.203 ^c
Any illicit drug use, <i>n</i> (%)	27 (39.1%)	7 (17.6%)	20 (57.1%)	11.65 ^c	.001^c
Number of illicit drug types used (<i>n</i> out of 9)	.81 ±1.30	.35 ±.77	1.26 ±1.54	-3.09 (51) ^c	.003^c
<i>Impulsivity</i>					
BIS-11 total score	62.74 ±11.05	61.88 ±11.49	63.54 ±10.73	-.62 (67)	.539

Note. Numbers are means ± standard deviations and statistical tests are independent samples *t*-tests, except where noted. BIS = Barratt Impulsivity Scale; d = days; *df* = degrees of freedom; na = not applicable; ms = milliseconds; mos = months; RAPI = Rutgers Alcohol Problems Index; RT = reaction time; yrs = years

Sex differences in error-related neural activation

^aFisher's exact test

^bEqual variances not assumed

^cPearson chi-square

Table 2. The five PCA components that together explain over 90% of between-subject variation in error-related ROI activations

A. ROI (x, y, z) Loadings	PC1	PC2	PC3	PC4	PC5
Anterior Cingulate (0, 22, 38)	0.79	0.08	0.32	-0.13	0.41
L Insula/IFG (-38, 20, -6)	0.84	-0.00	-0.14	-0.34	-0.25
L Inferior Parietal Lobe: Angular Gyrus (-62, -44, 34)	0.68	0.23	-0.59	-0.05	0.27
L Striatum (-12, 10, -10)	0.66	-0.67	-0.00	0.01	0.06
R Insula/IFG (42, 18, -6)	0.85	0.09	-0.19	-0.08	-0.26
R Inferior Parietal Lobe: Supramarginal Gyrus (58, -44, 30)	0.54	0.60	-0.03	0.55	-0.06
R Striatum (14, 10, -10)	0.62	-0.61	0.08	0.42	-0.05
R pre-SMA (4, 30, 54)	0.64	0.32	-0.61	-0.12	-0.10
B. Variance Explained					
Percent explained by component	50.54	17.03	11.02	7.94	4.85
Cumulative percent explained	50.54	67.57	78.53	86.53	91.38

Note. **A.** Loadings on each ROI of each component. MNI coordinates of ROIs are in parentheses. IFG = inferior frontal gyrus; L = left; MNI = Montreal Neurological Institute; PC = principal component; PCA = principal component analysis; R = right; ROI = region of interest; SMA = supplementary motor area, **B.** Variance explained by each component.

Figure 1. Spheres representing center of coordinates of our eight regions of interest. Yellow: left inferior parietal lobe: angular gyrus; green: right inferior parietal lobe: supramarginal gyrus; red: anterior cingulate; orange: right supplementary motor area; blue: left insula/inferior frontal gyrus; purple: left striatum; aqua: right striatum; pink: right insula/interior frontal gyrus.