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Neural Response to Social Exclusion Moderates the Link between Adolescent Anxiety Symptoms and Substance Use

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Abstract

Background: Substance use (SU) typically increases from middle to late adolescence. Anxiety is one factor associated with greater SU, although variability in who uses substances remains. Some models suggest that brain-based susceptibility markers could reveal which adolescents are at higher risk for psychopathology, but it is unknown whether these individual differences attenuate or accentuate the association between anxiety and elevated SU even if normative. The present study addressed this gap by testing whether neural response to social exclusion moderates the association between anxiety symptoms and increased SU from middle to late adolescence.

Method: Participants were 181 Mexican-origin adolescents (48% female, 16–17 years old) who completed a social exclusion task during a functional magnetic resonance imaging scan, and questionnaires about their SU and anxiety symptoms. Analyses focused on neural response to social exclusion vs. inclusion within three regions of interest, and change in SU across two years.

Results: Dorsal anterior cingulate cortex (dACC) response to social exclusion, but not subgenual ACC or anterior insula, moderated the relation between anxiety symptoms and SU, such that

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Some of these data on substance use and neural response to social exclusion were presented as a poster at the Flux Congress conference in 2019 (73) (Reference below). The work is substantially different, however, because analyses included different variables. The poster involved internalizing symptoms with the Mood and Anxiety Symptoms Questionnaire (MASQ), specifically the subscales of anxious arousal, anhedonic depression, and general distress. Original research questions were more focused on anxiety than depression, so the separate analyses presented in our manuscript relied on data from the Screen for Childhood Anxiety and Related Disorders (SCARED) instead, which were finalized and prepared for written publication. Results presented in this manuscript (with the SCARED) have not been presented or published anywhere else.

Beard SJ, Chahal R, Venticinque J, Hastings PD, Robins RW, Guyer AE (2019): Association between internalizing symptoms and substance use from early to late adolescence: The moderating role of neural response to social exclusion. Poster presented at: Flux Congress, Society for Developmental Cognitive Neuroscience Annual Conference; August 31, 2019; New York City, NY.

Disclosures

The authors have no conflicts of interest to disclose.

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higher anxiety symptoms predicted a greater relative increase in SU only for those youth with a lower dACC response to exclusion.

Conclusions: Blunted dACC response to social exclusion may serve as a neural susceptibility marker of altered conflict monitoring or emotion regulation in middle adolescence that, in combination with high levels of anxious feelings, elevates risk for onset of and/or increased SU by late adolescence. These findings have implications for designing targeted interventions to mitigate adolescent SU.

Keywords

Substance use; Adolescent brain; Anxiety; Social exclusion; Peers; Stress

Nearly 60% of U.S. high school seniors report lifetime alcohol use, and 36% report past-year marijuana use (1). Anxious adolescents are at high risk for substance use (SU) even at subclinical levels (2); however, not all anxious youth engage in SU. One framework suggests that brain-based susceptibility markers, and particularly neural sensitivities to experiences such as social exclusion, could reveal which adolescents are at higher risk for SU, such as heavy SU beyond normative experimentation (3). Indeed, not all SU is problematic; however, earlier and greater use during late adolescence heighten risk for future problems in adulthood (1). Adolescents' sensitivity to social exclusion might moderate the link between anxiety and increased SU, such that a stronger neural response to exclusion magnifies associations between anxiety and SU, whereby anxious youth with heightened sensitivity are more likely to use substances in late adolescence than less-sensitive youth. Moreover, little is known about these processes in populations of adolescents at risk for both anxiety and SU, including Mexican-origin adolescents (4–7). Thus, the present study tested whether neural response to social exclusion functions as a vulnerability factor that, when combined with high anxiety, contributes to increased SU in Mexican-origin adolescents.

Social exclusion threatens the human need to belong (8), eliciting an emotional response (e.g., social pain) and a violation of an "unwritten rule" to be included (e.g., expectancy violation) (9–11). Adolescents spend considerable time with peers and are highly sensitive to social experiences (12,13), with social exclusion a common and distressing event (14–16). Moreover, adolescents with anxiety are highly sensitive to social exclusion, demonstrating greater self-reported sensitivity (17) and heightened neural response to exclusion (18). Additionally, substance-using young adults show heightened neural activity in regions that process social exclusion, compared to non-users (19–21). Whether neural response to distressing social experiences reflects susceptibility or resistance to increased SU in the face of anxiety, especially from middle-to-late adolescence when SU typically elevates, has not been tested.

One metric of sensitivity is derived from neural activity during the Cyberball task (22,23), in which participants are included and excluded in a ball-tossing game. Cyberball-induced exclusion engages brain regions collectively referred to as the "social pain" system (24,25), including the anterior insula (AI), subgenual anterior cingulate cortex (sgACC), and dorsal ACC (dACC) (24,26,27). Activity in the dACC may particularly reveal individual differences, as some work found greater dACC response to social exclusion (27–29) whereas

other work has not (26,30). One meta-analysis revealed that dACC activation to exclusion (versus inclusion) was greater in studies using longer durations of trials, whereas those with shorter durations reported greater sgACC response; it is possible that long inclusion phases might diminish activity related to expectancy violation (29). Additionally, although a different meta-analysis reported infrequent dACC activation to exclusion, four of the studies found peak activations within the bounds of the dACC, albeit assigned different labels such as medial prefrontal cortex (30). Involvement of the ACC may also reflect developmental variation; youth typically show greater sgACC activation to exclusion than adults (24), whereas adults show heightened dACC activation (29). The idea that sgACC and AI activity may reflect emotional arousal, and dACC activity reflects conflict monitoring and emotion regulation, suggests these regions may have common and unique moderating effects with anxiety in predicting SU.

Neural sensitivity to social exclusion has been linked to daily SU in young adults. Marijuana users aged 18–25 did not show significant AI activation to social exclusion (versus inclusion), whereas non-using controls did (20). Both groups showed greater ventral ACC (vACC; an area including sgACC) activity, but only users demonstrated a positive association between vACC response and self-reported conformity (i.e., changing one's mind based on others' arguments), suggesting marijuana users may be less explicitly-aware of social expectations. Anxious adolescents are more likely to use substances (2,31–33), including Mexican-origin adolescents for whom high anxious arousal is associated with alcohol use (6). Adolescents' self-reported rejection has been associated with SU (14,34,35), and sgACC response to exclusion has predicted deviant behavior (36). Thus, associations between anxiety and SU may vary by neural response to socially distressing events. Indeed, a clearer picture of why SU increases for some youth, and whether anxiety is an indicator of which youth, necessitates going beyond main effects to include interactions.

The present study examined whether anxiety interacts with neural response to social exclusion to predict increased SU in Mexican-origin youth, a population underrepresented in neuroscience research, despite earlier onset of alcohol use (4,5), vulnerability to internalizing disorders (6,7), and exposure to discrimination (37–39). A region-of-interest approach focused on sgACC, dACC, and AI response to exclusion versus inclusion, such that the relation between anxiety and increased SU was expected to be magnified in adolescents with greater sensitivity to exclusion. Higher anxiety in middle adolescence was expected to predict a greater increase in SU by late adolescence, particularly for adolescents with greater neural response to exclusion in all three of the "social pain" regions (i.e., higher neural sensitivity amplifies the effect with a steeper slope). Secondary analyses tested sex as another moderator given sex differences in adolescent anxiety (40,41) and SU (42), although given the nascent evidence from which to draw, specific hypotheses were not proposed for the direction or regions involved. Lastly, self-reported distress from the task was tested as a moderator to explore parallels between brain activity and distress. Distress post-game might represent "state" anxiety, whereas anxious symptoms represent "trait" anxiety, along with neural response as an individual difference. Similar patterns were expected, whereby anxious youth with greater distress would report more SU than those with less distress.

Methods and Materials

Participants

Participants were 229 adolescents (M_{Age} at scan=17.16 years, SD= 0.44, 49.3% self-reported female) enrolled in a neurobiology sub-study (36,43,44) of the California Families Project (CFP), an ongoing 15-year longitudinal study (see Supplemental Materials). The sub-study oversampled youths with elevated but sub-clinical levels of depression, based on self-reported symptoms in 9th grade (age 14–15 years) from the computerized Diagnostic Interview Schedule for Children-IV (DISC-IV) (45), and General Distress and Anhedonic Depression subscales of the Mood and Anxiety Symptom Questionnaire (46). Of the original 229 adolescents in the sub-study, 10 were ineligible for scanning, and two had unavailable data from scanner malfunction, resulting in 217 youths who completed Cyberball. Another 36 participants were excluded for poor scan quality (e.g., excessive motion). Thus, the final analytic sample included 181 adolescents, who completed the Cyberball task and self-reported anxiety and SU.

Procedure

Data were collected during two home interviews and a neuroimaging research facility visit. The first home visit occurred at approximately age 16, when adolescents self-reported on their SU. At age 16–17, adolescents visited a research facility to participate in the MRI scan, and self-reported their anxiety symptoms. Data from these two visits are considered Time 1. The second home visit occurred when participants were approximately age 18, when they self-reported their SU again; these data represented Time 2.

Measures

Substance use.—The Alcohol, Tobacco, and Other Drugs survey (47) assessed past-3-months use of beer, wine/wine coolers, hard liquor, and marijuana. For example, adolescents indicated yes/no to, “In the past 3 months, how many times have you used or tried marijuana?” to which participants responded 1=“Never”; 2=“Less than once per week”; 3=“About once per week”; 4=“Two or three times per week”; 5=“Almost every day or every day”. Values were rescored to 0 (Never) to 4 (Daily/Almost Daily) and summed into a composite with possible scores of 0–16. Time 1 scores were overall relatively low, ranging from 0–6 (M=0.88, SD=1.49, N=178; Cronbach’s α=.71), and Time 2 was higher but still relatively low ranging from 0–8 (M=1.41, SD=1.86, N=175; Cronbach’s α=.79) (see Supplemental Materials).

Anxiety symptoms.—Adolescents self-reported their past-3-months anxiety symptoms using the Screen for Child Anxiety Related Emotional Disorders (SCARED) (48); an example item is, “I get really frightened for no reason at all,” with response options 0=“Not True”, 1=“Somewhat true or sometimes true”, and 2=“Very true or often true”. Sum scores across all subscales were computed (α=.92; missing n=4). Scores were 0–45 before Winsorizing within 2 SD; and 0–42 after. Although not designed for diagnosis, scores ≥25 may indicate an anxiety disorder (49), and 39 adolescents (22%) scored ≥25. All results were replicated with the DISC-IV (44).

Cyberball task.—Neural response to social exclusion was elicited via Cyberball, as described in prior work (36) and in our Supplemental Materials. Participants were told they would play a ball-tossing game with two computerized players and asked to imagine same-aged peers. Adolescents played 12 rounds of Cyberball, six Inclusion (I) and six Exclusion (E), in the same pseudorandom order: I-E-I-I-E-I-E-I-E-E-E-I. Rounds lasted 36s, comprised of a fixation point (4s), "Begin Match!" notification (2s), and 10–11 ball tosses (22–23s) followed by a reloading screen (7–8s). The functional scan was one 7min-23s-long run.

Post-scan task experience.—To measure how participants felt approximately 20 min after Cyberball, adolescents indicated 1="Not at all" to 5="Very much so" the degree to which they felt included and excluded during the game, as well as what percentage of the time the ball was thrown to them, respectively.

Post-scan need-threat.—To measure subjective distress, adolescents completed the Need-Threat Scale (24,50), rating 12 subjectively-experienced consequences that threaten four basic human needs: self-esteem ("I felt liked"), belongingness ("I felt rejected"), meaningfulness ("I felt invisible"), and sense of control ("I felt powerful"), from 1="Not at all" to 5="Very much," and averaged (Cronbach's α=.91).

Neuroimaging Data

See Supplement for scan parameters and preprocessing steps. For first-level processing, Cyberball was modeled as a block design using Analysis of Functional NeuroImages (AFNI: www.afni.nimh.nih.gov/afni (51)). Exclusion and Inclusion were modeled as boxcar functions with an amplitude=1 using duration modulation (dmBLOCK). Linear contrasts were calculated comparing blood-oxygen level-dependent (BOLD) responses in Exclusion > Inclusion.

A structural ROI approach was used to assess BOLD responses to Exclusion > Inclusion within bilateral sgACC, dACC, and AI, selected a priori based on previous publications. Right and left sgACC ROIs were created from right and left Brodmann Area (BA) 25 masks from the Talairach-Tournoux database within AFNI, transformed to MNI space using "tta2mni" then modified to include only BA25 areas under the genu of the corpus callosum posterior to y=30 and identifiable as "cingulate cortex" with AFNI's "whereami" function. The resultant ROI was similar to significant clusters of sgACC reported in studies with adolescents (24,30,52); volume was 43 voxels for left-sgACC and 50 voxels for right-sgACC. Right and left dACC ROIs were constructed using the "cingulate cortex" mask in the MNI database and modified with a rostral boundary of y=32 consistent with established criteria (53) and a caudal boundary of y=0. The resulting volume was 195 voxels for left-dACC, and 221 voxels for right-dACC. The AI ROI was created with all voxels within the left and right insula masks anterior to the y=0 plane. The volume was 396 for left-AI, and 393 voxels for right-AI. For all three ROIs, right and left masks were averaged to create bilateral ROIs (Figure 1A). Within each ROI mask, per participant average beta values for the linear contrast of Exclusion > Inclusion were extracted for use in analytical models (36). To confirm activity in the ROIs for the contrast of interest,

whole brain analyses were conducted using "3dttest++" with the "-Clustsim" option for multiple-comparison correction. A threshold of p=.001 and 40 voxel minimum cluster size, using nearest-neighbor faces-touch clustering, was applied to whole-brain maps (Figure 1B shows whole-brain clusters per ROI).

Statistical Analyses

RStudio 1.1.456 (54) software was used to test neural response in each ROI as moderators of age-16 anxiety and age-18 SU. Since SU had many zeros, zero-inflated Poisson regressions were used with the "zeroinfl" function in "pscl" package. Analyses controlled for age-16 SU to examine relative increases in SU from age 16 to 18, and were conducted separately per ROI, with each model including the interaction term of ROI response by anxiety. Each analysis included both a "count model" of continuous SU, and a "zero-inflated" model of binary use versus non-use. Significant interactions were interpreted via simple slopes estimated at varying levels of neural response to exclusion (low being ≤1 SD of the median −.05, high being >1 SD of −.05). Interactions were visualized using median-split (low being below −.05 and high being above −.05) and geom-smooth method "glm" with X as anxiety, Y as age-18 SU, and group as low/high activation for each ROI. Recruitment status based on age-15 depressive symptom scores was a covariate (0=no symptoms, n=52; 1=elevated symptoms, n=129). Two-way interactions with sex and anxiety, and sex and neural response were tested. Primary analyses were replicated with the Need-Threat Scale to test the interaction of anxiety and distress, distress and neural response, and distress and neural response in addition to anxiety.

Results

Preliminary Analyses

Anxiety levels were moderate, whereas SU was relatively low at age 16 (Table 1). Social exclusion in the Cyberball task elicited activity in the AI, sgACC, and dACC, along with parietal and prefrontal regions that were not selected a priori as ROIs (Figure 1). Post-scan, adolescents felt more excluded (M=3.63, SD=1.01) than included (M=2.54, SD=.81; paired-t=9.76, p<.001) and felt included (i.e., the ball was thrown to them) for 32% of throws and excluded for 61% of throws. SU at either time point was not significantly correlated with anxiety or neural responses in the three ROIs.

Anxiety ($F_{1,163}$=12.62, p<.001) and game-related distress ($F_{1,175}$=13.83, p < .001) were higher in females than in males. Sex differences were not found for SU at age 16 (p=.24) or 18 (p=.87) or sgACC (p=.40), dACC (p=.51), or AI (p=.37) activity. Given the anxiety/distress differences, sex was a covariate in all analyses.

Primary Analyses

Hypotheses focused on interaction effects, with anxiety symptoms expected to predict increased SU in adolescents with stronger neural responses to social exclusion vs. inclusion (i.e., the slope would be steeper). Each model contained main effects of covariates (sex, recruitment status) and predictors (anxiety, neural response in one ROI at age 16), as well as an interaction term between anxiety and neural response. Main effects mirrored correlational

analyses, revealing that neural response alone did not predict SU. The interaction effect indicated that less response in the dACC during mid-adolescence moderated the link between anxiety and an increase in late-adolescent SU (Table 2). For some tests, however, the count model diverged from the zero-inflated model, suggesting that level of SU differs from binary use/none in some cases. Further, simple slopes analysis estimating low as ≤1 SD of the median and high as >1 SD revealed that at low levels of dACC response, age 16 anxiety symptoms significantly and positively predicted age 18 SU (β=.98, *SE*=.06, z=.86, p=.043). Anxiety did not predict SU at high levels of dACC response (p=.49), indicating that stronger dACC response to social exclusion buffered against greater anxiety increasing the risk for SU. A median split was used for visualization purposes, whereby Figure 2 presents a median split between "low" and "high" activation (below and above the median of −.05), showing a significant slope for low but not high dACC response. This interaction effect, however, was not found for the AI or sgACC. Confidence intervals indicated that the interaction coefficient between dACC activity and anxiety symptoms is estimated to fall between −.19 and −.01 while not including zero, providing further evidence that although this effect is small, it is reliable in our sample of 181 adolescents (Table 2).

Secondary Analyses

Given sex differences in anxiety and subjective distress (but not neural response) in this sample, two-way interaction effects with sex were tested. The interaction of anxiety and sex was not significant. A significant interaction effect was found for sex by AI response to exclusion (β=1.54, *SE*=.76, z=2.04, p=.042). Simple slopes analysis showed that for female adolescents, AI activation significantly and positively predicted age 18 SU (β=1.33, *SE*=.03, z=.91, p=.044); for male adolescents, AI response did not predict SU (p=.23). No bivariate interactions were found for sex by dACC (p=.12) or sex by sgACC (p=.51). For visualization purposes, Figure 3 presents the relation between AI response and SU with separate lines for female and male adolescents, in which there is a significant slope for female but not male adolescents.

Lastly, game-related subjective distress was associated with anxiety and sgACC response to exclusion, but not with SU, or dACC or AI response to exclusion (Table 1). No interaction effect of distress and anxiety was found (Table 3). However, a significant interaction between distress and dACC response was found, similar to what was observed for anxiety, in which distress to exclusion modestly predicted SU at low dACC activation (β=.55, *SE*=.28, z=1.96, p=.049), but not at high dACC activation (p=.82). Interaction effects were non-significant for distress with insula or sgACC. The significant interaction between dACC activity and anxiety remained when accounting for distress (β=−.16, *SE*=.07, z=−2.25, p=.02). When including both interaction terms in the model, dACC response still moderated the link between anxiety and SU (β=−1.42, *SE*=.20, z=−1.97, p=.044), while the interaction between distress and anxiety was non-significant (p=.23).

Discussion

The present study investigated whether adolescents' anxiety symptoms in combination with neural sensitivity to social exclusion predicted increased SU over two years, hypothesizing

that anxious adolescents with *high* sgACC, dACC, and AI activity would show steeper increases. Hypotheses were partially supported, whereby only dACC reactivity to social exclusion moderated the relation between anxiety and SU indicated by a modest interaction effect; however, this was limited to the dACC, and adolescents with high anxiety showed increased SU only when they demonstrated *low* dACC activity during exclusion. For adolescents with less dACC activation, anxiety was associated with a steeper increase in SU, whereby high anxiety predicted more SU but low anxiety predicted less SU; in addition, anxiety was unrelated to SU for those with higher dACC response, suggesting that high dACC activity buffered against SU. The same pattern was evident for youths' state of distress after the game. Additionally, female adolescents with *higher* AI response reported slightly higher SU, whereas AI response was unrelated to SU for male adolescents. The current study contributes to the literature by showing that lower dACC response to social exclusion, combined with higher anxiety, predicted increased SU in Mexican-origin adolescents, a population at high risk of both anxiety (6,7) and SU (4,5).

Blunted dACC response to exclusion signified risk for increased SU among adolescents with higher anxiety, whereas heightened dACC response buffered against anxiety predicting elevated SU. This pattern may reflect the dACC's role in emotion regulation (55). Less dACC activity to exclusion could mean either less engagement of cognitive control and self-regulation, which may lead to greater SU; or alternatively, anxious individuals may seek substances to alleviate emotional distress and physiological arousal. First, anxiety may lead to increased SU for those adolescents who disengage from processing socially-conflicting information through reduced dACC activity during social stress. This possibility might partially explain discrepancies in dACC involvement noted in prior work (26,29,30). Second, it could be that adolescents with *less* dACC activation during exclusion cope with anxiety through SU, rather than cognitively processing this distressing event as might be done by adolescents whose neural sensitivity to social distress is higher. This interpretation aligns with the *negative affect regulation model* (57,58), in which anxious individuals seek substances to alleviate emotional distress and physiological arousal. Distress did not interact with anxiety to predict SU, but did interact with dACC activity; the effect of dACC response and anxiety did not change when controlling for distress. Although studies have reported main effects of higher response in the social pain regions (i.e., dACC, sgACC, and AI) and greater use of substances in young adults (20) and older adults (59), and greater risk-taking in adolescents (60–62), other work has shown main effects of decreased dACC response to peer rejection (63) and attributions of racism (64), and low dACC activity during response inhibition among stimulant users (65). These findings suggest an association between SU and dACC hypoactivity, which mirrors our findings that anxiety predicted greater SU specifically among adolescents with a lower dACC response.

Distress felt during the game was not associated with dACC response, but was correlated with anxiety, and sgACC response consistent with past work (24,56). Other work (20) has indicated that young-adult marijuana users with more vACC (region including the sgACC) activity to exclusion reported more conformity, suggesting that marijuana users are less explicitly aware of social expectations; however, marijuana users did not show significant AI activation, whereas non-users did. That we found no significant associations of AI response with anxiety, SU, or distress was surprising given that AI response is positively associated

with distress (24,66), as well as the role of the insula more broadly in adult anxiety disorders (67), and addiction (68). One modest interaction was found, in that the link between AI activity and SU depended on sex. Female adolescents with higher AI response showed slightly increased SU from age 16 to 18, whereas those with lower AI response reported slightly less SU; this interaction did not emerge in male adolescents. While this interaction effect was small, it is possible that SU relates to the proposition that males and females differ in how internal and external cues are translated into subjective awareness (69).

The current study has some limitations. Analyses included one timepoint of neural response and anxiety symptoms, leaving it unknown whether the moderation effect changes across adolescence, and leaving the directionality of effects between anxiety and neural response undetermined. Findings also need to be replicated. Because neural response was measured during mid-adolescence, comparisons to results from young adult samples (20) are limited. Continuation of the longitudinal study of neural processing and SU into young adulthood, the peak period of SU, would be informative; however, a strength of the current study was its large sample of participants in mid-adolescence when SU begins to escalate. Although the results advance understanding about an ethnic group understudied in neuroscience research, other within-group factors (e.g., cultural values) could play a role (34,36,70), and generalization of results to other racial/ethnic groups is limited. While SU often occurs in social contexts (12,71,72), peer rejection could contribute to comorbidity of anxiety and solitary SU. Alternatively, youth may increase drug-seeking to re-establish social status in peer groups, as rejected individuals often strive for acceptance (66,73,74). Future work needs to replicate our findings, and disentangle the settings of adolescents' SU to better inform how anxiety and neural sensitivity to exclusion contribute to SU, e.g., via a solitary versus social pathway.

In conclusion, our study provides new evidence that anxiety predicts increased SU from middle to late adolescence, but only in youth who demonstrated less neural reactivity to experiences of being socially excluded. For adolescents with heightened neural response in the dACC, anxiety did not predict increased SU. Despite their identification as regions integral in "social pain," this pattern was specific to the dACC, but not the sgACC or AI. This suggests one neurophysiological link between anxiety and SU may involve an expectancy-violation component (10,11) of social-information processing to a greater extent than an emotional-distress component (24,36). These findings may also help inform prevention and intervention efforts, as pinpointing biologically-based moderators is crucial (75). Such biological markers may help identify youth at risk for problematic SU, in turn increasing precision of programs. For example, programs to mitigate bullying and SU may only be effective for some youth, due to differences in the neural processing of social information. Interventions can also target individual-level strategies, such as managing threat appraisals and coping with exclusion (76,77). Most interventions for both SU and bullying tend to target externalizing behaviors, but the current findings bolster the need to also target internalizing problems (32). Furthermore, the present results explained a prospective increase in SU from the middle to the end of high school, which is important given the typical increases observed in SU across these ages. The unique combination of higher anxiety and lower neural reactivity was shown to be important in understanding increased SU in adolescence, and thus, extends existing knowledge of not

only neurobiological mechanisms of social processing, but also of internalizing pathways to SU in late adolescence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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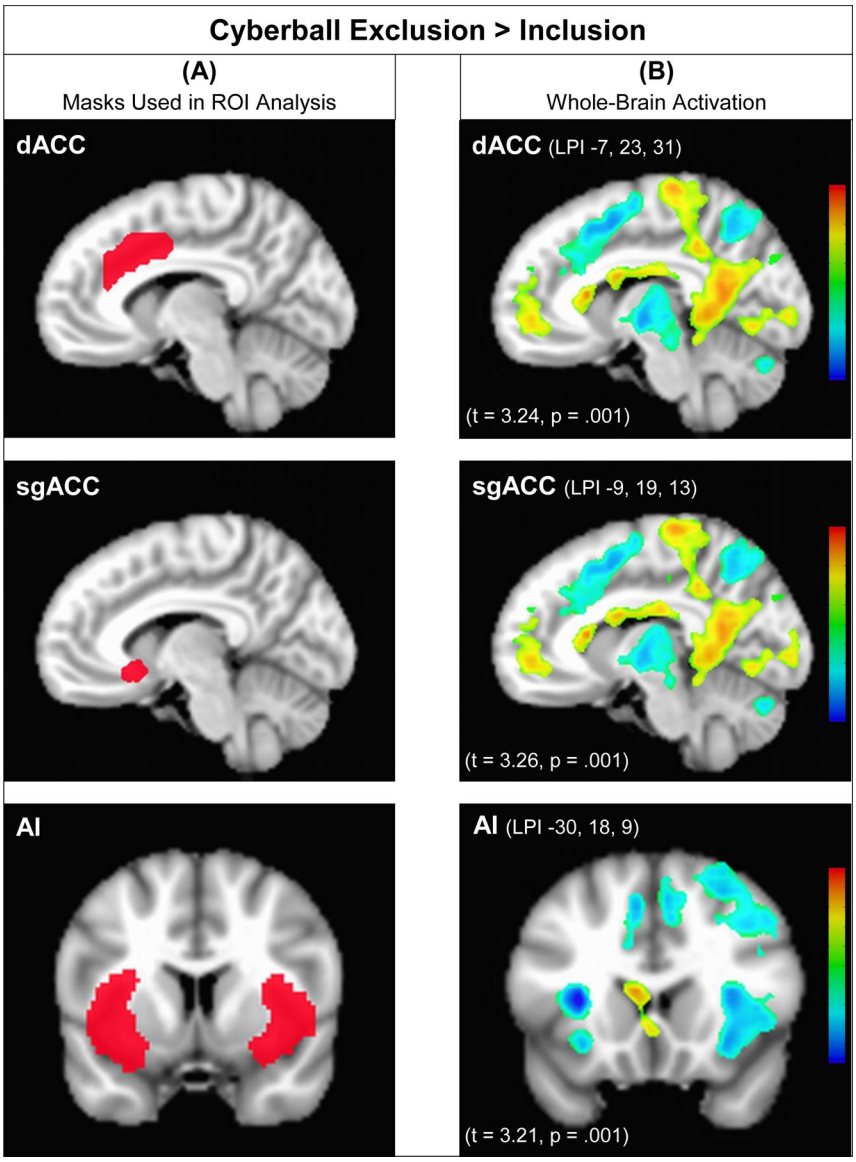

Figure 1.

(A) Masks used for region-of-interest (ROI) analysis, created anatomically using AFNI atlases (see Method and Materials), for the dorsal anterior cingulate cortex (dACC), subgenual anterior cingulate cortex (sgACC), and anterior insula (AI). Standardized beta coefficients associated with Exclusion > Inclusion were extracted. **(B)** Whole-brain analysis results, demonstrating significant clusters of activation to social Exclusion > Inclusion during the Cyberball task in select bilateral ROIs: dACC, sgACC, and AI. Coordinates are in LPI orientation, and MNI space with maps overlaid onto the MNI template in AFNI.

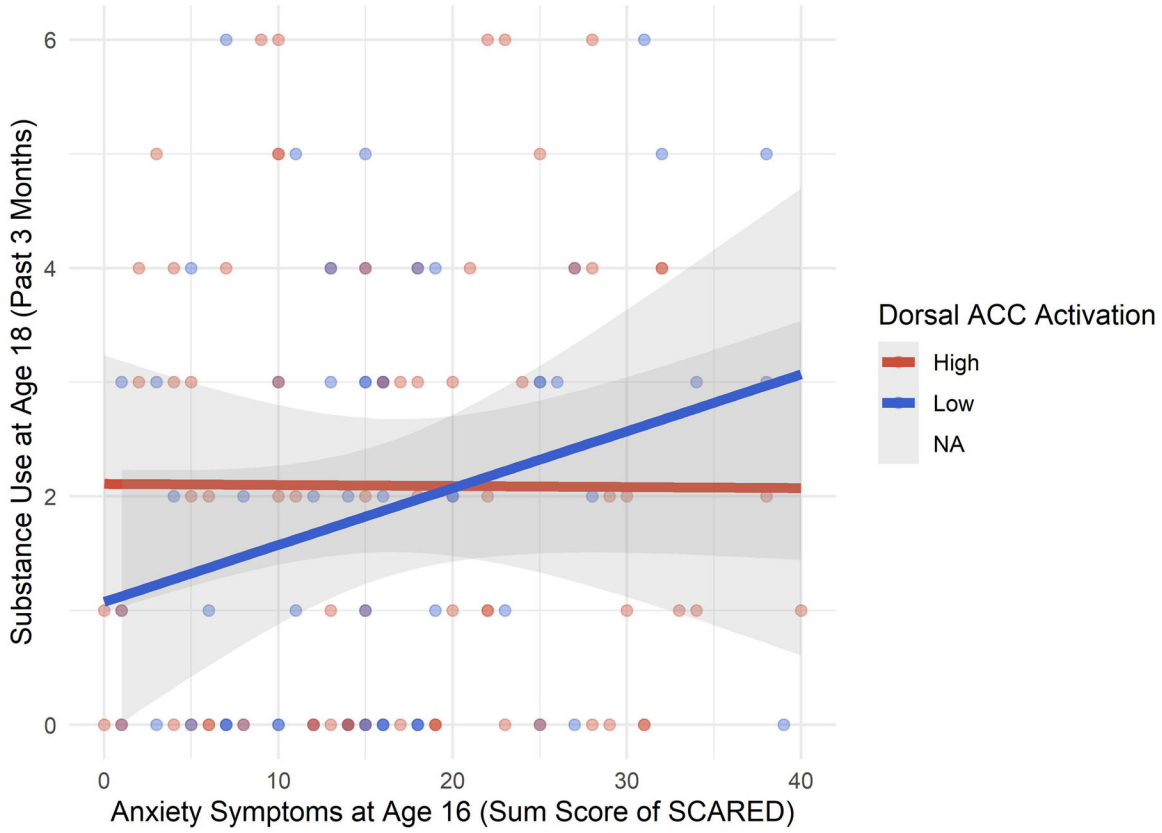

Figure 2.

Interaction plot representing the moderating role of neural response to social exclusion in the dorsal anterior cingulate cortex (dACC) between anxiety symptoms at age 16 and later substance use (SU) at age 18. Adolescents with lower dACC response (below median of −.05) reported higher SU when they also experienced higher anxiety, whereas those with lower anxiety reported *less* SU. Adolescents with higher dACC (above median of −.05), however, reported similar SU regardless of anxiety. Regression models included continuous dACC response and covariates of sex, recruitment status representing risk of depression, and previous SU at age 16; and simple slopes estimated at low being ≤1 SD of the median, and high being >1 SD. Median split of dACC response was done for visualization purposes.

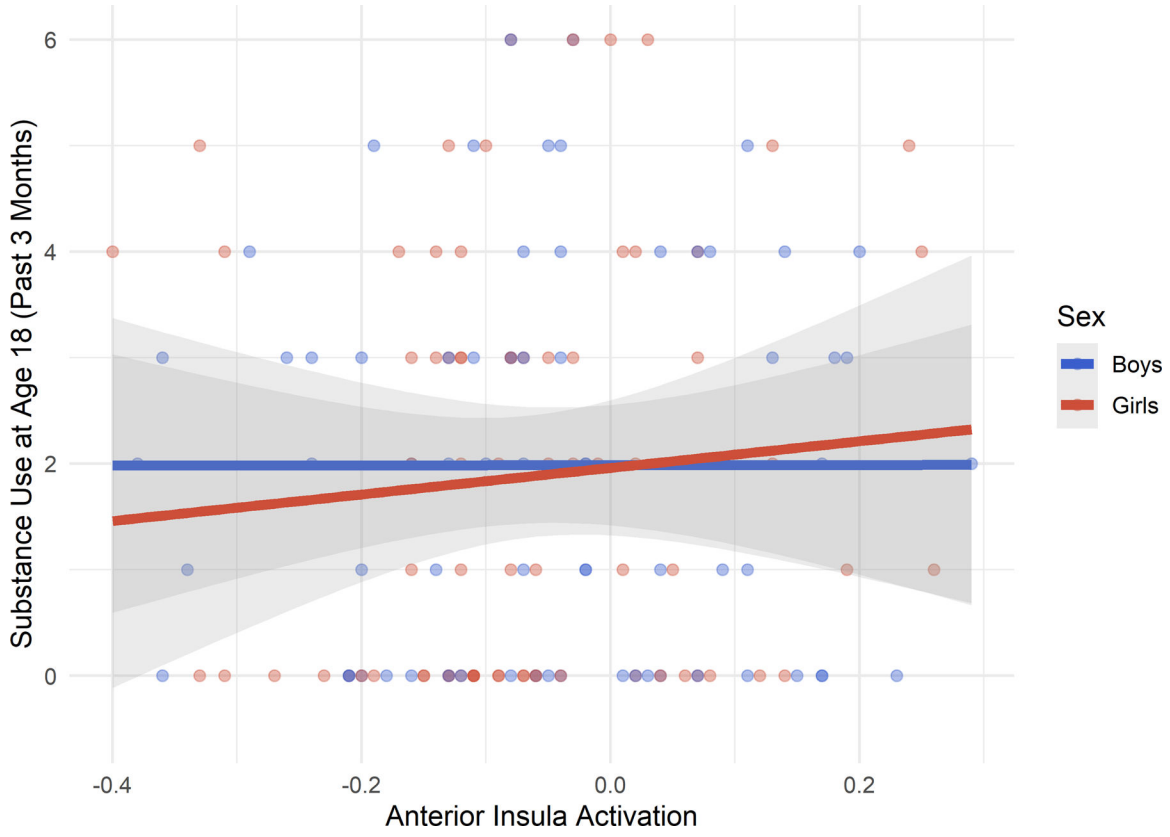

Figure 3.

Interaction plot representing the partial moderating role of sex between neural response to social exclusion in the anterior insula (AI) at age 16 and later substance use (SU) at age 18. Female adolescents with heightened AI response reported slightly higher SU, whereas those with lower AI response reported slightly lower SU. Male adolescents did not show differences in SU by level of AI response to social exclusion. Regression models included continuous dACC response and covariates of sex, recruitment status representing risk of depression, and previous SU at age 16. Grouping was done for visualization purposes. Note: Three-way interaction of sex × anterior insula × anxiety symptoms was not significant.

Table 1.

Descriptive statistics and zero-order correlations among covariates of sex and recruitment status, anxiety symptoms, substance use (SU), and neural response to social exclusion during Cyberball in three regions of interest (ROI).

Variable	*M (SD)*	1	2	3	4	5	6	7	8	9	10
1. Sex	0.48 (.50)	-									
2. Recruitment status	.29 (.43)	−.26**	-								
3. Age at MRI scan	16.38 (.54)	−.01	.07	-							
4. Substance use (Age 16)	.88 (1.49)	−.10	.05	.03	-						
5. Substance use (Age 18)	1.41 (1.86)	.01	.13	.01	.01	-					
6. Anxiety symptoms	15.97 (10.12)	−.40**	.26**	.09	.02	.09	-				
7. dACC	−.04 (.16)	.05	.13	−.03	.02	.03	.01	-			
8. sgACC	.03 (.20)	−.07	.05	.03	.04	−.03	.07	.45**	-		
9. Anterior insula	−.05 (.14)	.07	.02	−.07	.01	.04	.03	.85**	.47**	-	
10. Post-scan distress (Need Threat Scale)	3.02 (.87)	−.28**	.11	−.08	−.03	.02	.27**	.02	.01	−.03	-

Note: $N = 181$.

* $p < .05$.

** $p < .01$,

*** $p < .001$.

Anxiety symptoms = sum score of Screen for Child Anxiety Related Emotional Disorders (SCARED; range 0–42). dACC = dorsal anterior cingulate cortex; sgACC = subgenual anterior cingulate cortex. Contrast in regions of interest (ROIs) are activation to Exclusion > Inclusion. Substance use is a sum of alcohol and marijuana use in past 3 months. Sex is coded as female = 0 ($N = 86$), male = 1 ($N = 95$). Recruitment status is coded as low = 0 ($N = 52$), and elevated = 1 ($N = 129$), and represents the risk of depression based on self-reported symptoms in 9th grade (age 14–15 years) from the computerized Diagnostic Interview Schedule for Children-IV (DISC-IV) (45), and General Distress and Anhedonic Depression subscales of the Mood and Anxiety Symptom Questionnaire (46).

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Table 2.

Results of zero-inflated Poisson regression models with interaction terms, with substance use (SU) predicted by anxiety symptoms, previous use at age 16, covariates of sex and recruitment status, and neural response to social exclusion in regions of interest (ROI).

Model	*β*	*SE*	*z*	95% Confidence Intervals	*P* value
Anxiety symptoms × dACC					
Count model (poisson with log link)					
Sex	−.07	.16	−0.44	−.38, .24	.66
Age 16 substance use	.19**	.06	3.06	.05, .21	.002
Anxiety	.03	.08	.34	−.02, .01	.74
Recruitment status	.03	.20	.17	−.35, .42	.80
dACC	.04	.07	.50	.09, 3.49	.62
Anxiety × dACC	−.16*	.07	−2.30	−.19, −.01	.021
Zero-inflated model (binomial with logit link)					
Sex	−.66	.72	−.92	−2.07, .75	.36
Age 16 substance use	−19.62	98.01	−.07	−7.39, 7.83	.81
Anxiety	−.10	.38	−.21	−.10, .06	.80
Recruitment status	−.53	.73	−.73	−1.96, .90	.47
dACC	−.17	.36	−.49	−2.47, 3.55	.63
Anxiety × dACC	−.53	.49	−1.09	−.90, .25	.21
Anxiety symptoms × sgACC					
Count model (poisson with log link)					
Sex	.00	.16	.02	−.31, .32	.91
Age 16 substance use	.19**	.06	2.96	.04, .21	.003
Anxiety	.01	.08	.09	−.02, .02	.89
Recruitment status	.08	.20	.39	−.32, .44	.69
sgACC	−.02	.07	.09	−.66, 1.77	.78
Anxiety × sgACC	−.08	.07	−1.22	−.11, .02	.22
Zero-inflated model (binomial with logit link)					
Sex	−.40	.68	−.59	−1.73, .93	.55
Age 16 substance use	−19.53	98.22	−.07	−18.90, 1.65	.64
Anxiety	−.08	.37	−.22	−.08, .06	.79
Recruitment status	−1.08	.78	−1.39	−2.59, .44	.16
sgACC	.34	.31	1.07	−4.07, 2.37	.28
Anxiety × sgACC	−.06	.34	−.17	−.36, .30	.71
Anxiety symptoms × AI					
Count model (poisson with log link)					
Sex	−.09	.17	−.51	−.41, .24	.60
Age 16 substance use	.18**	.07	2.72	.03, .21	.006
Anxiety	.02	.08	.15	−.02, .01	.71
Recruitment status	.01	.20	.03	−.39, .40	.61

Model	β	SE	z	95% Confidence Intervals	P value
AI	.08	.07	.97	−.30, 4.1	.30
Anxiety × AI	−.14	.09	−1.59	−.22, .02	.11
Zero-inflated model (binomial with logit link)					
Sex	.81	.73	−1.10	−2.25, .63	.27
Age 16 substance use	.18**	.07	2.72	−6.13, 5.84	.81
Anxiety	−.20	.40	−.50	−.14, .04	.62
Recruitment status	−.59	.73	−.81	−2.03, .85	.42
AI	.03	.37	.08	−1.76, 2.17	.80
Anxiety × AI	−.80†	.45	−1.77	−1.19, .06	.077

Note: $N = 181$.

† $p < .10$,

* $p < .05$, and

** $p < .01$.

Anxiety symptoms = sum score of Screen for Child Anxiety Related Emotional Disorders (SCARED; range 0–42). dACC = dorsal anterior cingulate cortex; sgACC = subgenual anterior cingulate cortex. Contrast in regions of interest (ROIs) are activation to Exclusion > Inclusion. Substance use is composite with sum of alcohol and marijuana in past 3 months. Sex is coded as female = 0 ($N = 86$), male = 1 ($N = 95$). Recruitment status is coded as low = 0 ($N = 52$), and elevated = 1 ($N = 129$), and represents the risk of depression based on self-reported symptoms in 9th grade (age 14–15 years) from the computerized Diagnostic Interview Schedule for Children-IV (DISC-IV) (45), and General Distress and Anhedonic Depression subscales of the Mood and Anxiety Symptom Questionnaire (46).

Analyses were replicated with data from the computerized NIMH Diagnostic Interview Schedule for Children (C-DISC) (46), for Generalized Anxiety Disorder (GAD) symptoms. Patterns were similar between DISC and SCARED data, including a significant interaction with activity in the dACC.

Table 3.

Results of zero-inflated Poisson regression models with interaction terms, with substance use (SU) predicted by anxiety symptoms, previous use at age 16, covariates of sex and recruitment status, and self-reported distress from the Need-Threat Scale.

Model	*β*	*SE*	*z*	95% Confidence Intervals	*P* value
Distress × Anxiety symptoms					
Count model (poisson with log link)					
Sex	.04	.16	.28	−.26, .35	.78
Age 16 substance use	.17*	.06	2.79	.05, .29	.01
Recruitment status	.10	.20	.47	−.30, .50	.64
Anxiety	−.05	.08	−.66	−.20, .10	.51
Distress	.12	.07	1.66	−.02, .26	.10
Anxiety × Distress	.06	.08	.77	−.09, .21	.44
Zero-inflated model (binomial with logit link)					
Sex	−.67	.66	−1.01	−1.97, .63	.31
Age 16 substance use	−14.66	7.73	−.19	−16.50, 13.50	.85
Recruitment status	−.66	.69	−.96	−2.01, .69	.34
Anxiety	−.11	.37	−.28	−.84, .63	.78
Distress	−.12	.32	−.39	−.76, .51	.70
Anxiety × Distress	.37	.35	1.06	−.31, 1.04	.29
Distress × dACC					
Count model (poisson with log link)					
Sex	.03	.16	.18	−.29, .34	.86
Age 16 substance use	.20**	.06	3.14	.07, .32	.00
Recruitment status	.04	.20	.19	−.36, .43	.85
Anxiety	−.01	.08	−.19	−.16, .13	.85
Distress	.09	.08	1.19	−.06, .24	.23
dACC	.00	.08	−.03	−.15, .15	.98
Distress × dACC	−.17*	.08	−2.02	−.33, −.004	.04
Zero-inflated model (binomial with logit link)					
Sex	−.50	.69	−.71	−1.86, .87	.48
Age 16 substance use	−2.68	4.95	−.04	−9.91, 9.90	.97
Recruitment status	−.63	.71	−.88	−2.01, .76	.38
Anxiety	−.01	.37	−.04	−.73, .71	.97
Distress	−.14	.33	−.41	−.79, .51	.68
dACC	−.17	.34	−.48	−.84, .51	.63
Distress × dACC	−.19	.35	−.53	−.87, .50	.60
Distress × sgACC					
Count model (poisson with log link)					
Sex	.03	.16	.21	−.29, .35	.84
Age 16 substance use	.18*	.06	2.78	.05, .30	.01

Model	β	SE	z	95% Confidence Intervals	P value
Recruitment status	.02	.21	.07	−.39, .42	.94
Anxiety	.00	.08	.02	−.15, .16	.99
Distress	.08	.08	1.05	−.07, .23	.29
sgACC	.01	.07	.15	−.13, .15	.88
Distress × sgACC	−.12	.08	−1.54	−.28, .03	.12
Zero-inflated model (binomial with logit link)					
Sex	−.42	.69	−.61	−1.77, .92	.54
Age 16 substance use	−22.38	6.83	−.03	−13.61, 11.17	.97
Recruitment status	−1.15	.77	−1.51	−2.66, .354	.13
Anxiety	.01	.38	.02	−.73, .74	.98
Distress	−.25	.34	−.74	−.92, .42	.46
sgACC	.31	.32	.98	−.31, .94	.33
Distress × sgACC	−.20	.40	−.49	−.98, .59	.62
Distress × AI					
Count model (poisson with log link)					
Sex	.01	.17	.08	−.32, .34	.94
Age 16 substance use	.18*	.07	2.67	.05, .31	.01
Recruitment status	−.04	.21	−.22	−.45, .36	.83
Anxiety	−.01	.08	−.07	−.17, .16	.95
Distress	.11	.08	1.38	−.05, .27	.17
AI	.04	.08	.48	−.12, .20	.63
Distress × AI	−.13†	.07	−1.78	−.26, .0127	.08
Zero-inflated model (binomial with logit link)					
Sex	−.55	.69	−.80	−1.90, .80	.43
Age 16 substance use	−2.26	4.67	−.04	−9.35, 8.95	.97
Recruitment status	−.75	.68	−1.10	−2.09, .59	.27
Anxiety	−.07	.36	−.20	−.78, .64	.85
Distress	−.08	.33	−.25	−.72, .56	.80
AI	.02	.35	.06	−.67, .72	.95
Distress × AI	−.03	.31	−.11	−.65, .58	.91

Note: $N = 181$.

† $p < .10$,

* $p < .05$, and

** $p < .01$.

Anxiety symptoms = sum score of Screen for Child Anxiety Related Emotional Disorders (SCARED; range 0–42). dACC = dorsal anterior cingulate cortex; sgACC = subgenual anterior cingulate cortex. Contrast in regions of interest (ROIs) are activation to Exclusion > Inclusion. Substance use is composite with sum of alcohol and marijuana in past 3 months. Sex is coded as female = 0 ($N = 86$), male = 1 ($N = 95$). Recruitment status is coded as low = 0 ($N = 52$), and elevated = 1 ($N = 129$), and represents the risk of depression based on self-reported symptoms in 9th grade (age 14–15 years) from the computerized Diagnostic Interview Schedule for Children-IV (DISC-IV) (45), and General Distress and Anhedonic Depression subscales of the Mood and Anxiety Symptom Questionnaire (46).