

Early Childhood Adverse Experiences, Inferior Frontal Gyrus Connectivity, and the Trajectory of Externalizing Psychopathology

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Objective: Early adverse childhood experiences (ACEs) have been linked to the development of both internalizing and externalizing psychopathology. In our prior work, we found that ACEs predicted reductions in the volume of the inferior frontal gyrus (IFG), a brain region important for impulse control and emotion regulation. Here we tested the hypothesis that ACEs might influence child behavioral outcomes through an impact on IFG functional connectivity, which may influence impulsive or risk-taking behavior.

Method: We examined the effects of prospectively assessed ACEs on IFG connectivity in childhood, and their relationship to the trajectory of subsequent psychopathology from late school age and early adolescence, using data from an 11-year longitudinal study of children starting in preschool that included 3 waves of resting state functional connectivity across childhood and early adolescence.

Results: ACEs predicted functional connectivity of both left and right IFG. Multi-level modeling of symptoms across 3 waves of assessments indicated that more ACEs predicted both internalizing and externalizing symptoms. However, altered IFG connectivity specifically predicted greater externalizing symptoms over time in middle childhood and early adolescence, as compared to internalizing symptoms. Longitudinal modeling indicating that the relationships between externalizing and functional connectivity were maintained across 3 waves of functional connectivity assessment.

Conclusion: These findings underscore the relationship of ACEs to later psychopathology, and suggest that connectivity of the IFG, a region known to play an important role in impulse control and emotion regulation, may play a key role in the risk trajectory of ACEs to externalizing problems. However, further work is needed to understand whether these relationships reflect a direct effect of ACEs or whether ACEs are a marker for other environmental or genetic factors that may also influence brain development and behavior.

Key words: functional connectivity, externalizing, inferior frontal gyrus, longitudinal, development

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Researchers and practitioners have increasingly recognized the detrimental impact of adverse childhood experiences (ACEs), such as the experience of trauma, parental mental illness, and exposure to poverty early in life, on a variety of developmental, behavioral, and health outcomes.¹ This recognition began with the landmark retrospective study of Felitti *et al.*,² which suggested that ACEs were linked to a higher risk of poor health behaviors associated with leading causes of death in adulthood. An increasing body of evidence has become available confirming this link.^{3,4} It has also been established that exposure to poverty early in life confers many of the same risk factors as exposure to trauma and parental mental illness,⁵⁻¹¹ although these related risk factors are difficult to disentangle.^{12,13} Furthermore, ACEs, including poverty, are associated with higher risk for a broad range of mental disorders, including both internalizing and externalizing disorders.^{14,15} What remains less clear, and critically important to the development of a preventive intervention, is the neural and physiological mechanism by which exposure to ACEs leads to higher risk for these negative outcomes.

Much of the prior work on the neural effects of exposure to early adversities such as ACEs and poverty has focused primarily on the structure of the amygdala and hippocampus. There are a range of

structural brain differences associated with various indicators of early adversity such as poverty, including reductions in whole brain gray and white matter volumes, as well as reduced thickness in some brain areas.^{16,17} One of the most consistent findings is an association between poverty indicators and reductions in hippocampal and amygdala volumes,¹⁸⁻²⁰ as well as one paper reporting a link between poverty and altered hippocampal and amygdala connectivity.²¹ Moreover, there is evidence that these alterations in hippocampal and amygdala volumes and connectivity partially mediate the influence of poverty on later mental health problems in children.^{19,21} Importantly, there is also evidence that experiences with other early ACEs, such as trauma, also have an impact on brain volumes in many of the same regions (i.e., hippocampus and amygdala) as shown for poverty.²² A much smaller body of literature has also demonstrated relationships between early ACEs and connectivity of these regions.²² Such findings in humans are consistent with the animal literature showing effects of stress and environmental enrichment on hippocampal and amygdala cell proliferation, and dendritic length and branching.^{23,24}

There is also a relationship between ACEs and/or poverty and deficits in prefrontal structure and function.²⁵⁻²⁸ These impairments include alterations in regions related to emotion regulation and impulse

control.^{29,30} A link between impairments in impulse control and the development of externalizing disorders has also been established,³⁰⁻³³ as well as a body of literature linking externalizing disorders to impaired structure, function, and connectivity of prefrontal regions.³⁴⁻³⁶ In our prior work, we have also found evidence for a link between reduced prefrontal volume and early ACEs,³⁷ with a particular association with the inferior frontal gyrus (IFG), a region associated with impulse control and emotion regulation.^{29,30} Furthermore, we found that reductions in IFG volume were associated with impaired emotion function and later depression and risk for poor health outcomes.³⁷ Other work has found that thinner IFG in early adolescence predicted greater drinking and externalizing psychopathology in later adolescence.³⁸ Moreover, some work has suggested that connectivity of the IFG may also be associated with impulsive actions.^{39,40} However, to our knowledge, whether ACEs is linked to IFG connectivity has not yet been examined.

The goal of the current study was to test the following hypotheses: 1) Do ACEs predict variation in IFG functional connectivity? 2) Do any ACE-related alterations in IFG connectivity predict externalizing or internalizing symptomatology across time? 3) Does IFG connectivity covary with externalizing or internalizing symptoms over time? 4) Do IFG connectivity and volume interact in predicting symptoms? 5) Does IFG functional connectivity mediate the relationships between ACEs and externalizing symptomatology?

METHOD

Participants

Participants were 211 children in a longitudinal study of preschool depression with 3 scan waves. Healthy children and those with a history of depression were invited for participation in scanning (see Figure S1, available online, for exclusion criteria). Of these participants, 156 had complete ACE data and usable scan data at one or more waves. All study methods were reviewed and approved by the Washington University School of Medicine institutional review board. Written informed consent and assent was obtained from all study participants.

Clinical Assessment

Before and including at the time of scan 1, children participated in behavioral assessments over 1 to 7 annual waves. This included parent and child report of psychopathology using age-appropriate psychiatric interviews (Preschool Age Psychiatric Assessment [PAPA]^{41,42}; ages 3 to 7 parent-only report; Child and Adolescent Psychiatric Assessment [CAPA]; age 8 parent report, and ages 9 and older parent and child report).^{42,43} In addition, demographic, psychosocial (including stressful and traumatic life events assessed using the PAPA/CAPA), and developmental characteristics were also assessed (for additional details, see Luby *et al.*⁴⁴). To examine the effect of prospectively collected early adverse childhood experiences (ACEs) on structural and functional connectivity brain outcomes, we created a score based in part on the original definition by Felitti *et al.*,² but adding exposure to poverty as an additional adversity building on the extant more recent neuroscience literature.^{16,45} This variable included: 1) a score of 1 if living below the poverty line based on income-to-needs at time-points T1, T2, and/or T3 (see Figure S1, available online); 2) sum of nonredundant traumatic events at T1, T2, or T3 (e.g., child sexual abuse, physical abuse); 3) maternal or paternal suicide attempts or completions through T3 (1 if present); 4) maternal or paternal substance abuse through T3 (1 if present); or 5) maternal or paternal other mental health disorder through T3

(1 if present). We chose to sum these events into a total ACE score rather than using an exploratory factor analysis, as such analyses can create sample-specific weightings that are less generalizable to future work. (See Table 1 for means and standard deviations and Figure S2 [available online] for the distribution of ACEs in the sample, and Table S1 [available online] for a breakdown by subcomponent.)

A childhood psychopathology measure score that spanned from preschool until the first scan was calculated for each child by determining whether a child met criteria for any psychiatric disorders based on the PAPA and/or CAPA before the first scan. During this period, children completed 5 assessments on average (SD = 2.8; range 2–11) behavioral assessments. We also created internalizing and externalizing psychopathology scores for each scan wave by summing the core major depression and anxiety disorder symptoms (internalizing) and the core

TABLE 1 Characteristics of the Sample (n = 156)^a

Characteristic	Scan 1 (n = 141)		Scan 2 (n = 127)		Scan 3 (n = 111)	
	%	n	%	n	%	n
Sex						
Female	48.9	69	48.8	62	50.4	56
Race/ethnicity						
White	57.4	81	52.0	66	46.9	52
African American	30.5	43	38.6	49	42.3	47
Other	12.1	17	9.4	12	10.8	12
Age (y)						
6	0.7	1	0.0	0	0.0	0
7	4.3	6	0.0	0	0.0	0
8	10.6	15	0.0	0	0.0	0
9	27.0	38	7.1	9	0.0	0
10	25.5	36	17.3	22	1.8	2
11	24.1	34	29.9	38	17.1	19
12	7.8	11	29.9	38	28.8	32
13	0.0	0	14.2	18	35.1	39
14	0.0	0	1.6	2	14.4	16
15	0.0	0	0.0	0	2.7	3
Parental education at scan						
High school diploma	7.1	10	8.7	11	9.3	10
Some college	41.1	58	42.5	54	46.3	50
4-Year college degree	23.4	33	20.5	26	17.6	19
Graduate education	28.4	40	28.3	36	26.8	29
Psychotropic medication use						
Yes	19.9	28	26.0	33	30.6	34
	Mean	SD	Mean	SD	Mean	SD
Age (y)	10.26	1.26	11.85	1.15	13.07	1.06
ACEs sum score	4.89	3.25	4.87	3.06	5.38	3.20
Average internalizing through S1	3.30	2.01	3.11	1.81	3.40	1.99
Average externalizing through S1	5.52	5.09	5.52	4.77	6.01	5.06

Note: ACEs = adverse childhood experiences.

^aThe number at each wave reflects the number of children with usable structural imaging data and available ACE data. There were 89 participants with the 3 full waves of usable scans, 45 with 2 usable scans, and 22 with only 1 usable scan. The children with 1 scan did not differ from those with 2 or 3 scans by sex (p = .5552), scan 1 age (p = .9076), ACEs (p = .4626), or mean psychopathology severity up to scan 1 (internalizing: p = .8144; externalizing: p = .5447).

attention-deficit/hyperactivity, oppositional defiant, and conduct disorder symptoms (externalizing).

Image Acquisition

Children were scanned up to 3 times approximately 12 to 15 months apart on a Siemens 3.0-T Tim Trio in a session that included 2 MPRAGE T1 structural scans and 2 resting state fMRI (rsfMRI) scans (see Supplement 1, available online).

Structural Image Processing

For each scan session, 2 MPRAGE scans were assessed visually, and the best in terms of low movement and good contrast were selected by blinded raters. Processing of structural data was accomplished using the FreeSurfer Longitudinal pipeline v5.3 (<http://surfer.nmr.mgh.harvard.edu>) and is described in Supplement 1, available online. We examined the relationship between IFG from the Desikan *et al.* atlas⁴⁶ at scan 1 and IFG connectivity at scan 1.

Functional Connectivity Processing

RsfMRI processing followed the recommendations of Powers *et al.*, as described in Supplement 1 (available online), and included a number of quality assurance approaches,⁴⁷⁻⁴⁹ resulting in usable rsfMRI data available for 123, 142, and 130 individuals, respectively, across the 3 scan waves.

We selected regions of interest (ROIs) in bilateral inferior frontal gyrus using coordinates provided in the Diekhoff *et al.* meta-analysis⁵⁰ of regions associated with cognitive emotion regulation, as we have used in our prior work on emotion regulation.⁵¹ The coordinates were as follows: $X = 48, Y = 25, Z = -4$; and $X = -48, Y = 26, Z = -6$. We created 6-mm-diameter spherical ROIs. The time-series from these 2 ROIs were correlated with the time-series at every other voxel in the brain to create 2 whole-brain voxelwise correlation maps for each child. Values in these maps were converted to z statistics using the Fisher r -to- z transformation. These maps were used as the dependent measures in the rsfMRI analyses.

We used linear regression implemented in in-house software (FIDL analysis package, <http://www.nil.wustl.edu/labs/fidl/index.html>) to examine whether ACEs predicted rsfMRI with either the left or right IFG at the first scan wave, controlling for sex and age. Results were thresholded based on AFNIs 3dClustSim (Version AFNI_16.2.09) at $p = .001$ and 35 contiguous voxels (315 mm^3) for a whole-brain false-positive rate of 0.05. Then longitudinal multilevel linear models (MLM) were implemented in SAS v9.3 (PROC MIXED) to determine whether ACEs or IFG connectivity predicted the trajectories of internalizing or externalizing symptoms over early childhood into early adolescence. These growth curve models included random intercept and random slope components (unstructured covariance matrix between the 2). Time was coded as wave number (centered at Scan 1). All models included age at scan 1 (centered at the mean), quadratic age at scan 1, and sex. Degrees-of-freedom calculations used the method of Kenward and Roger.⁵² We used similar growth curve models to ask whether externalizing symptoms (as internalizing symptoms were not significant; see below) and IFG connectivity predicted by ACEs covaried across scan waves. Finally, we asked whether IFG connectivity mediated the relationships between ACEs and externalizing symptoms.

RESULTS

Participant characteristics at each scan are provided in Table 1. Figure S1 (available online) details the study flow, including drop-out rates and reasons.

ACEs and IFG Connectivity

Figure 1 shows the average pattern of connectivity between the left (Figure 1A) and right (Figure 1C) IFG as a context for understanding relationships to ACEs. ACEs predicted connectivity at the first scan wave with 6 regions for the left IFG (Table 2; Figure 1B) and 1 region for the right IFG (Table 2; Figure 1D). On average, connectivity between the right IFG and the right precentral gyrus was negative, and ACEs predicted stronger negative connectivity between these regions (Table 2). On average, connectivity between the left IFG and the right cuneus was negative, and ACEs predicted stronger negative connectivity between these regions (Table 2). In contrast, on average, connectivity between the left IFG and the culmen as well as the bilateral inferior parietal lobule was negative, and greater ACEs predicted reduced negative connectivity between these regions. On average, connectivity between left IFG and left DLPFC was positive, and ACEs predicted stronger positive connectivity. There was no significant connectivity on average between left IFG and the declive, but ACEs predicted stronger positive connectivity. All of these relationships remained significant when controlling for child psychopathology up to the time of scan (all $p < .001$). (See Supplement 1, available online, for analyses distinguishing between deprivation (i.e., poverty) and trauma.^{12,13})

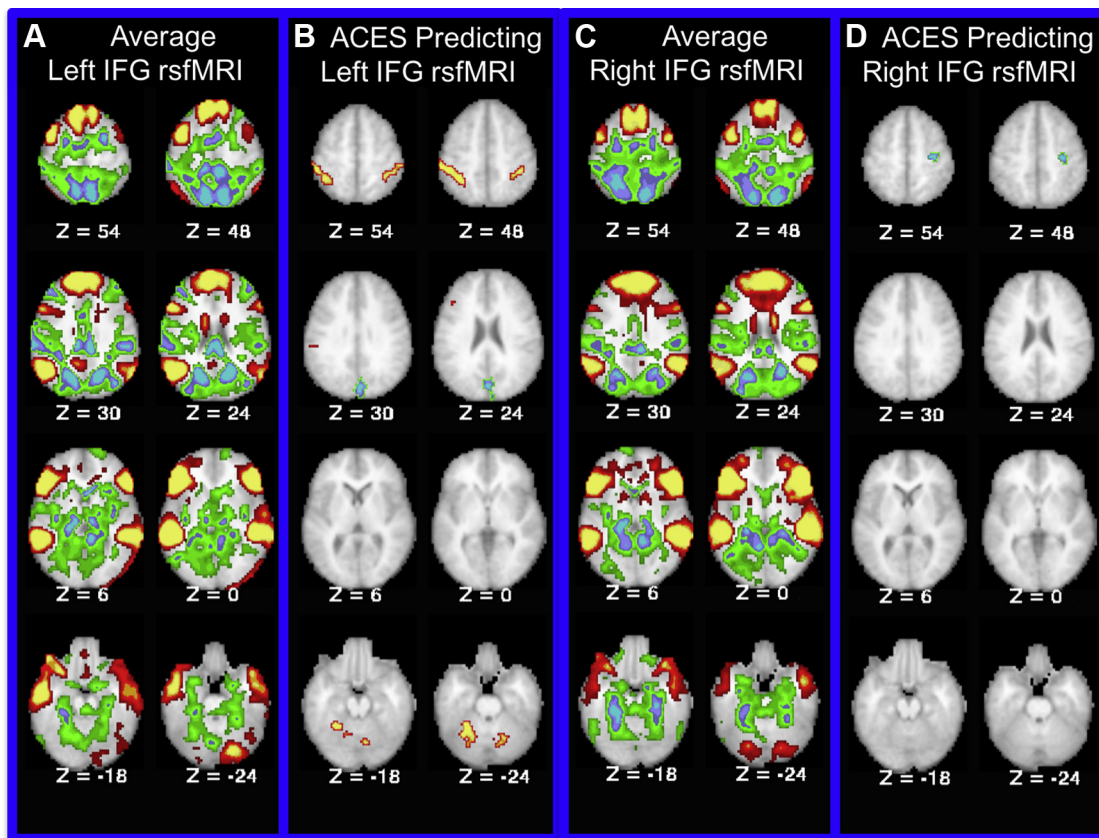
Subsequent Externalizing and Internalizing Symptoms

We examined whether ACEs predicted the trajectory of externalizing or internalizing symptoms across the follow-up waves starting at scan 1. ACEs strongly predicted both externalizing and internalizing symptoms (see Table S2, available online). Both of these relationships were main effects that did not interact with time, suggesting that greater ACEs predicted higher symptoms at all 3 waves, but that ACEs did not influence the rate of increase or decrease in symptoms across time.

We then examined whether the IFG connectivity predicted by ACEs also predicted the trajectory of externalizing or internalizing symptoms. As shown in Table S3 (available online), connectivity between IFG and each of the 5 regions predicted by ACEs also significantly predicted a main effect of externalizing symptoms (passing false discovery rate [FDR] correction), although there were no interactions with time (i.e., overall greater externalizing symptoms but not an increase over time). All of these relationships other than left IFG to left DLPFC remained significant even when controlling for psychopathology before scan 1 (see Table S4, available online). None of the connectivity measures predicted internalizing symptoms after FDR correction (see Table S5, available online).

Next, we asked whether the variation in IFG connectivity across the 3 scan waves covaried with externalizing symptoms. As shown in Table S6 (available online), there were 3 significant main effect relationships that survived FDR correction: left IFG to left culmen and both left and right inferior parietal, including that externalizing was associated with altered connectivity across scan waves (Figure 2A). There was also one significant interaction with scan wave for the left IFG to the right declive (Figure 2B), such that the relationship to externalizing was stronger in the early scan waves than the last scan wave.

We then examined whether connectivity mediated the effects of ACEs on externalizing symptoms. To do so, we computed additional MLMs with both ACEs and IFG connectivity as main effects, interactions with time, and interactions with each other. In each of these models, the main effect of ACEs remained highly significant ($p < .005$), but none of the connectivity effects remained significant (see Table S7, available online).

FIGURE 1 Inferior frontal gyrus (IFG) functional connectivity

Note: (A) Average resting state functional magnetic resonance imaging (rsfMRI) of the time-series from the left inferior frontal gyrus (IFG) region of interest (ROI) and every other voxel in the brain, thresholded at $p < .001$. (B) Regions for which adverse childhood experiences (ACEs) predicted rsfMRI with left IFG, thresholded at $p < .001$ and 35 contiguous voxels, for a whole-brain false-positive rate of $p = .05$ based on AFNIs 3dClustSim. (C) Average rsfMRI of the time-series from the right IFG ROI and every other voxel in the brain, thresholded at $p < .001$. (D) Regions for which ACEs predicted rsfMRI with right IFG, thresholded at $p < .001$ and 35 contiguous voxels, for a whole-brain false-positive rate of $p = .05$ based on AFNIs 3dClustSim.

IFG Connectivity and IFG Volume

We examined whether IFG volume from scan wave 1 was associated with the IFG connectivity predicted by ACEs at scan wave 1. There were no significant correlations that survived FDR correction ($r < |0.19|$, $p > .045$). Next, we determined whether there were any interactions between IFG volume and connectivity in predicting externalizing symptoms. As shown in Table S8 (available online), in models that included both volume and connectivity, the connectivity measures continued to predict externalizing symptoms, whereas IFG volume did not. There were no significant interactions (see Table S7, available online).

Role of ACEs

Some researchers have argued that poor child outcomes are carried through parental psychopathology that is transmitted to children through either genetic or environmental factors, and that ACEs are just an epiphenomenon. Thus, we examined whether the relationships between ACEs and functional connectivity and ACEs and psychopathology held if one controlled for maternal education, familial psychopathology, and maternal depression at the time of the scan. All of the findings held robustly even when controlling for these factors (all $p < .001$).

DISCUSSION

The goals of the current analyses were to determine the degree to which ACEs predicted connectivity of the same IFG area showing altered volume in our prior work, and whether ACE-related connectivity predicted either externalizing or internalizing symptoms over childhood and early adolescence. Extending prior work, we found that ACEs predicted connectivity of the IFG to bilateral posterior parietal cortex, cuneus, premotor cortex, DLPFC, and the cerebellum. Most importantly, connectivity between IFG and all of the regions predicted by ACEs also predicted the average severity of externalizing symptoms over childhood and early adolescence, but did not predict internalizing, suggesting evidence for a specific relationship of IFG connectivity to subsequent externalizing psychopathology.

ACEs were associated with more negative connectivity between the right IFG and right precentral gyrus. The precentral gyrus is often associated with motor function, and right-sided activation has been seen during successful inhibition.⁵³ In contrast, ACEs predicted less negative connectivity of the left IFG with the bilateral inferior parietal lobule, left dorsal prefrontal cortex, and 2 regions of the cerebellum (i.e., the culmen and declive). Interestingly, the bilateral parietal and dorsal prefrontal regions were ones that showed average negative connectivity with the IFG

TABLE 2 Adverse Childhood Experiences (ACEs) Predicting Scan 1 Resting State Functional Magnetic Resonance Imaging With Left and Right Inferior Frontal Gyrus

Seed Region	Region Name	Average Fisher <i>r</i> to <i>z</i> With Seed Region ^a	Brodmann Areas	X	Y	Z	Size (mm ³)	<i>r</i> With ACEs ^b
Right inferior frontal gyrus	Right precentral gyrus	-.05***	4	32	-19	55	891	-.44
Left inferior frontal gyrus	Culmen (cerebellum)	-.06***	NA	-23	-56	-22	1395	.57
	Declive (cerebellum)	-.001		15	-68	-21	549	.46
	Left dorsolateral prefrontal	.04*	46	-45	27	20	333	.42
	Right cuneus	-.05***	19	3	-82	30	1278	-.45
	Left inferior parietal lobule	-.09***	40	-40	-43	50	3888	.57
	Right inferior parietal lobule	.05***	40	39	-41	52	1791	.49

Note: NA = not applicable.

^aTo illustrate the direction of "typical" connectivity.

^bFor descriptive purposes, to illustrate the direction of the relationships. Significance is not indicated since the regions were selected based on their significant relationship to ACEs.

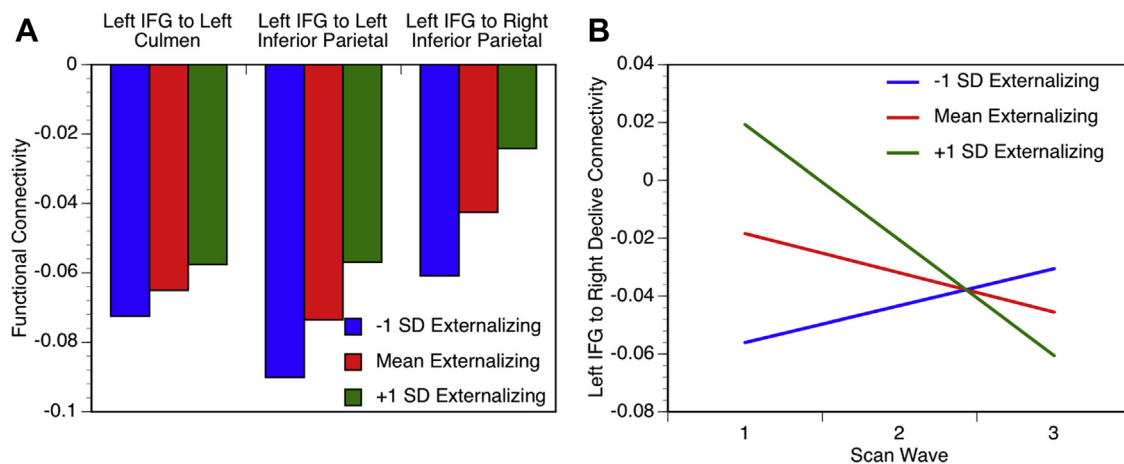
p* < .05; *p* < .01; ****p* < .001.

and are part of the parietal cortex and dorsal frontal cortex that are often considered part of the default mode network.⁵⁴ It has been hypothesized that negative correlations between regions involved in cognitive control and impulse regulation, including IFG, and regions in the default mode network may be necessary for effective cognitive and emotional function.⁵⁴ Thus, the fact that ACEs was associated with a reduction in such negative correlations is consistent with an association between ACEs and behaviors associated with poor impulse control (e.g., externalizing symptoms). The cerebellar regions also showed average negative connectivity and are close to the part of the cerebellum that has been shown to display functional connectivity with the default mode network.⁵⁵ Thus, it is possible that this pattern is related to the same role hypothesized for the negative connectivity between IFG and the parietal and dorsal frontal regions of the default mode network.

Much of the earlier work on the relationship of ACEs and poverty to brain structure and function and to psychopathology has provided a

strong evidence for a link between the hippocampal/amygdala structure and function and the development of internalizing psychopathology. Furthermore, our prior work on ACEs and the volume of IFG also suggested a relationship to internalizing pathology. Here we provide evidence for a potentially different pathway that may relate ACEs to externalizing psychopathology. Our findings replicate, extend, and connect prior work linking 1) ACE and poverty exposure to prefrontal function,^{25,26} and 2) alterations in prefrontal function and externalizing psychopathology.^{34,35,56} We found that ACEs predicted the connectivity of the IFG in childhood, and that the connectivity of the IFG in turn predicted the severity of externalizing psychopathology over middle childhood and early adolescence. We also found that, for a subset of the regions (left IFG to culmen and bilateral inferior parietal), the relationship between variation in connectivity and variation in externalizing symptoms was maintained across all 3 scan waves. Importantly, this variation in IFG connectivity did not predict internalizing

FIGURE 2 Externalizing and functional connectivity



Note: (A) Graph of relationships of externalizing symptoms to left inferior frontal gyrus (IFG) to left culmen and right and left inferior parietal. These connections showed a significant main effect of externalizing symptoms (see Table S5, available online). (B) Graph of relationship of externalizing symptoms to left IFG to right declive connectivity across scan waves. This connection showed a significant externalizing by time interaction (see Table S5, available online).

psychopathology, providing evidence for a more specific relationship of IFG functional connectivity and externalizing psychopathology. As noted above, in prior work we had found that IFG volume was related to later depression and physical health, but not externalizing symptoms. The current findings of a relationship between IFG connectivity and externalizing is more consistent with a putative role for IFG in impulse control and inhibition.^{39,40} Furthermore, prior work has also found that thinner IFG in early adolescence predicted greater drinking and externalizing psychopathology in later adolescence.³⁸ Thus, although speculative, one hypothesis is that variation in impulse control might be a factor linking IFG connectivity to later externalizing psychopathology. It is surprising that we did not find a link between IFG volume externalizing psychopathology. It is possible that this suggests a specific role for the connections of the IFG rather than for the function or structure of the IFG itself. However, it is also possible that IFG volume/thinning might predict psychopathology in this sample when the children are older, a result that would be consistent with previous work.³⁸

We found that these connectivity predictions of externalizing symptoms remained significant, except for the left IFG to the left DLFPC, even if we controlled for child psychopathology up to the time of the first scan, suggesting that they were predicting ongoing and/or newly developing externalizing psychopathology over and above risk from prior psychopathology. However, neither ACEs nor IFG connectivity interacted with time in predicting externalizing symptoms across waves, suggesting that they predicted an overall increase in externalizing across childhood and adolescence, but not the rate of increasing symptoms. It is possible that evidence for ACEs and/or IFG connectivity predicting increasing externalizing symptom severity with time will emerge as these children age into later adolescence and adulthood, as the normative increases in risk taking and substance use that occur during this time period may exacerbate already-present externalizing symptoms.

Our analyses did not show that IFG connectivity mediated the relationship of ACEs to externalizing. However, the relationships of ACEs to IFG connectivity does provide some clues as to one potential neurobiological mechanism that may be contributing to the negative long-term outcomes all too frequently associated with early poverty and adversity. In future work, it would be important to examine further ways in which brain connectivity may interact with other potential mechanisms or mediators to predict outcome in children who have experienced early adversity. This includes examining interactions across brain regions the function or structure of which might be affected by ACEs (i.e., hippocampal/amygdala and prefrontal), interactions with ongoing environmental factors (e.g., continued exposure to adversity versus improvement), and/or the influences of interventions provided at different developmental stages.

We cannot rule out the possibility that poor child outcomes are carried through genetic or environmental transmission of parental psychopathology and that ACEs are just an epiphenomenon.⁵⁷ However, experiments of nature and interventions that improve income levels reduce child psychopathology.^{58,59} If the effects, at least for poverty, were being driven solely by genetic predisposition, one would not expect such a reduction. We also examined whether the relationships between ACEs and functional connectivity held if one controlled for maternal education, familial psychopathology, and maternal depression at the time of scan, and all findings held robustly. Thus, although these covariates may not have captured all potential confounding factors and although further research is needed to address this question, we think that there is intriguing evidence consistent with a causal role for ACEs, although genetics could clearly also be playing a role. In addition, our primary analyses used an ACE score that combined indicators of poverty and indicators of trauma, both of which

demonstrated the same relationships to IFG connectivity and psychopathology outcomes. However, there is other work suggesting potentially dissociable effects of deprivation and trauma.^{12,13} Thus, it will be important to continue to examine these questions in future work, although this is challenging in community-based samples such as the one presented here, given that deprivation and trauma all too frequently occur together. Furthermore, it will also be important to examine other factors that may moderate the relationship between ACEs and later child outcomes, such as parent or other caretaker support.

Although this sample provides a unique opportunity to examine prospectively assessed adversity and poverty experienced early in life on child brain and mental health outcomes, it also has its limitations. During recruitment in preschool, children were oversampled for early signs and symptoms of depression, which may make this sample less representative of the general population. Moreover, the currently available data for this sample do not include direct performance-based measures of impulse control or emotional regulation. However, ongoing follow-up waves have incorporated such measures, allowing us to directly test this hypothesis in future work.

The current data extend the existing literature suggesting important links between early adversity and poverty, IFG connectivity, and later externalizing psychopathology. The association that we found of IFG connectivity with externalizing but not internalizing psychopathology fits with the extant literature on the role of the IFG in impulse control and emotion regulation,^{29,30} combined with work on impairments in impulse control and emotion regulation in externalizing psychopathology.³¹ These data add to the literature documenting the long-lasting negative impacts of early adversity, and highlight the critical need to make progress in prevention or intervention efforts that either reduce the occurrence of such adversity or provide buffers or treatments that ameliorate its long-term negative consequences.

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Ms. Tillman served as the statistical expert for this research.

Drs. Luby, Barch, and Belden had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Luby, Barch, Belden; Acquisition of data: Belden, Luby, Barch; Analysis and interpretation of data: Tillman, Whalen, Barch, Belden; Drafting of the manuscript: Luby and Barch; Critical revision of the manuscript for important intellectual content: Luby, Barch, Whalen, Belden; Statistical analysis: Tillman, Whalen; Obtained funding: Luby, Barch; Administrative, technical, or material support: Tillman; Study supervision, Luby, Barch, Belden.

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