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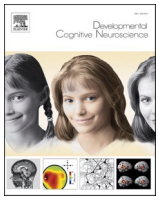

Childhood adversity is associated with reduced BOLD response in inhibitory control regions amongst preadolescents from the ABCD study

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ABSTRACT

Adolescence is characterized by dynamic neurodevelopment, which poses opportunities for risk and resilience. Adverse childhood experiences (ACEs) confer additional risk to the developing brain, where ACEs have been associated with alterations in functional magnetic resonance imaging (fMRI) BOLD signaling in brain regions underlying inhibitory control. Socioenvironmental factors like the family environment may amplify or buffer against the neurodevelopmental risks associated with ACEs. Using baseline to Year 2 follow-up data from the Adolescent Brain Cognitive Development (ABCD) Study, the current study examined how ACEs relate to fMRI BOLD signaling during successful inhibition on the Stop Signal Task in regions associated with inhibitory control and examined whether family conflict levels moderated that relationship. Results showed that greater ACEs were associated with reduced BOLD response in the right opercular region of the inferior frontal gyrus and bilaterally in the pre-supplementary motor area, which are key regions underlying inhibitory control. Further, greater BOLD response was correlated with less impulsivity behaviorally, suggesting reduced activation may not be behaviorally adaptive at this age. No significant two or three-way interactions with family conflict levels or time were found. Findings highlight the continued utility of examining the relationship between ACEs and neurodevelopmental outcomes and the importance of intervention/prevention of ACES.

Early adolescence is a sensitive period for neurodevelopment when the brain may be vulnerable to adversity such as chronic stress; however, neuroplasticity provides opportunity for resilience (O'Connor et al., 2021; Romeo and McEwen, 2006; Sisk and Gee, 2022). Understanding how forms of adversity, like adverse childhood experiences (ACEs), interact with socioenvironmental factors that amplify or mitigate risk to influence neurodevelopment is warranted to improve outcomes.

ACEs represent traumatic or stressful events such as abuse, extreme economic hardship, and family history of psychiatric disorders (Felitti et al., 1998;; Ports et al., 2020). ACEs can disrupt biological systems (Cooke et al., 2023; Soares et al., 2021) and are associated with poor health outcomes (e.g., development of psychopathology, chronic diseases; Green et al., 2010; McLaughlin et al., 2012; Toth and Cicchetti, 2013). Additional research is necessary to understand ACEs' impact on early adolescent neurocognitive development, where the intersection between developmental timing and stress may increase susceptibility.

One proposed mechanism linking ACEs to poor health outcomes is how chronic stress exposure disrupts hypothalamic–pituitary–adrenal (HPA) axis feedback (O'Connor et al., 2021). Pre-clinical models have shown that chronic stress leads to a blunted response in adult rodents (Harris et al., 2004; Helmreich et al., 1997; Magariños and McEwen, 1995; Martí and Armario, 1997). Compared to adults, adolescent rodents exposed to chronic stress demonstrate a prolonged stress response while also displaying faster recovery to baseline (Romeo et al., 2004; Romeo et al., 2006; Vázquez and Akil, 1993), positing a unique interaction between pubertal and HPA axis development. These findings suggest early adolescence is a sensitive period to stress exposure, which has implications for neurodevelopment (Danese and McEwen, 2012; McLaughlin et al., 2019; O'Connor et al., 2021).

The prefrontal cortex (PFC) undergoes substantial neurodevelopmental changes throughout adolescence (Casey et al., 2008) and supports higher-order, executive functioning that guides self-directed behaviors (Hofmann et al., 2012; Lezak et al., 2004). The PFC's prolonged development and high glucocorticoid receptor density may

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increase sensitivity to HPA axis dysregulation and ACEs (Lupien et al., 2009; McEwen et al., 2016; McEwen and Morrison, 2013; Romeo and McEwen, 2006). Chronic stress has been associated with the loss of dendrites and spines in the medial PFC (mPFC) in rodents (Radley et al., 2004, 2006); in humans, it has been linked with reduced structural volume in the mPFC, insula, and anterior cingulate cortex (ACC; Ansell et al., 2012), and weaker frontoparietal network connectivity in adults (Liston et al., 2009). In youth exposed to adversity, similar patterns of reduced structural volume and thickness have been found in prefrontal regions; however, the directionality of alterations in frontoparietal network connectivity is mixed and vary across adversity subtype (McLaughlin et al., 2019). The PFC's susceptibility to stress likely has downstream implications for executive functioning domains like inhibitory control (McEwen et al., 2016; McEwen and Morrison, 2013).

Inhibitory control is a multi-faceted construct characterized by successful suppression of a response to stimulus (Aron, 2007). One aspect of inhibitory control is response inhibition which is linked with brain regions including the inferior frontal gyrus (IFG; Aron et al., 2003; Aron et al., 2014; Swick et al., 2008), the dorsomedial prefrontal cortex (dmPFC; Garavan et al., 2002), and the ACC (Carter and Van Veen, 2007); although regions can vary based on the inhibitory control task (Littman and Takács, 2017). For the Stop Signal Task (SST), in which individuals must inhibit a prepotent response when a "stop" signal is presented, adults frequently recruited the dorsolateral prefrontal cortex (dlPFC), dorsal ACC (dACC), insula, and IFG (Zhang et al., 2017); similar regions are activated in youth (Chaarani et al., 2021; Whelan et al., 2012). Specifically, within the baseline Adolescent Brain Cognitive Development (ABCD) Study® sample (n= 5547, ages 9 and 10), cortical brain regions activated during successful inhibition on the SST include the IFG, dACC, and pre-supplementary motor area (pre-SMA) and deactivated regions included the somatosensory cortex, ventromedial PFC, and precuneus. These findings are consistent with SST activation patterns in a large sample of 14-year-old adolescents (N= 1846; Whelan et al., 2012) and in a subsample of healthy adolescent controls (n= 124, *M* age= 16.5 years; van Rooij et al., 2015). Across development, there are age-related differences in BOLD response during inhibitory control tasks such as the SST; however, directionality of activation patterns is region dependent and have been primarily examined in smaller, cross-sectional samples (Weiss and Luciana, 2022). Current findings suggest that during successful inhibition on the SST, healthy adolescents (n=9, ages 12–19, *M* age= 15.7; Rubia et al., 2000) show reduced activity in the left middle and inferior frontal gyri and increased activity in the IFG compared to adults (Rubia et al., 2000), while other samples show age-related decreases in late childhood/adolescent brain activity in the medial PFC and left dACC compared to adults (n= 27, ages 9–19, *M* age = 13.7; Cohen et al., 2010). Consistent with these findings, other studies have shown age-related increases in the inferior and middle PFC, and right ACC and decreases in the ventromedial PFC, right superior frontal lobe, and supplementary motor cortex (n= 31, ages 13–19; Rubia et al., 2013). Overall, findings suggest that adolescence is a key developmental period for refinement of inhibitory control neural activation.

During adolescence, performance on response inhibition tasks broadly improves across development, and some studies suggest these improvements extend into young adulthood (Weiss and Luciana, 2022). However, individuals with ACE history demonstrate poorer inhibitory control performance in addition to altered brain activation patterns (Johnson et al., 2021; Lund et al., 2020; Merz et al., 2013; van der Bij et al., 2020), suggesting a disruption in inhibitory control development. In studies using the SST (Hart et al., 2018; Lim et al., 2015; Mueller et al., 2010) adolescents and young adults with ACE history (N= 66, n=22 exposed to abuse; *M* age= 17.2 years; 37% female) demonstrated increased BOLD signal in dmPFC and ACC (Lim et al., 2015) and reduced fronto-cingulo-striatal network connectivity (Hart et al., 2018) during failed inhibition; no group differences were found during successful inhibition (Hart et al., 2018; Lim et al., 2015). In comparison, younger adolescents exposed to adversity (N= 33, n=12 with stress exposure; *M* age= 13.5, 58% female) showed increased BOLD signaling in the dACC, inferior PFC, and posterior insula during successful inhibition (Mueller et al., 2010). These studies included smaller, cross-sectional samples and were heterogenous in defining ACEs, limiting generalizability.

While adolescent neuroplasticity may increase vulnerability to environmental insults, this adaptability also provides an opportunity for resiliency (Sisk and Gee, 2022). Currently, little is known about what factors may amplify or protect against ACEs' effects on neurocognitive development. Aligned with the differential susceptibility model, individuals differ in their responsiveness to both positive and negative contexts (Belsky and Pluess, 2009a; Boyce, 2016; Boyce and Ellis, 2005) creating a risk and resilience continuum for neurodevelopmental outcomes (Belsky and Pluess, 2009b; Ellis et al., 2011). Therefore, youth with ACE history may show greater sensitivity to positive environmental inputs (Albott et al., 2018) suggesting opportunities for resiliency during adolescence (Colich et al., 2021; Sisk and Gee, 2022). The family environment has been shown to influence neurocognitive development within the context of stress (Bush et al., 2020). Aspects of the family environment such as increased family conflict have been identified as a mechanism for increased behavioral impulsivity (Gebru et al., 2023) and have linked impulsivity with increased risk-taking behaviors (Wang et al., 2021) during early adolescence. In comparison, supportive caregiving can reduce the impact of environmental stressors (Colich et al., 2021; Rudolph et al., 2020) and low socioeconomic status (Brody et al., 2019; Whittle et al., 2017) on prefrontal brain development, which broadly supports executive functioning development. Behaviorally, positive family environment (Schroeder and Kelley, 2009) and parenting behaviors (Valcan et al., 2018) are linked with greater inhibitory control in youth. Together, findings suggest that across the spectrum, the family environment can influence ACE-related neurodevelopmental risk. However, no studies—to our knowledge—have examined whether aspects of the family environment moderate the cumulative risk of ACEs on fMRI BOLD response in inhibitory control regions.

Therefore, the current study examined how ACEs relate to fMRI BOLD signaling in regions of interest (ROIs) underlying inhibitory control during successful inhibition on the SST in a three-year longitudinal design using the ABCD Study® sample. To assess potential factors that may alter ACE-related risk, additional analyses examined whether family conflict levels were a moderator. In addition to between-person effects, we also assessed whether the relationships between ACEs, family conflict, and BOLD response differed over time (i.e., from baseline to Year 2 follow-up). As follow-up, we conducted brain-behavior correlations between significantly predicted ROIs and behavioral measures of impulsivity to clarify directionality of findings. We predicted that individuals with greater ACEs would demonstrate reduced BOLD response, and this effect would be less pronounced in youth from families reporting less conflict. Further, we anticipated that reduced BOLD response would be correlated with greater behavioral impulsivity and poorer task performance.

1. Methods

1.1. Participants and design overview

Current study participants were part of the Adolescent Brain Cognitive Development (ABCD) Study® cohort of 11,876 children recruited in 2016 through 2018 at ages 9 or 10 years from 21 sites throughout the United States (Jernigan and Brown, 2018; Volkow et al., 2018). Recruitment occurred in a stratified probability sample of eligible schools to match the demographic profile (sex, race/ethnicity, socioeconomic status, urbanicity) of the American Community Survey enrollment statistics within catchment regions (Garavan et al., 2018). All study procedures were approved by the centralized University of California, San Diego Institutional Review Board. Parental consent and youth assent was collected at each study visit. At baseline and even year

follow-ups, caregiver and youth attended one to two sessions and completed a comprehensive battery of questionnaires and underwent brain magnetic resonance imaging (MRI) and cognitive testing. No imaging was completed at odd year follow-ups.

2. Measures

2.1. Demographic variables and covariates

Demographic variables including sex assigned at birth, race, and ethnicity were reported at the study baseline, and caregiver education attainment, household income, visit, and age were measured at each session (Barch et al., 2018). Of note, given the greater rates of ACEs in minoritized racial and ethnic groups within our sample (Stinson et al., 2021), we controlled for race and ethnicity in the present analyses. All demographic information was based on caregiver report. Caregivers completed the Child Behavior Checklist (CBCL), which measures youth psychopathology in the past 6 months (Achenbach, 2009); age-corrected T-scores for the internalizing symptom scale were utilized in the current analyses. Both youth and parents completed the Pubertal Development Scale at each time point (Petersen et al., 1988) to assess youth's pubertal stage; youth report was used in the present analyses.

2.2. Assessment of adverse childhood experiences from baseline (Y0) to 2-year (Y2)

ACE categories were defined based on measurements collected at the ABCD Study baseline (Y0), Year 1 (Y1), and Year 2 (Y2) follow-up visits (Barch et al., 2018; Gonzalez et al., 2021; Hoffman et al., 2019; Karcher et al., 2020; Lisdahl et al., 2018; Zucker et al., 2018). Cumulative ACE risk scores were coded (Stinson et al., 2021) based on caregiver and youth reports of events from an ACE category (e.g., emotional abuse, physical neglect; Evans et al., 2013). For some ACE categories (e.g., household substance use), information was incorporated across multiple surveys. See Table 1 for administration timeline of included measures. ACE categories included emotional, physical, and sexual abuse, household substance use, mental illness in household, parental separation/divorce, family member involvement with legal system, emotional and physical neglect, extreme financial adversity, racial discrimination, bullying, domestic violence, grief, community violence, natural disaster, witnessing death or destruction in a war zone, witnessing or being present during an act of terrorism, car accident, or other significant accident requiring medical attention. More detailed information about ACEs coding has been outlined elsewhere (Stinson et al., 2021).

Table 1
Administration Timeline of Measurements Utilized to Code Cumulative ACE Risk Score.

	Timepoint		
Measure	Y0	Y1	Y2
Kiddie Structured Assessment of Affective Disorders and Schizophrenia (K-SADS)	X	X	X
Parental Monitoring Scale (PMS)	X	X	X
Child Report of Parent Behaviors Inventory (CRPBI)	X	X	
Family History Assessment Module Screener (FHAMS)	X		
Adult Self Report (ASR)	X		X
Adverse Life Events Scale (ALE)		X	X
PhenX Demographic Survey	X	X	X
Perceived Discrimination Scale		X	X

Notes. Y0 represents baseline assessment and Y1–2 represents Year 1 and 2 follow-up assessments.

2.3. Measurements utilized to code cumulative ACE risk score

2.3.1. Kiddie structured assessment of affective disorders and schizophrenia (K-SADS)

A primary measurement of ACEs was based on caregiver report on the computerized version of K-SADS for DSM-5 post-traumatic stress disorder (Kobak et al., 2013). This measure asked about their child's lifetime experience for the following events: emotional, physical, and sexual abuse; domestic violence; community violence; traumatic grief; natural disaster; fire; experience of war zone or terrorism; car accident or other significant accident. Youth's experience of bullying was reported on the K-SADS background survey also completed by caregivers.

2.3.2. Parental monitoring scale (PMS)

The PMS measured youth's perspectives on parental awareness of whereabouts and involvement in the youth's daily activities (Karoly et al., 2016). The PMS was used as a proxy to assess for physical neglect.

2.3.3. Child report of parent behaviors inventory (CRPBI)

The CRPBI assessed youth's assessment of caregiver(s) warmth and comforting behaviors and served as a proxy measurement of emotional neglect. (Schaefer, 1965; Barber, 1997).

2.3.4. Family history assessment module screener (FHAMS)

The Family History Assessment Module Screener (FHAMS) measured caregiver report of psychopathology in first and second-degree relatives of the youth (Brown et al., 2015; Rice et al., 1995). Report of first-degree relatives (i.e., either parent or full or half siblings) experiencing mental health or substance use disorders fulfilled criteria for mental illness or substance use in the household categories, respectively.

2.3.5. Adult self report (ASR)

The ASR measured parental self-report of psychopathology in the last 6 months (Achenbach, 2009). In addition to the FHAMS, the ASR was used as a source to fulfill the ACE categories of mental illness or substance use in the household.

2.3.6. Adverse life events scale (ALE)

The ALE assessed parent and youth report of youth's exposure to various traumatic experiences (Grant et al., 2004; Tiet et al., 2001). Information provided on this scale contributed to the following ACE categories: household substance use and mental illness, parental separation or divorce, and family member involvement in the criminal justice system. Either parent or youth report of these events contributed to the ACE risk score for these categories.

2.3.7. PhenX demographic survey

The Demographic survey assessed parent report of family background information (Stover et al., 2010). Information for both parental separation or divorce and financial adversity was drawn from this survey for ACE categories. For financial adversity, this survey assessed experiences of being unable to afford food, inability to fully pay rent/-mortgage, eviction, power utilities turned off, or inability to access healthcare due to affordability in the last year (Diemer et al., 2013).

2.3.8. Perceived discrimination scale

The Perceived Discrimination scale integrated questions from the 2006 Boston Youth Survey (Garnett et al., 2014) and Measure of Perceived Discrimination (Phinney et al., 1998) and was used to assess youth-report of experiences of discrimination based on multiple identities. Of note, only questions regarding discrimination related to racial or ethnic background were included in the current study.

2.4. Assessment of family environment

2.4.1. Family environment scale (FES)

An adapted form of the FES 54-item scale (from PhenX Toolkit; Moos and Moos, 1976) was used to assess family dynamics on 6 subdomains: conflict, cohesion, activity-recreational and intellectual-cultural orientation, expressiveness, and organization. Beginning at Y2, all 6 FES subscales were administered to caregivers, but only the conflict subscale was administered at Y0. For the current study, only the conflict subscale was included. The conflict subscale measured one dimension of family connectedness, where conflict relates to family disagreements with statements like "We fight a lot in our family" or "Family members rarely become openly angry." Responses were dichotomized, and greater scores reflected greater family conflict. Significant differences between caregiver and youth report were found in the ABCD Study, with youth reporting less conflict (Gonzalez et al., 2021). From Y0 to Y2, caregiver scores demonstrated greater ability to differentiate between families with varying levels of risk within the ABCD sample (Gonzalez et al., 2021). Due to these differences, caregiver report of family conflict at Y0 and Y2 visits were used in the current analyses. While the conflict subscale showed small effect sizes, it had one of the largest effect sizes within the culture and environment battery suggesting its strength in assessing familial relationships in this sample (Gonzalez et al., 2021).

2.5. Impulsivity behavioral outcomes

2.5.1. Modified UPPS-P impulsive behavior scale- short form (UPPS-P)

The modified UPPS-P is a 20-item measure adapted from the full UPPS-P (Cyders et al., 2007) and adult UPPS-P short form (Lynam, 2013) that captured four aspects of impulsivity: positive and negative urgency, lack of premeditation, lack of perseverance, and sensation seeking. These measures were initially developed in adults, so a youth version with 40-items was later developed (Zapolski et al., 2010). To reduce length, a modified version consistent with the UPPS-P short form and youth version was created for the ABCD Study. Each subscale was used as outcomes in brain-behavior analyses.

2.5.2. PhenX behavior inhibition/behavioral approach system (BIS/BAS) scales

The PhenX BIS/BAS (Pagliaccio et al., 2016) is a modified 20-item version of the longer, 24-item version developed by Carver and White (1994). The BIS/BAS was used to assess differences in behavioral activation in four domains: drive, fun seeking, reward responsiveness, and behavioral inhibition. The BIS sum score was used as an outcome in brain-behavior analyses.

2.6. fMRI acquisition

Imaging protocols were harmonized across all 21 sites using three 3 T scanners (i.e., Siemens Prisma, General Electric 750, and Philips) that used adult-sized coils with multiband echo planar imaging capabilities. The Data Analysis, Informatics and Resource Core (DAIRC) of ABCD processed all scans to ensure quality and consistency across sites. Corrections were made for head motion (Cox, 1996), B_0 (Holland et al., 2010), non-linearity distortions (Jovicich et al., 2006), and between-scan motion for each participant. Before fMRI analysis, a total of 16 frames were removed to maintain T1 signal and voxel time series. ROI values were extracted using average time courses for cortical surface-based ROIs using FreeSurfer's anatomically defined parcellations (Desikan et al., 2006a, 2006b; Destrieux et al., 2010) and subcortical ROIs (Fischl et al., 2002). General linear models in AFNI's 3dDeconvolve (Cox, 1996) modeled task-related activation strength. Outputs included GLM beta coefficients and standard errors of the mean for each voxel, vertex, or ROI time series. ROI beta coefficients and standard errors were averaged for the two runs, and averages across runs were also calculated. Further information regarding fMRI pre-processing or fMRI processing for task-based analyses can be found here (see Casey et al., 2018; Hagler et al., 2019).

2.7. fMRI task

2.7.1. Stop signal task (SST)

The SST was developed to measure behavioral response inhibition (Logan et al., 1984). On frequent "Go" trials, participants must press a button as quickly and accurately as possible when seeing an arrow pointing left or right, and in comparison, on "Stop" trials (16.67% of trials), participants are instructed to inhibit the button press when viewing a vertical arrow. During this task, the Stop Signal Delay (SSD; i.e., time between Go and Stop trials) is designed to keep response inhibition accuracy around 50%. When a trial is successfully inhibited, the SSD increases by 50 ms and decreases by 50 ms during unsuccessful inhibitory responses. The task includes 300 "Go" trials and 60 "Stop" trials across two trial runs. Further information about the SST design can be found in Casey et al. (2018). The current study contrasted correct stop > correct go BOLD response to model successful inhibition compared to response to stimulus.

2.8. Whole-brain SST successful inhibition activation

In the ABCD Study baseline sample youth completing the SST demonstrated greater BOLD signaling in these regions during successful inhibition: IFG, dACC, pre-SMA, and subcortically in the putamen and caudate; decreased response was found in the left postcentral somatosensorimotor cortex, precuneus, and vmPFC (n= 5547; Chaarani et al., 2021).

2.9. SST QC & behavioral performance

The ABCD DAIRC procedures define adequate performance on the SST within these boundaries: number of Go trials <50, correct go < 60%, incorrect and late go and go omissions < 30%, > 300 total Go trials, and a stop success rate <20% or > 80% (Hagler et al., 2019). At baseline, the rate of overall successful inhibition was 51.4% (Chaarani et al., 2021). To limit confounds due to unreliable signal, youth with behavioral performance below the outlined performance criteria were excluded (n= 1990) from current analyses.

2.10. Statistical analyses

Analyses utilized data from the ABCD 4.0 data release (DOI: https://doi.org/10.15154/1523041) and were conducted in R (v4.2.0; R Development R Core Team, 2022). In the primary analyses, ACE scores were treated as continuous variables and were log-transformed to address right-skewedness. Correlations between all primary variables of interest and ROIs were conducted (see Fig. 1 for visualization of correlation matrix and see supplement for specific numerical values). For descriptive statistics, ANOVAs and correlations were run to examine the relationships between ACE scores and sociodemographic factors, relevant covariates, and SST behavioral performance indices. Supplemental analyses were conducted to examine differences in demographics and relevant covariates between those included and excluded from the overall sample due to performance on the SST (see supplement). The primary models were estimated using a linear mixed-effects (LME) design using the lme4 package (Bates et al., 2014). All LME models accounted for the independent second-level random effects of MRI model and subject (i.e., repeated measure analyses).

For the first set of analyses, primary predictors in each model included continuous ACE scores, time (i.e., Y0 and Y2 session), and an ACEs-by-time interaction. The following demographics and covariates were included: sex assigned at birth, age, race, ethnicity, caregiver educational attainment, household income, CBCL internalizing symptoms, and pubertal status. Outcome variables included task-based BOLD

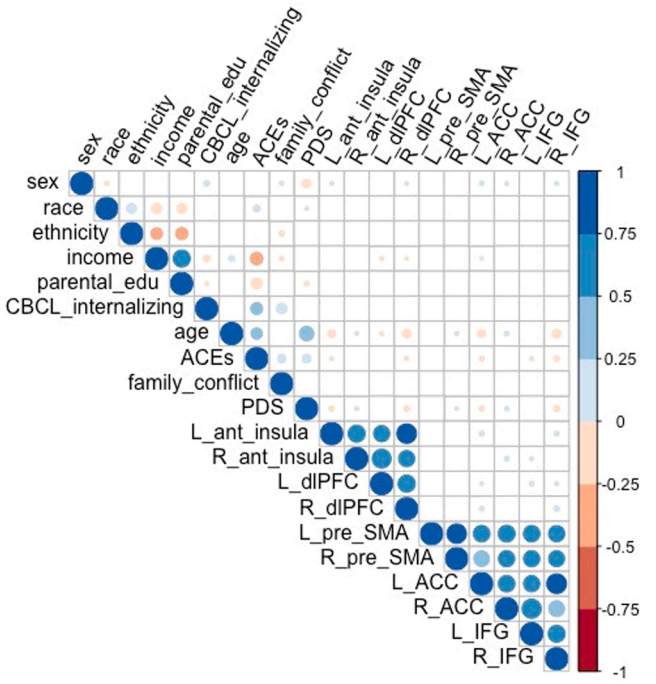

Fig. 1. *Correlations between Primary Variables of Interest and Dependent Variables. Notes.* L/R_ ant_insula= Left and Right anterior insula, L/R_dlPFC= Left and Right Dorsolateral Prefrontal Cortex, L/R_pre-Supplementary Motor Area, L/R_ACC= Left and Right Anterior Cingulate Cortex, L/R_IFG= Left and Right Inferior Frontal Gyrus. Correlation matrix depicts significant correlations between primary variables of interest and dependent variables (regions of interest). Shades of blue depict positive correlations and shades of red depict negative correlations. See supplement for specific numeric information.

signaling related to successful inhibition at Y0 and Y2 visit in predetermined ROIs underlying inhibitory control (i.e., dlPFC, ACC, anterior insula, opercular IFG, and pre-SMA). Separate LMEs were conducted for each ROI outcome bilaterally. After controlling for demographics and covariates, we tested whether levels of family conflict moderated the overall relationship between continuous ACE scores and ROIs BOLD response and whether this differed over time with an ACE x family conflict levels x time three-way interaction. Post-hoc Pearson correlations were conducted to examine brain-behavior relationships between average BOLD response in significantly predicted ROIs and UPPS-P scores, BIS scores, and task performance indices. Given the hypothesized differences in ROI BOLD response as a function of ACE exposure, brain-behavior correlations for self-reported behavior (i.e., UPPS-P and BIS scores) and task behavioral indices were run separately for those with low versus high ACE scores (based on a mean split to support further interpretation of BOLD activation patterns within the context of differential ACEs risk). Benjamini-Hochberg corrections were used to adjust significance levels for brain-behavior correlations to reduce false discovery rate at .05 level (Benjamini and Hochberg, 1995); these corrections provided a threshold of 0.012. All other results were considered significant at the $p < .05$ level.

3. Results

3.1. Demographic, covariate, and behavioral task analyses

See Table 2 for the full ABCD cohort at Y0 and total current sample (n = 9080) demographics at Y0 (n = 7895) and Y2 (n = 4972). Compared to the full ABCD sample at Y0, our current sample was more likely to be non-Hispanic, White and reported greater household income and higher caregiver education attainment. See Table 3 for information regarding relationships between ACE scores and sociodemographic factors,

Table 2
Demographics for the Full Adolescent Brain Cognitive Development (ABCD) Study Cohort and the Current Study Sample.

	Full Y0 Sample (%) N= 11,876	Current Y0 Sample (%) n= 7895	Current Y2 Sample (%) n= 4972
Sex assigned at birth (Female)	48	49	48
Youth identifies as White	63	70	71
Youth identifies as Black	16	12	11
Youth identifies as Asian American	2	2	2
Youth identifies as other racial group/multiracial	17	16	16
Ethnicity			
Youth identifies as Hispanic or Latinx	20	18	18
Caregiver Education			
Less than HS Diploma	5	3	3
HS Diploma/GED	10	7	7
Some College	26	24	23
Bachelor	25	27	28
Postgraduate	34	39	39
Household Income			
< 50 K	27	26	21
>= 50 K & <100 K	26	29	29
>=100 K	38	45	50

Notes. HS= High school. Table includes proportions of demographic groups in the full ABCD 4.0 baseline sample and the baseline and Year 2 samples utilized in present analyses. Y0 represents baseline assessment and Y2 represents Year 2 follow-up assessment.

relevant covariates, and SST behavioral indices. Across time points, youth from minoritized racial and ethnic groups reported greater rates of ACEs. Youth from families with greater household income and caregiver educational attainment reported fewer ACEs. Further, youth with greater ACE scores reported more mature pubertal status, greater family conflict levels, greater internalizing symptoms, were younger, and had poorer SST performance. There were no significant differences in ACE scores related to sex assigned at birth. Follow-up analyses demonstrated significant differences in demographics and relevant covariates between those included versus excluded from the present analyses due to SST behavioral performance (n=1990; see supplement). Specifically, those excluded were more likely to be male, identify as Black or multiracial/other racial group, and Hispanic/Latino and were more likely to report lower household education and income. Further, those excluded reported greater levels of ACEs and family conflict.

3.2. ACEs

Greater ACEs significantly predicted lower BOLD signaling (contrast: correct stop > correct go) in the left (t-value = −2.17, β = −0.022, SE = 0.010, $p = 0.030$) and right (t-value = −2.15, β = −0.022, SE = 0.010, $p = 0.032$) pre-SMA and in the opercular region of the right IFG (t-value = −1.98, β = −0.020, SE = 0.010, $p = 0.048$; see Fig. 2). ACE scores were not a significant predictor in the left IFG or bilaterally in the ACC, dlPFC, or anterior insula. Time and ACE by time interactions did not survive statistical thresholding.

3.3. Family Conflict

Greater family conflict significantly predicted greater BOLD signaling in the left (t-value = 2.42, β = −0.022, SE =0.0092, $p = 0.020$) and right (t-value = 2.02, β = −0.020, SE = 0.0092, $p = 0.043$) anterior insula and the left pre-SMA (t-value = 2.33, β = −0.022, SE = 0.0093, $p = 0.020$; see Fig. 3). No significant two- or three-way interactions between ACEs, family conflict, and time were related to activation in

Table 3
Descriptive Relationships Between ACE Scores Across Covariates and SST Behavioral Performance Indices at Baseline (Y0) and 2 Year (Y2) Visits.

Covariates/SST Indices	Y0: ACE scores by group n= 7895			Y2: ACE scores by group n= 4972		
	M	SD	p-value	*M*	SD	p-value
Sex assigned at birth						
Female	1.98	1.61	0.09	3.28	2.24	.30
Male	2.04	1.69	-	3.35	2.25	-
Ethnicity						
Hispanic/Latino	2.05	1.63	0.35	3.54	2.21	**<0.001**
Non-Hispanic	2.00	1.65	-	3.27	2.25	-
Race						
White	1.91	1.57	-	3.04	2.10	-
Black	2.47	1.81	**<0.001**	4.52	2.27	**<0.001**
Asian American	0.95	1.18	**<0.001**	1.78	1.42	**<0.001**
Multiple/Other racial group	2.25	1.78	**<0.001**	3.93	2.48	**<0.001**
Caregiver education						
Less than HS Diploma	2.36	1.74	-	3.97	2.36	-
HS Diploma/GED	2.47	1.76	0.62	4.30	2.46	0.22
Some College	2.61	1.82	**0.04**	4.33	2.40	0.11
Bachelor	1.92	1.61	**< 0.001**	3.15	2.10	**< 0.001**
Postgraduate	1.59	1.37	**< 0.001**	2.60	1.88	**< 0.001**
Household income						
< 50 K	2.76	1.91	-	4.66	2.51	-
>= 50 K & < 100 K	2.08	1.59	**< 0.001**	3.69	2.27	**< 0.001**
>= 100 K	1.54	1.32	**< 0.001**	2.53	1.74	**< 0.001**
Covariates/SST Indices	Y0 Descriptive			Y2 Descriptive		
	M	SD	r	*M*	SD	r
Pubertal Development Status	1.67	1.09	0.04***	2.51	1.06	0.06***
Age at visit (years)	9.94	0.63	-0.011	11.92	0.64	-0.03*
Family conflict levels	2.49	1.95	0.20***	2.43	1.97	0.17***
CBCL Internalizing (t-scores)	48.21	10.4	0.32***	47.6	10.29	0.30***
SST: Correct Stop Rate (%)	51	6	-0.030**	51	6	-0.035**
SST: Correct Go Rate (%)	85	9	-0.10***	88	8	-0.15***
SST: SSRT (secs)	303	67.39	0.014	275	58.24	0.040**

Notes. HS= High School, CBCL= Child Behavior Checklist, SST= Stop Signal Task. Y0 represents baseline assessment and Y2 represents Year 2 follow-up assessment. Table presents differences in ACE scores across categorical socio-demographic factors and correlations between ACEs and continuous covariates/SST behavioral indices at baseline and Year 2 in our current sample. For categorical demographic variables with more than 2 levels, a comparison group was used (see comparison group in bold). For continuous variables, correlation coefficients were reported to provide directionality. Significance values represent significant relationships between ACEs and variable of interest. * p<.05. **p<.01.***p<.001

selected ROIs.

3.4. Covariates

Caregiver education was related to BOLD response; youth with caregiver education attainment of high school diploma or higher showed greater BOLD signaling compared to youth with parental education of some high school in the left and right opercular IFG, left and right pre-SMA, left and right ACC, and the right dlPFC (all p's < 0.05). Male youth demonstrated greater BOLD response bilaterally in the ACC (p's < 0.001) and the left opercular IFG ($p < 0.01$) compared to females. Older youth had reduced BOLD response bilaterally in the opercular IFG (p's < 0.001) and anterior insula (p's < 0.01) compared to younger youth. Other covariates (income, CBCL internalizing scores, pubertal development stage, race, and ethnicity) did not predict BOLD response within ROIs.

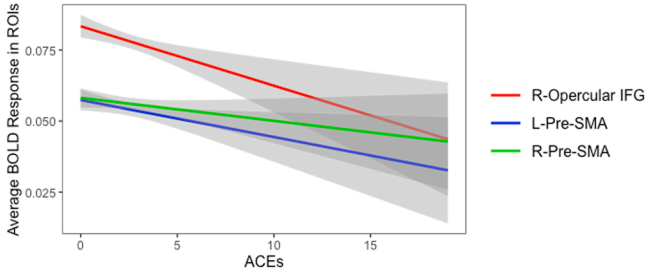

Fig. 2. *Greater ACEs Predict Lower BOLD Response in ROIs Underlying Inhibitory Control. Notes*. Graph shows bivariate relationships between adverse childhood experience (ACE) scores and BOLD response in the opercular region of the right inferior frontal gyrus (IFG) and the left and right pre-supplementary motor area (pre-SMA; shaded portions represent standard error). The graphed data for all three regions represents the mean BOLD response across time (assessed at baseline and Year 2 follow-up visits). As ACE scores increase, BOLD response in these regions decreases.

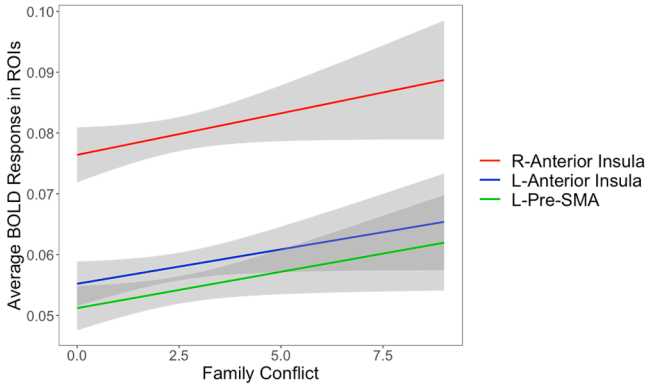

Fig. 3. *Greater Levels of Family Conflict Predict Greater BOLD Signaling in the Anterior Insula and Pre-SMA. Notes.* Graphs shows bivariate relationships between levels of family conflict and BOLD response bilaterally in the anterior insula and in the left pre-supplementary motor area (pre-SMA; shaded portions represent standard error). The graphed data for all three regions represents the mean BOLD response across time (assessed at baseline and Year 2 follow-up visits). As family conflict scores increase, BOLD response in these regions increases.

3.5. Brain-behavior correlations

3.5.1. SST behavioral performance

For SST behavioral performance, negative correlations were found between mean SSRT and activation in the right ($r(12{,}863) = -0.047$, $p < 0.001$) and left ($r(12{,}863) = -0.052$, $p < 0.001$) pre-SMA and the right opercular IFG ($r(12{,}863) = -0.048$, $p < 0.001$). Positive correlations were found between rate of correct stop and activation in the right ($r(12{,}863) = 0.026$, $p = 0.003$) and left ($r(12{,}863) = 0.026$, $p = 0.003$) pre-SMA and the right opercular IFG ($r(12{,}863) = 0.041$, $p < 0.001$). For rate of correct go, positive correlations were found in the left ($r(12{,}863) = 0.061$, $p < 0.001$) and right ($r(12{,}863) = 0.040$, $p < 0.001$) pre-SMA and right opercular IFG ($r(12{,}863) = 0.073$, $p < 0.001$).

3.5.2. UPPS-P

In the left pre-SMA, youth with lower ACE scores demonstrated negative correlations with UPPS lack of premeditation ($r(7294) = -0.032$, $p = 0.006$) and positive urgency ($r(7294) = -0.028$, $p = 0.02$) scales. In the right pre-SMA, negative correlations were found with UPPS positive urgency scale ($r(7294) = -0.024$, $p = 0.04$) for youth with lower ACEs. However, after Benjamini-Hochberg corrections,

relationships with positive urgency were no longer significant (see supplement). No significant correlations were found between the UPPS subscales and BOLD signaling in the right opercular IFG. In youth with greater ACE scores, no correlations survived statistical thresholding.

3.5.3. BIS

Regardless of ACEs scores, no significant correlations were found between ROIs and BIS scores.

4. Discussion

Research suggests that ACEs are associated with poorer inhibitory control and altered BOLD signaling in related ROIs cross-sectionally during adolescence (Johnson et al., 2021; Lund et al., 2020; van der Bij et al., 2020); however, less is known about this relationship longitudinally from late childhood to early adolescence in larger, more diverse samples. Further, few studies have investigated socio-environmental factors that may amplify or attenuate risk associated with ACEs. To address these gaps, the present study examined the longitudinal relationship between ACEs and BOLD signaling during successful inhibition in ROIs (i.e., IFG, ACC, pre-SMA, dlPFC, anterior insula) implicated in inhibitory control in preadolescents enrolled in the ABCD Study. Further, we examined whether family environment (i.e., levels of family conflict) moderated this relationship. Two- and three-way interactions with time were also analyzed to assess whether these relationships differed from late childhood (Y0) to early adolescence (Y2). We found that during successful inhibition, there was a dose-dependent relationship with greater ACEs and lower BOLD response in regions related to inhibitory control at Y0 and Y2, after controlling for demographic variables, pubertal status, and internalizing symptoms.

Specifically, greater ACE scores were linked with reduced BOLD response during inhibitory trials compared to go trials in the right opercular IFG and in the left and right pre-SMA at both Y0 and Y2, when youth were approximately ages 10 and 12. In the present analyses, ACE by time interactions were nonsignificant suggesting that the relationships between ACEs and BOLD response did not differ from Y0 (late childhood) to Y2 (early adolescence) in our selected ROIs; our ability to detect potential longitudinal changes in these relationships may have been limited by the shorter developmental window captured by the ABCD sample at these time points. The IFG and pre-SMA have previously been associated with inhibitory control (Aron et al., 2014; Chaarani et al., 2021; Whelan et al., 2012; Zhang et al., 2017) with hypothesized roles in detection of inhibitory cues and anticipation of and physically stopping a motor response, respectively (Hampshire et al., 2010; Obeso et al., 2013). In the baseline ABCD sample (n=5547; Chaarani et al., 2021), greater brain activation was found in the IFG and pre-SMA during successful inhibition on the SST at ages 9 and 10 years old; other large samples have noted similar patterns of greater BOLD response on the SST during mid-adolescence (Whelan et al., 2012) and in healthy adolescent control groups (van Rooij et al., 2015). Further, small, cross-sectional studies examining age-related effects on neural response in healthy preadolescents/adolescents have typically found greater brain activation in the IFG and inferior PFC during successful inhibition on the SST (Rubia et al., 2000; Rubia et al., 2013). These broader patterns of greater activation during successful inhibition are also consistent with activation patterns on other inhibitory control tasks (e.g., Go/No-go) during adolescence (Cope et al., 2020; Kang et al., 2022; Paige et al., 2024; Weiss and Luciana, 2022). Given the prior evidence demonstrating a pattern of greater activation in regions such as the IFG and pre-SMA during typical development, this would suggest that the reduced BOLD activation in the IFG and pre-SMA is less advantageous for development of these regions.

To further investigate whether the directionality of brain activation (i.e., reduced activation) within the context of ACE exposure was linked with behavior in our sample, we conducted analyses to examine brain-behavior relationships in regions significantly predicted by ACEs. After correcting for multiple comparisons, brain-behavior correlations revealed that in youth with fewer ACEs, greater BOLD response was related to more premeditation (i.e., left pre-SMA) While this correlation was small, this suggests that greater BOLD response may be behaviorally advantageous, which is consistent with findings of greater neural activation during successful inhibition on the SST during typical development (Chaarani et al., 2021; van Rooij et al., 2015; Whelan et al., 2012). In contrast, the brain-behavior relationships were abnormally flat in youth with a history of greater ACE exposure, suggesting decreased BOLD response during inhibitory trials compared to go trials was not advantageous to downstream impulsivity at this age. In addition, significant correlations were found between greater BOLD activation in the pre-SMA and IFG and better behavioral performance indices on the SST (i.e., mean SSRT, rate of correct stop and go). Taken together, these findings are consistent with general pattern between ACEs and altered BOLD response in inhibitory control regions in youth, although the specificity within regions and directionality of findings differ depending on developmental period. In a smaller, but slightly older sample (n=33; *M* age= 13.5), Mueller and colleagues (2010) reported increased BOLD signaling in the dACC, inferior PFC, and posterior insula during successful inhibition on a similar task, while we found reduced activation in a larger and younger sample. Thus, the directionality of the impact of ACEs potentially differs based on age and other demographic factors. Also, our findings correspond with models suggesting alterations in neural networks underlying inhibitory control may confer future risk for negative outcomes (e.g., mood and substance use disorders) commonly associated with ACEs (Wesarg et al., 2020; Zelazo, 2020). Research suggests that alterations in executive functioning broadly increases risk for risky substance use (Fava et al., 2019; Oshri et al., 2018; Silveira et al., 2020; Trossman et al., 2021) and psychopathology (Trossman et al., 2021; Wesarg et al., 2020; Zelazo, 2020) in youth with ACEs, emphasizing the importance of continuing to examine these potential mechanisms across development.

Preclinical models have demonstrated that chronic stress is linked with fewer dendritic spines in animals (Radley et al., 2004, 2006) and smaller structural volume (Ansell et al., 2012) in frontal brain regions in adult humans. In youth, adversity exposure has been linked with reduced structural volume and thickness in prefrontal regions in addition to altered frontoparietal network connectivity (McLaughlin et al., 2019). Further, ongoing activation of the norepinephrine system results in increased limbic activation, but inhibited PFC activation (Arnsten, 2009); over time, this could result in reduced BOLD response in the PFC during executive functioning tasks. Disruptions in HPA axis functioning have also been identified as a mechanism linking chronic stress to brain outcomes (O'Connor et al., 2021). Likewise, the endocannabinoid (eCB) system modulates HPA-axis function and has shown sensitivity to early life stress in preclinical models (Goldstein Ferber et al., 2021; Hillard, 2018; Morena et al., 2016). Cannabinoid-1 receptors are distributed throughout the PFC (Hillard, 2018), and there is preliminary evidence that eCB signaling is related to executive functioning performance (Fagundo et al., 2013; Hill et al., 2006). Coupled with rapid brain organization during adolescence, alterations in brain structure and neuromodulation could contribute to changes in brain activation patterns in adversity exposed youth (McEwen et al., 2016; McEwen and Morrison, 2013).

The second study aim was to examine whether family conflict moderated the relationship between ACEs and BOLD signaling and assess whether this relationship changed over time. Main effects of family conflict were found in the left and right anterior insula and the left pre-SMA, where youth in families reporting greater conflict demonstrated greater BOLD signaling compared to youth in families reporting less conflict. In addition to playing a key role in inhibitory processing, the anterior insula has also been implicated in emotionally salient processing (Uddin et al., 2017); this elevated activation suggests heightened sensitivity to emotional experiences like interpersonal conflict (Cosgrove et al.,2020; Koban et al., 2014) and is consistent with

findings of disrupted connectivity in adults (Lupien et al., 2009). Yet, no significant interactions between ACEs and family conflict were found in relation to activation patterns in the selected ROIs, and there were no significant changes in these relationships from late childhood (Y0) to early adolescence (Y2). Other imaging studies examining family-level factors (i.e., parental acceptance) in the ABCD study have found nonsignificant contributions on brain outcomes (Brieant et al., 2021; Demidenko et al., 2021); however, the family environment could have greater impact later in development or during broader developmental windows. While these findings are inconsistent with the differential susceptibility framework, conceptualizing resiliency and intervention opportunities from this perspective holds promise (van IJzendoorn, et al., 2020). Studies should continue to integrate other aspects of the family environment (i.e., family cohesion, family expressiveness) in addition to other levels of support (i.e., peer, community-level) to better characterize risk and resiliency across adolescent development.

While not the primary focus, other covariates (i.e., caregiver education levels, age, sex at birth) were independent predictors of BOLD signaling. Higher parental education attainment was related to greater BOLD signaling in the IFG, ACC, pre-SMA, and dlPFC, which is consistent with research demonstrating a positive relationship between parental education and activation in inhibitory control regions (Cascio et al., 2022). Reported sex differences in activation patterns are consistent with findings in the adult literature where males show greater BOLD response during successful inhibition (Weafer, 2020). Further, age-related differences in BOLD response suggest inefficiency in neural recruitment in the IFG and anterior insula, which may reflect ongoing development in these regions (Luna et al., 2010; Constantinidis and Luna, 2019).

Study limitations include that the current ABCD Study design utilized direct and indirect measurements of ACE categories; for example, emotional and physical neglect were measured indirectly through youth report of caregiver warmth and parental monitoring, respectively. Future work should incorporate explicit measurements of ACEs in addition to relying on youth report. The present ACEs scoring did not account for experiences of discrimination related to marginalized identities other than ethnoracial identity. The current ACEs scoring also does not account for frequency, timing, or severity of each adverse event or incorporate weighting of events. These limitations reflect how cumulative risk scores cannot account for individual differences within experiences; future work should explore dimensional approaches to ACE assessments (McLaughlin et al., 2021; McLaughlin and Sheridan, 2016) and account for the differential impact of developmental timing, frequency, and chronicity of adverse events. Future research should also continue to characterize how ACEs influence adolescent brain development in large and diverse samples; following these relationships over time is necessary to better understand how developmental timing impacts the directionality of brain activation patterns. Within the ABCD Study sample, there was discordance between youth and caregiver reports of family conflict (Gonzalez et al., 2021), and there was limited variability in reported levels of family conflict. Caregiver report of family conflict was used in the present analyses, which may have impacted our understanding of family conflict's true relationship on brain outcomes. Due to ACEs established relationship with poor health outcomes (Green et al., 2010; Toth and Cicchetti, 2013), future work should continue to investigate risk and resiliency pathways to improve adolescent health outcomes and capitalize on individual, familial, and community-level strengths. The current study also utilized pre-determined ROIs, which limits conclusions on how brain activity influences or interacts with the region in addition to relationships between ACEs and BOLD signaling in other brain areas (Van Den Heuvel and Pol, 2010). Use of whole-brain analysis techniques in future work would provide better localization of activation and clarify relationship between ACEs and activation in other brain regions. Finally, compared to the ABCD sample at Y0, the current sample was underrepresented in marginalized groups (i.e., caregiver/parental education, household income level, race) due to exclusion criteria to ensure quality imaging data and the COVID-19 pandemic's impact on in-person data collection at Y2. Further, those excluded due to poor behavioral performance were also more likely to be from minoritized groups. While these differences in demographic factors were controlled for in the present analyses, these limitations in our sample potentially impact generalizability to the larger ABCD sample.

5. Conclusions

To our knowledge, the present study is the largest geographically and demographically diverse sample to date to examine the relationship between ACEs and ROIs related to inhibitory control in a longitudinal design from late childhood to early adolescence. Overall, results suggest that even in late childhood and early adolescence, youth with ACE history show alterations in BOLD signaling while successfully engaging in an inhibitory control task, and this pattern of activation was linked with increased behavioral impulsivity. Our findings build upon established work highlighting potential risk associated with ACEs during early adolescent development and emphasize the need for investment in early detection and further prevention of ACEs to reduce associated risk. Aligning with the National Center for Injury Prevention's prevention strategy for ACEs, this level of intervention would require top-down investment in community-informed services to ensure individuals (e.g., social-emotional skill building), families (e.g., economic support), and communities (e.g., promotion of healthy social norms, preschool/childcare enrichment, increased access to primary and mental health care) receive the resources they need to reduce adversity risk (CDC, 2021).

CRediT authorship contribution statement

Christine L. Larson: Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Funding acquisition, Data curation, Conceptualization. **Alexander L. Wallace:** Writing – review & editing, Writing – original draft, Data curation. **Gabriella Y. Navarro:** Writing – review & editing, Writing – original draft. **Krista M. Lisdahl:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Ryan M. Sullivan:** Writing – review & editing, Visualization, Validation, Formal analysis, Data curation, Conceptualization. **Elizabeth Ashley Stinson:** Writing – review & editing, Writing – original draft, Visualization, Validation, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The authors do not have permission to share data.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.dcn.2024.101378.

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