Sex-Specific Vulnerability to Externalizing Problems: Sensitivity to Early Stress and Nucleus Accumbens Activation Over Adolescence

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ABSTRACT

BACKGROUND: Exposure and sensitivity to early-life stress (ELS) are related to increased risk for psychopathology in adolescence. While cross-sectional studies have reported blunted nucleus accumbens (NAcc) activation in the context of these associations, researchers have not yet assessed the effects of ELS on developmental trajectories of activation. We examined whether trajectories are affected by stress and the moderating role of biological sex in predicting vulnerability to symptoms of psychopathology.

METHODS: Adolescents (n = 173) completed 3 assessments at 2-year intervals across puberty (ages 9–18 years). At baseline, we assessed objective ELS and stress sensitivity using the Traumatic Events Screening Inventory for Children. At all time points, we assessed NAcc activation using the Monetary Incentive Delay task and externalizing, internalizing, and total problems using the Youth Self-Report. We examined correlations between NAcc trajectories (extracted using linear mixed-effects models) with ELS and stress sensitivity and conducted multivariate regression analysis to examine the interaction of NAcc trajectories and biological sex in predicting symptoms of psychopathology.

RESULTS: Symptoms increased over adolescence. Stress sensitivity, but not objective ELS, was associated with decreasing trajectories of NAcc activation. Biological sex interacted with NAcc trajectories to predict psychopathology; boys, but not girls, with decreasing NAcc activation had more severe externalizing problems in adolescence. These findings were replicated in the putamen and caudate but not in the medial prefrontal cortex or control brain regions.

CONCLUSIONS: NAcc activation may be a sex-specific marker of externalizing problems in adolescence. Efforts to reduce stress sensitivity may help to decrease symptoms of psychopathology in adolescent boys.

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Early-life stress (ELS) is alarmingly prevalent (1,2). Nearly 40% of children in the United States have a Child Protective Services investigation prior to age 18 (3), and over 13% of children have confirmed maltreatment (4). These cases reflect more severe forms of ELS such as abuse or neglect; far more children experience moderate levels of ELS, such as being bullied, experiencing financial strain, or moving. Importantly, however, not all children respond similarly to stressors in their environment.

Objectively assessed ELS affects a range of domains including physical health (2) and cognitive performance (5) and is associated with various forms of psychopathology (6,7). Stress sensitivity, the tendency to have an outsized subjective response to stressors, has also been linked to psychopathology (6,9). Importantly, girls tend to be more reactive to stressors in their environment than boys (10). Furthermore, whereas girls are more likely to develop internalizing problems such as depression and anxiety, boys are more likely to experience externalizing problems such as disruptive behavioral disorders (11).

ELS has also been found to alter reward processing during adolescence. The brain region that is associated most strongly with reward processing is the nucleus accumbens (NAcc) (12). Perhaps not surprisingly, therefore, researchers have documented associations between ELS and alterations in NAcc activation during adolescence. Numerous cross-sectional studies have reported anomalous NAcc activation during reward tasks in participants who have experienced ELS (13). For example, Mehta et al. (14) found that previously institutionalized adolescents had blunted NAcc activation during the anticipation of reward versus the anticipation of nonreward. Furthermore, activation in the NAcc was blunted in adolescents, but not in children, who had experienced more severe ELS (15). Adults who experienced more severe ELS have also been found to have decreased activation in the NAcc (16,17). Notably, additional factors such as prenatal exposure to nicotine (18) are also associated with blunted NAcc activation, and the summarized literature is not experimental. Therefore, while these studies provide a contextual framework for how ELS may affect the brain and symptoms of psychopathology, they do not imply causality. Although Ho et al. (9) found that greater stress sensitivity was related to poorer white matter coherence in the right frontal uncinate fasciculus in
adolescents, no study has yet examined the relationship between stress sensitivity and brain function.

Several investigators have linked alterations in reward circuitry to psychopathology in adolescence. For example, Goff et al. (15) reported that decreased NAcc activation was associated with more severe symptoms of depression. Similarly, Hanson et al. (19) reported that the relationship between emotional neglect and depressive symptoms was partially mediated by decreased activation in the ventral striatum in adolescents. There have also been equivocal findings in this area. Whereas Hawes et al. (20) found that children with disruptive behavioral disorders had blunted NAcc activation, Bjork et al. (21) found that adolescents with externalizing disorders had greater NAcc activation than healthy control participants. Yau et al. (22) reported that in children with a parent with alcoholism, but not in control participants, NAcc activation was positively related to externalizing problems. Finally, using data from the Adolescent Brain Cognitive Development (ABCD) Study, Schettini et al. (23) found that boys with smaller right NAcc volumes had more externalizing problems.

It is important to note that almost all these studies are cross-sectional. Few researchers have conducted repeated assessments of neural activation, and even fewer have described trajectories of NAcc activation in adolescents (see Table S1 for a list of the design and contrasts for each study). Thus, it is possible that alterations in reward circuit activation precede the onset of psychopathology. For example, high-risk youths have been found to have decreased activation in the reward response compared with control participants (24,25), although researchers have not yet elucidated the timing and developmental course of these effects. The current study was designed, in part, to address this issue.

Adolescence is characterized by protracted brain development in the striatum and by an increase in symptoms of psychopathology, both of which have been linked to exposure to ELS. We hypothesized that participants who experienced more severe objective ELS and exhibited greater stress sensitivity would have attenuated NAcc activation across adolescence, which in turn would increase their risk for symptoms of psychopathology. We also examined whether biological sex and NAcc activation interact to predict subsequent internalizing and externalizing problems. Importantly, other brain regions have been implicated in ELS and in psychopathology. Therefore, we also analyzed activation in the putamen, caudate, and medial prefrontal cortex (mPFC) in addition to control regions.

### METHODS AND MATERIALS

#### Participants and Procedure

A total of 225 adolescents from the San Francisco Bay Area participated in a longitudinal study assessing the effects of ELS on psychobiological development. At time 1, participants were between ages 9 and 13 years, and boys and girls were matched on pubertal status (therefore, boys were older than girls on average at all assessments) (Table 1). Participants returned for a second (time 2) and third (time 3) follow-up assessment at approximately 2-year intervals (Figure 1). At all 3 time points, parents or legal guardians provided written consent and children provided verbal assent to participate in the study. The Stanford Institutional Review Board approved all study procedures.

The current study included participants who completed the ELS interview, underwent functional magnetic resonance imaging (fMRI), and self-reported symptoms of psychopathology. For more information regarding exclusion criterion for the study and fMRI data, see Recruitment and Exclusion Criterion in the Supplement. Our core analysis strategy—longitudinal mixed-effects modeling using maximum likelihood estimation—allowed us to fully utilize all available data (173 participants who completed at least 1 time point).

#### Table 1. Characteristics of the Sample by Biological Sex

<table>
<thead>
<tr>
<th>Variable</th>
<th>Boys, n = 70</th>
<th>Girls, n = 103</th>
<th>Statistic, p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian/Asian American</td>
<td>7 (10.0%)</td>
<td>14 (13.6%)</td>
<td>$\chi^2_{1}=3.40$, p = .638</td>
</tr>
<tr>
<td>Biracial</td>
<td>17 (24.3%)</td>
<td>18 (17.5%)</td>
<td></td>
</tr>
<tr>
<td>Black/African American</td>
<td>6 (8.6%)</td>
<td>5 (4.9%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latin-X</td>
<td>4 (5.7%)</td>
<td>10 (9.7%)</td>
<td></td>
</tr>
<tr>
<td>Other Race</td>
<td>5 (7.1%)</td>
<td>6 (5.8%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>31 (44.3%)</td>
<td>50 (48.5%)</td>
<td></td>
</tr>
<tr>
<td>Pubertal Status Time 1</td>
<td>1.94 (0.70)</td>
<td>2.08 (0.80)</td>
<td>$t_{71}=-1.14$, p = .256</td>
</tr>
<tr>
<td>Income-to-Needs Ratio Time 1</td>
<td>1.30 (0.53)</td>
<td>1.26 (0.57)</td>
<td>$t_{149}=0.52$, p = .602</td>
</tr>
<tr>
<td>Objective Early-Life Stress</td>
<td>6.98 (4.65)</td>
<td>6.26 (5.08)</td>
<td>$t_{171}=0.94$, p = .348</td>
</tr>
<tr>
<td>Stress Sensitivity</td>
<td>-0.17 (0.62)</td>
<td>0.04 (0.51)</td>
<td>$t_{171}=-2.41$, p = .017</td>
</tr>
<tr>
<td>Age at Time 1, Years</td>
<td>11.88 (0.93)</td>
<td>11.18 (1.06)</td>
<td>$t_{139}=3.82$, p &lt; .001</td>
</tr>
<tr>
<td>Age at Time 2, Years</td>
<td>13.76 (1.04)</td>
<td>13.10 (1.19)</td>
<td>$t_{171}=2.91$, p = .004</td>
</tr>
<tr>
<td>Age at Time 3, Years</td>
<td>15.81 (0.99)</td>
<td>15.32 (1.17)</td>
<td>$t_{100}=2.59$, p = .011</td>
</tr>
<tr>
<td>Total Problems at Time 1</td>
<td>36.51 (21.30)</td>
<td>37.29 (22.89)</td>
<td>$t_{171}=0.35$, p = .723</td>
</tr>
<tr>
<td>Internalizing at Time 3</td>
<td>10.79 (7.32)</td>
<td>17.32 (9.51)</td>
<td>$t_{132}=-4.32$, p &lt; .001</td>
</tr>
<tr>
<td>Externalizing at Time 3</td>
<td>11.14 (6.95)</td>
<td>11.57 (8.07)</td>
<td>$t_{132}=-0.32$, p = .747</td>
</tr>
</tbody>
</table>

Values are presented as n (%) or mean (SD).
Nucleus Accumbens Activation and Externalizing Problems

**Figure 1.** Distribution of age across time points. Each row is a different participant. Red dots are time 1, green dots are time 2, blue dots are time 3. The top section shows participants with usable scan data at 1 time point followed by those who had 2 and 3 usable scans, respectively.

For descriptions of the assessment of income-to-needs ratio and pubertal staging, see Income-to-Needs Ratio and Pubertal Assessment in the Supplement.

**ELS Assessment**

We administered the Traumatic Events Screening Inventory for Children (26) at baseline, obtaining information about 30 different stressors in childhood in addition to an open-ended question. If a stressor was endorsed, participants reported their subjective severity rating indicating how scared they felt at the time of the stressor. Coders who were blinded to the interview determined the objective severity of each event using a modified version of the UCLA Life Stress Interview coding system (27). Agreement among coders was high (intraclass correlation coefficient [ICC] = 0.99) (28). The severity of ELS was calculated based on the sum of the maximum score of each type of stressor reported so as to not give too much weight to the scores of participants who reported many events. The prevalence of objective ELS in our sample is presented in Table S2.

Stress sensitivity was calculated by residualizing a child’s cumulative subjective stress severity score from the panel’s cumulative objective stress severity score (i.e., variance in subjective ratings after regressing out objective ratings). Negative values indicate low stress sensitivity or a reduced stress response; positive values indicate high stress sensitivity or a heightened stress response (9).

**Youth Self-Report**

Participants completed the Youth Self-Report (YSR) (29). This 112-item questionnaire indexes the severity of problems experienced over the last 6 months measured on a 3-point scale (0, not true; 2, very true or often true). These items yield total raw scores for internalizing, externalizing, and total problems (see Figure S1 for the distribution of scores across time points). Internalizing problems are calculated by summing the anxious/depressed, somatic complaints, and withdrawn subscales. Externalizing problems are calculated by summing the aggressive behavior and rule-breaking behavior subscales.

**MRI Scan Acquisition**

Scanning sequences were acquired using a 3T MRI scanner (Discovery MR750 scanner; GE Healthcare) equipped with a 32-channel head coil (Nova Medical). See MRI Scan Acquisition in the Supplement for information about the acquisition parameters and see Scanner Upgrade/COVID-19 Status in the Supplement for information about controlling for COVID-19 data collection status and the scanner upgrade, hereby referred to as collection status.

**Monetary Incentive Delay Task**

Children completed a child-friendly version of the Monetary Incentive Delay (KIDMID) task at each time point. The rewarding stimulus (typically monetary) was replaced with points redeemed for prizes (Figure S2) (30). Monetary tasks have reliably been found to recruit the NAcc during reward in children, adolescents, and adults (30,31). The KIDMID task consists of 72 pseudorandomized 6-second trials (locked to 3-volume acquisitions). Participants viewed an incentive cue, anticipated the incentive, responded to the target, and viewed the trial outcome (±5; ±0). For information regarding the procedure, missed trials, reaction time, and performance, see KIDMID Procedure and Performance on the KIDMID task in the Supplement (Table S3).

We examined the bilateral NAcc to probe reward circuitry. We used an 8-mm sphere; the center coordinates are based on Wu et al. (32). We converted the center coordinates from Talairach space to Montreal Neurological Institute space using the icm2mni function (https://www.brainmap.org/icbm2tal/). The NAcc coordinates (x = ±12, y = 12, z = −7) are from a meta-analysis of 27 studies of reward anticipation (31). We assessed activation in 3 additional reward regions spanning the striatum and prefrontal cortex (putamen, caudate, and mPFC) and 6 control regions spanning parietal, default mode, and visual areas (angular gyrus, cingulate gyrus [posterior division], occipital fusiform gyrus, occipital pole, and inferior frontal gyrus opercularis and triangularis) to examine the specificity of our findings to NAcc activation (see Reward-Related ROIs and Control Regions in the Supplement) (Figures S6 and S7).

**Preprocessing**

We preprocessed the functional images using fMRIPrep version 20.2.1 (33). fMRIPrep aligns anatomical and functional images, resamples functional data into the desired template space, applies slice-timing correction, identifies motion outliers, and derives regressors such as white matter and cerebrospinal fluid. Details regarding the preprocessing are discussed in Preprocessing in the Supplement. We conducted additional standard preprocessing steps using AFNI version 18.2.04 (34), presented in AFNI Preprocessing in the Supplement. Then, we extracted percent signal change for the NAcc by calculating the mean signal across the whole task and then subtracting the mean from the activation at each volume acquisition (or repetition time) and dividing by the mean signal to derive a continuous measure of percent signal change.
Statistical Analyses

Sample Characteristics. All analyses were conducted using R version 4.0.2. First, we characterized the sample in terms of demographic and clinical variables, examining biological sex differences in our measures of interest.

Time Course and Whole-Brain Analysis. We analyzed the time course data across hit and missed trials (Figure S3) and conducted whole-brain analysis at each time point (see Whole-Brain Analysis in the Supplement and Figure S4) to ensure that the KIDMID task recruited the NAcc.

Stability of NAcc Activation. We tested the stability (reliability) of neural activation in the NAcc over the 4-year period in both conditions and contrasts using ICC (calculated based on 2-way mixed-model; 3,j) (35). We conducted a series of linear mixed-effects models and extracted each individual’s estimated intercept and slope (referred to as the trajectory) of NAcc activation and of internalizing and externalizing problems across adolescence. We winsorized estimated neural trajectories to minimize the impact of extreme cases (see Sensitivity Analysis: Non-Winsorized Values in the Supplement). All analyses controlled for collection status, and we applied the Bonferroni correction to account for multiple comparisons (adjusted p value = .017). The models used for the primary analyses are presented in Equations in the Supplement.

Primary Analysis. First, we examined whether greater objective ELS and stress sensitivity predicted decreasing NAcc trajectories. Next, we assessed the main effect and interaction between NAcc trajectories and biological sex in predicting symptoms of psychopathology. Finally, we examined whether greater objective ELS and stress sensitivity predicted more severe internalizing and externalizing problems in adolescence. In the presence of a significant main effect or interaction, we conducted post hoc analyses to determine whether findings were specific to internalizing or externalizing problems. In the presence of a significant interaction involving biological sex, we conducted a follow-up simple slope analysis to examine whether the findings were significant in boys and/or girls. A schematic with our primary statistical framing and findings is presented in the Supplement (Figure S5).

Supplemental Analysis. To ensure that our findings were insensitive to modeling decisions, we conducted sensitivity analyses 1) examining raw psychopathology and T scores at time 3 (see Sensitivity Analysis: Time 3 YSR Data in the Supplement), 2) using nonwinsorized NAcc values (see Sensitivity Analysis: Non-Winsorized Values in the Supplement), and 3) examining only the 63 participants with usable data at all 3 time points (see Sensitivity Analysis: Missing at Random in the Supplement). In exploratory analyses, we examined whether objective ELS and stress sensitivity were related to the NAcc intercept and whether NAcc trajectories interacted with biological sex to predict trajectories of internalizing or externalizing problems.

Finally, to examine the specificity of activation to the NAcc, we examined activations in 3 additional reward-related regions (putamen, caudate, mPFC) and 6 control regions (angular gyrus, cingulate gyrus [posterior division], occipital fusiform gyrus, the occipital pole, and inferior frontal gyrus opercularis and triangularis).

RESULTS

Sample Characteristics

Demographic characteristics and sample means are presented in Table 1. The sample is representative of the broader San Francisco Bay Area population (i.e., racially and ethnically diverse, high income). Information about handedness, distributions of the YSR (Figure S1), and relations of objective ELS and stress sensitivity with demographic variables is presented in Demographics and Stress Variables in the Supplement.

Time Course and Whole-Brain Analysis

Across all trials, time course analyses revealed that there was greater activation in the NAcc during the anticipation of reward than during the anticipation of nonreward (time 1: t_{145} = 5.64, p < .001; time 2: t_{122} = 10.01, p < .001; time 3: t_{106} = 8.32, p < .001) (Figure S3). Across hit trials, there was greater activation in the NAcc during the receipt of reward than the receipt of nonreward (time 1: t_{145} = 3.73, p < .001; time 2: t_{122} = 3.12, p = .002; time 3: t_{106} = 2.73, p = .007) (Figure S3). The whole-brain analysis displaying activation in the NAcc during the KIDMID task at each time point is presented in Figure S4.

Stability of NAcc Activation

Across all trials, the anticipation of reward versus anticipation of nonreward contrast had an ICC value of 0.32 in the NAcc. This value is weak to modest but suggests shared variance in signal over time (see Discussion for a more nuanced review of relevant issues). However, there was very poor reliability of the receipt of reward versus receipt of nonreward contrast (ICC = 0.08) across all trials (and 0.04 across hit/correct trials). These values for anticipation are consistent with ICC values that have been reported in other longitudinal fMRI studies (36,37) and are higher than those in the ABCD dataset, which has an explicit objective of modeling longitudinal brain activation (38). Given our interest in the longitudinal development of reward circuitry (focus on shared variance across development), we examined the anticipation of reward versus anticipation of nonreward contrast in all subsequent analyses.

Development of Psychopathology and NAcc Activation

When controlling for collection status and biological sex, internalizing (β = 0.11, p = .025) and externalizing (β = 0.12, p = .014) problems increased across adolescence. Furthermore, there was a main effect of biological sex on internalizing problems such that girls had more severe problems than boys (β = 0.30, p = .014). Internalizing and externalizing problems in adolescence were significantly correlated in both boys (r = 0.62, p < .001) and girls (r = 0.68, p < .001). NAcc activation during the anticipation of reward versus the anticipation of nonreward did not increase significantly across adolescence (β = 0.11, p = .054).

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All analyses were conducted using R version 4.0.2. First, we characterized the sample in terms of demographic and clinical variables, examining biological sex differences in our measures of interest.

Time Course and Whole-Brain Analysis. We analyzed the time course data across hit and missed trials (Figure S3) and conducted whole-brain analysis at each time point (see Whole-Brain Analysis in the Supplement and Figure S4) to ensure that the KIDMID task recruited the NAcc.

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Finally, to examine the specificity of activation to the NAcc, we examined activations in 3 additional reward-related regions (putamen, caudate, mPFC) and 6 control regions (angular gyrus, cingulate gyrus [posterior division], occipital fusiform gyrus, the occipital pole, and inferior frontal gyrus opercularis and triangularis).
Stress, NAcc Trajectories, Biological Sex, and Psychopathology

Greater stress sensitivity ($\beta = -0.15$, $p = .043$), but not objective ELS ($\beta = 0.09$, $p = .258$), predicted decreasing NAcc trajectories. There was a significant interaction of biological sex and NAcc trajectories in predicting psychopathology ($\beta = 0.10$, $p < .001$) even after controlling for baseline total problems. The interaction was significant for externalizing ($\beta = 0.43$, $p = .002$), but not for internalizing ($\beta = -0.08$, $p = .528$), problems. Follow-up simple slope analysis indicated that boys ($\beta = -0.28$, $p < .001$), but not girls ($\beta = 0.12$, $p = .210$), with decreasing NAcc trajectories had greater externalizing problems in adolescence (Figure 2). Finally, objective ELS ($\beta = 0.06$, $p = .008$) and stress sensitivity ($\beta = 0.05$, $p = .019$) predicted more severe symptoms of psychopathology. Specifically, objective ELS predicted internalizing ($\beta = 0.23$, $p = .002$) and externalizing ($\beta = 0.18$, $p = .016$) problems, whereas stress sensitivity only predicted internalizing problems ($\beta = 0.18$, $p = .014$; externalizing: $\beta = 0.04$, $p = .834$). Consistent with the MacArthur framework, we did not test for mediation given that there was no significant association between stress sensitivity and externalizing problems in adolescence (39).

Supplemental Analysis

We obtained a similar pattern of findings when using raw and T scores from time 3 (see Sensitivity Analysis: Time 3 YSR Data in the Supplement) and nonwinsorized values (see Sensitivity Analysis: Non-Winsorized Values in the Supplement). We also reran our primary analyses including only participants with usable data across all 3 time points (who did not differ on demographic, clinical, or neural measures at baseline) (see Attrition in the Supplement) and obtained a similar pattern of results (see Sensitivity Analysis: Missing at Random in the Supplement), suggesting that our results were insensitive to the missing data assumption: missing at random (40).

Exploratory analyses examining the NAcc intercept and trajectories of psychopathology are presented in Exploratory Analyses in the Supplement.

We obtained a similar pattern of findings in the putamen and caudate as we observed in the NAcc. Specifically, trajectories of activation in these regions were related to stress sensitivity, and decreasing activation predicted more externalizing problems in boys (see Reward-Related ROIs in the Supplement). Trajectories of activation across the NAcc, putamen, caudate, and mPFC during the anticipation of reward versus anticipation of nonreward were correlated ($rs = 0.17–0.87$ except for the mPFC and caudate ($r = 0.12, p = .121$). Importantly, we did not observe a similar pattern of findings in the mPFC or control brain regions (see Reward-Related ROIs and Control Regions in the Supplement), underscoring the specificity of our findings concerning stress sensitivity, biological sex, and externalizing problems to activation in the striatum.

DISCUSSION

ELS has been found to be related to alterations in reward circuitry and an increased risk for developing psychopathology. Here, we built on previous research by conducting and analyzing data from repeated assessments over adolescence and by examining both objectively assessed ELS and participants’ sensitivity to stress. In a series of longitudinal analyses, we found that internalizing and externalizing problems increased across adolescence. Furthermore, we found that stress sensitivity, but not objectively assessed ELS, was associated with a higher NAcc intercept and decreasing trajectories of NAcc activation over adolescence. Finally, adolescent boys, but not girls, with decreasing NAcc activation exhibited more severe externalizing problems in adolescence. We found the same pattern of results in the putamen and caudate, highlighting the role of the striatum in stress sensitivity and risk for developing externalizing problems in adolescent boys.

Researchers have posited that ELS is characterized by blunted NAcc activation in adolescence (14,15); however, researchers have not examined longitudinal patterns of NAcc activation and the effects of stress sensitivity. Although our findings require replication, they provide important insights...
Nucleus Accumbens Activation and Externalizing Problems

Concerning NAcc activation and the development of psychopathology across development.

Investigators have posited that rates of maturation in adolescents are different in the striatum than they are in regions like the prefrontal cortex (41), possibly contributing to higher sensation seeking and impulsivity, and to diminished top-down control, in adolescence (42). In fact, whereas the prefrontal cortex is characterized by protracted brain development into adulthood (43), during adolescence there are increases in dopamine (41) and high levels of NAcc activation (44). Although speculative, the observed positive association between stress sensitivity and NAcc intercepts at age 9 may reflect stress acceleration, which makes it more difficult for children to control externalizing-related problems.

Our findings complement research showing that adolescents and adults with attention-deficit/hyperactivity disorder have blunted task-related NAcc activation (45–47). Our findings also extend findings reported by Hawes et al. (20) that adolescents with a sole diagnosis of disruptive behavioral disorders have more blunted NAcc activation than adolescents who also have callous-unemotional traits. We found that decreasing NAcc activation over adolescence, which may reflect insensitivity to reward, predicted the development of externalizing problems in boys. Relatedly, adolescents who were exposed to higher stress were less sensitive to reward in a decision-making task (48). If boys experience decreasing sensitivity to reward over adolescence, it may contribute to the increased impulsivity and sensation seeking that have been documented in adolescents with more severe externalizing problems (49) (see Hyperactivation in the NAcc in the Supplement).

Notably, our findings complement results reported by Hanson et al. (19) that blunted NAcc activation in a sample of children and adolescents mediated the relationship between emotional neglect and depressive symptoms. Because stress sensitivity was not related to externalizing problems in the current study, we did not conduct a mediation analysis; nevertheless, both studies highlight the importance of conducting longitudinal fMRI assessments, and both studies implicate blunted activation in reward regions as a risk factor for the development of subsequent psychopathology.

We also assessed the temporal stability of percent signal change in the NAcc during the KIDMID task. We found low stability of the anticipation of reward versus anticipation of nonreward contrast. Certainly, this is an important consideration in interpreting our findings, but we should note that our reliability coefficients are comparable to that reported by Braams et al. (44), who assessed NAcc activation in 8- to 27-year-old participants twice over 2 years. In fact, the ABDC dataset has lower stability than we do here (38). It is possible that in longitudinal fMRI studies, repeated administrations of the same task desensitizes participants to the stimuli (50), leading them to habituate to the stimuli over time. Notably, participants in our sample felt less excited toward our reward cue across time (see Post-Scan Questionnaires in the Supplement). Altering perceptual components may decrease habituation but introduce methodological challenges.

Low ICC values may reflect neurodevelopmental changes over time in our sample. The approximately 4-year interval spanned by our assessments encompasses a large portion of adolescence. Reward processing and, specifically, the striatum undergo profound changes during this period [e.g., (44)], which may contribute to the discrepancies in blood oxygen level-dependent signal across time points. Distinguishing the contribution of methodological difficulties from true developmental changes is a crucial task for longitudinal studies [see Herting et al. (51) for a review of test-retest reliability in longitudinal task-based fMRI]. For a more detailed discussion of ICC, see Neural Stability Considerations and Suggestions for Improving Stability in Longitudinal Neuroimaging Studies in the Supplement.

We should note some limitations of this study. First, we had a community sample that did not experience the most severe levels of ELS. Experiences of more severe abuse and neglect likely have stronger effects on psychopathology and neural activation; thus, assessing trajectories of reward circuitry in more severely maltreated youths is an important direction for future research. Second, we conducted a number of statistical tests; the relationship between stress sensitivity and the trajectory of NAcc activation was small and did not survive correction for multiple comparisons, thereby underscoring the need to examine these constructs in larger samples. In addition, despite our efforts to ensure a robust and reliable signal, the ICC value for the NAcc in our study was low, although this may, in part, reflect developmental changes. In addition, while we think that our study yields important insights concerning the impact of stress sensitivity on adolescent reward processing and symptomatology, our findings should nevertheless be interpreted with caution. Finally, we focused on the NAcc in this study. Although we conducted supplemental analyses examining the putamen, caudate, mPFC, and several control regions, future researchers with larger samples should examine the longitudinal effects of ELS and stress sensitivity on different brain networks.

Despite these limitations, our study has several significant strengths, including the longitudinal examination of trajectories of neural activation from childhood through adolescence, which allowed us to assess intraindividual variability and development more dynamically than is done by cross-sectional assessments and to analyze dimensionally both objectively assessed ELS and stress sensitivity. By indexing symptoms of psychopathology at younger ages, we hope to improve the identification of samples at risk for developing clinically significant symptoms at older ages. Early prevention efforts may alleviate the experience of stress across development.

Conclusions

Conclusions drawn from cross-sectional examinations of NAcc activation in adults speak to the adverse effects of ELS decades after exposure to the stressors. Conducting longitudinal fMRI assessments in adolescents promises to advance our understanding of neurodevelopment because we are capturing changes in activation while teens are still in a stressful environment or relatively shortly after exposure to the stressor. Most studies conducted to date have assessed associations of ELS with reward brain regions cross-sectionally; in contrast, we collected and analyzed neuroimaging and behavioral data from 3 time points, which allowed us to assess longitudinal relationships among ELS and stress sensitivity,
trjectories of reward-related brain activation, and symptoms of psychopathology. Our findings indicate that elucidating trajectories of reward circuitry over adolescence is important for understanding the development of externalizing problems, particularly in adolescent boys.

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ARTICLE INFORMATION

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