IMPORTANCE Adverse childhood experiences (ACEs) have been associated with poor mental and physical health outcomes. However, the mechanism of this effect, critical to enhancing public health, remains poorly understood.

OBJECTIVE To investigate the neurodevelopmental trajectory of the association between early ACEs and adolescent general and emotional health outcomes.

DESIGN, SETTING, AND PARTICIPANTS A prospective longitudinal study that began when patients were aged 3 to 6 years who underwent neuroimaging later at ages 7 to 12 years and whose mental and physical health outcomes were observed at ages 9 to 15 years. Sequential mediation models were used to investigate associations between early ACEs and brain structure, emotion development, and health outcomes longitudinally. Children were recruited from an academic medical center research unit.

EXPOSURE Early life adversity.

MAIN OUTCOMES AND MEASURES Early ACEs in children aged 3 to 7 years; volume of a subregion of the prefrontal cortex, the inferior frontal gyrus, in children aged 6 to 12 years; and emotional awareness, depression severity, and general health outcomes in children and adolescents aged 9 to 15 years.

RESULTS The mean (SD) age of 119 patients was 9.65 (1.31) years at the time of scan. The mean (SD) ACE score was 5.44 (3.46). The mean (SD) depression severity scores were 2.61 (1.78) at preschool, 1.77 (1.58) at time 2, and 2.16 (1.64) at time 3. The mean (SD) global physical health scores at time 2 and time 3 were 0.30 (0.38) and 0.33 (0.42), respectively. Sequential mediation in the association between high early ACEs and emotional and physical health outcomes were found. Smaller inferior frontal gyrus volumes and poor emotional awareness sequentially mediated the association between early ACEs and poor general health (model parameter estimate = 0.002; 95% CI, 0.0002-0.056) and higher depression severity (model parameter estimate = 0.007; 95% CI, 0.001-0.021) in adolescence. An increase from 0 to 3 early ACEs was associated with 15% and 25% increases in depression severity and physical health problems, respectively.

CONCLUSIONS AND RELEVANCE Study findings highlight 1 putative neurodevelopmental mechanism by which the association between early ACEs and later poor mental and physical health outcomes may operate. This identified risk trajectory may be useful to target preventive interventions.

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Published online October 30, 2017.

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here is growing evidence that psychosocial adversity experienced during childhood increases risk for poor physical and mental health outcomes later in life. In 1998, the landmark study of Felitti et al1 provided the first evidence for an association between adverse childhood experiences (ACEs) and increased risk for later physical health problems using retrospective data from an epidemiologic sample. Notably, these novel findings, which challenged existing models of disease, were not embraced by the scientific and medical community until more recent prospective longitudinal investigations and meta-analyses confirmed this association.2-4 After this, numerous studies have begun to investigate the mechanisms by which early psychosocial adversity, defined as deprivation and/or threat, such as abuse, neglect, and poverty, becomes biologically embedded in the developing child, contributing to poor emotional and physical health outcomes.5-12

Miller et al13 have proposed a theoretical model for the mechanisms by which early ACEs become biologically embedded to increase risk for later physical disease. Early childhood appears to be a particularly sensitive period for the negative effects of adversity, given greater plasticity of developing neural and other physiologic systems.6 The model by Miller et al13 accounted for behavioral and physiological processes and their interactions and outlined a process by which ACEs impact cells of the developing immune system to mount excessive inflammatory responses, developing into a chronic pro-inflammatory phenotype. This inflammatory state stimulates endocrine and autonomic responses, further accentuating risk.13,14 Behaviorally, ACEs promote hypervigilance to threat, a focus on immediate gratification over future reward, and poorer emotion regulation, shaping interactions with the environment and leading to increased health risk behaviors (eg, poor dietary choices, risky behaviors).13

Childhood psychosocial adversity has been shown to explain more than 20% to 30% of all onsets of mental disorders.15,16 More specifically, a large body of literature links ACEs, particularly abuse (threat) and neglect (deprivation), to risk for depression later in life.17-21 There is also evidence that early ACEs are associated with impaired emotion development during childhood, evidenced by decreased emotional awareness and regulation.22,23 Such deficits in emotion development have been theorized to be key to the developmental psychopathology of depression.24 Further, deficits in emotion awareness have been associated with increasing body mass index across later childhood, a well-established risk factor for poor health outcomes.25 These findings taken together suggest that emotion development may be a key and underrecognized factor in the risk trajectory linking early ACEs and later adolescent depression and physical health problems.

A rapidly growing related database has demonstrated that exposure to adversity, most often indexed by poverty, is associated with reductions in brain gray and white matter volumes.26-28 One of the most well-replicated human findings is an association between childhood adversity/poverty and reductions in hippocampal and amygdala volume.28,29 There are much retrospective data from adults linking these changes to risk for later psychopathology as well as some prospective data.29,30

Meaning

Findings elucidate a possible mechanistic pathway by which early childhood adversity leads to poor emotional and physical health outcomes and suggests specific targets for prevention.

Also of interest but less well investigated is the effect of early ACEs on alterations in the structure and function of the prefrontal cortex (PFC).31-38 Findings suggest a decrease in PFC volume broadly in addition to alterations in measures of PFC function relevant to emotion regulation.33 However, the regional specificity of PFC volume deficits associated with early ACEs remains unclear, as well as any role of such changes in the risk trajectory to poor health outcomes. One plausible mechanistic pathway contributing to the biological embedding of early ACEs is a model whereby early ACEs alter the development of the PFC, resulting in impaired emotional and behavioral functioning and leading to later emotional and physical health risk (Figure 1). Investigations of such pathways represent a critical gap in the literature, which is important for understanding and targeting this increasingly well-established risk trajectory with broad public health implications.

We sought to investigate whether volumetric alterations in specific PFC subregions involved in the expression and regulation of emotion were linked to the association between early ACEs, emotion function at school age, and depression/health in adolescence using data from a longitudinal neuroimaging study. We first examined regional specificity by investigating whether any specific PFC subregion was associated with early

Figure 1. Conceptual Model of Biological Embedding of Adversity With Mediating Associations

ACEs indicates adverse childhood events; S1, scan 1; T2, time 2; T3, time 3.

a1, the association between early ACEs and prefrontal subregion volumes; a2, the association between early ACEs and emotion/behaviors; b1, the association between prefrontal subregion volumes and physical/emotional health outcomes; b2, the association between emotion/behaviors and physical/emotional health outcomes; c, the direct effect between early ACEs and physical/emotional health outcomes; d1,2, the association between prefrontal subregion volumes and emotion/behaviors.
ACEs. We then examined whether the PFC subvolume associated with early ACEs was associated with reduced emotional functioning and whether these 2 variables operated as sequential mediators in the association between early ACEs and later depression severity and global physical health (GPH) problems in adolescence.

Methods

Participants
We used data from the Preschool Depression Study, a 15-year longitudinal neuroimaging study that examined preschool-aged children. Building on early behavioral waves, 3 waves of neuroimaging in middle to late childhood were added. At baseline, 306 children aged 3.0 to 5.11 years and their primary caregivers were recruited from the St Louis, Missouri, area, and a screening checklist was used to oversample preschoolers with elevated symptoms of depression. Analyses for the current study were conducted in a subsample (n = 119) with data on all of the variables of interest in each risk trajectory (depression, n = 116; GPH, n = 109). Not all participants experience ACEs. We used early ACEs data from behavioral waves when children were aged 3.0 to 7.11 years, magnetic resonance imaging data from scan 1 (ie, S1) when participants were aged 6.11 to 12.9 years, and behavioral data collected at time 2 (ie, T2) when participants were aged 9.3 to 14.3 years and time 3 (ie, T3) when participants were aged 10.7 to 15.7 years for this analysis. Of the 210 children who completed S1, 35 participants were missing ACEs data, 29 were missing other relevant data for the depression analyses, and 37 were missing other relevant data for the GPH analyses. Table 1 provides descriptive statistics for variables used in the mediation models of the sample (n = 119). Parental written consent and child assent in children aged 4 years and older for a protocol approved by the institutional review board at Washington University were obtained prior to study participation.

Measures

Early Adverse Childhood Experiences
To examine the effect of prospectively collected early ACEs on brain outcomes, we created an early ACEs score using the life events section of the Preschool Age Psychiatric Assessment (conducted at each assessment that occurred between ages 3.0 to 7.11 years) based on parent report. There was no cut-off or threshold for the ACEs score. Therefore, for this analysis early childhood was defined as the developmental period from ages 3 to 8 years. The ACEs variable was adapted from the original definition by Felitti et al but also included exposure to poverty because of its established role in brain development. The variables included in the ACEs sum score are included in the Box. All variables were coded as absent or present (0 vs 1), and adverse experiences (other than poverty) were only counted multiple times if they were nonredundant (eg, child was abused at age 3 years and again at age 4 years). For a more detailed description of the ACEs construct, see eTable in the Supplement.

Emotion Awareness
Emotion awareness was measured using the poor emotion awareness subscale of the Emotion Expression Scale for Children, which operationally defines poor emotion awareness as “difficulty labeling internal emotion experience” (eg, “Sometimes I just don’t have words to describe how I feel”). The poor awareness subscale is based on 8 child-reported items that are rated using a 5-point Likert-type scale (1 indicating not at all true and 5, extremely true). The subscale score is calculated by summing the 8 items.

Table 1. Statistics Used in Mediation Models

<table>
<thead>
<tr>
<th>Variables</th>
<th>Score, Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early ACEs</td>
<td>5.44 (3.46)</td>
</tr>
<tr>
<td>IFG volume, cm³ (S1)</td>
<td>27.16 (2.88)</td>
</tr>
<tr>
<td>Emotion awareness (T2)</td>
<td>17.37 (6.34)</td>
</tr>
<tr>
<td>Global physical health (T3)</td>
<td>0.33 (0.42)</td>
</tr>
<tr>
<td>Depression severity (T3)</td>
<td>2.16 (1.64)</td>
</tr>
<tr>
<td>Age, y (S1)*</td>
<td>9.65 (1.31)</td>
</tr>
<tr>
<td>Whole-brain volume, cm³ (S1)*</td>
<td>1139.48 (101.11)</td>
</tr>
<tr>
<td>Global physical health (T2)*</td>
<td>0.30 (0.38)</td>
</tr>
<tr>
<td>Depression severity (PS)*</td>
<td>2.61 (1.78)</td>
</tr>
<tr>
<td>Depression severity (T2)*</td>
<td>1.77 (1.58)</td>
</tr>
</tbody>
</table>

Abbreviations: ACEs, adverse childhood events; IFG, inferior frontal gyrus; PS, preschool; S1, scan 1; T2, time 2; T3, time 3.

* Used in models as covariates.

Box. Variables Included in the Early ACEs Score

- Poverty
- Traumatic life events
- Parental arrest
- Parental hospitalization
- Crash with motor vehicle, plane, or boat
- Unintentional burning, poisoning, or drowning
- Attacked by an animal
- Death of adult loved one
- Death of sibling or peer
- Domestic violence
- Hospitalized, visited emergency department, or had invasive medical procedure
- Man-made disaster
- Natural disaster
- Physical abuse
- Sexual abuse, sexual assault, or rape
- Witnessed someone threatened with harm, seriously injured, or killed
- Other traumatic life event
- Parental psychiatric disorders
- Parental suicidality
- Parental substance use disorder
- Other parental psychiatric disorder

Abbreviation: ACEs, adverse childhood events.
Depression Severity
Depression severity was measured during early childhood using parent-reported data on the Preschool Age Psychiatric Assessment at baseline and at outcome (T2 and time 3, ie, T3) based on parent and child report on the Child and Adolescent Psychiatric Assessment. Parent and child report were combined using the “either/or” rule, as has been established in child affective disorder research. Depression severity was calculated as the number of 9 core Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition) depression symptoms endorsed by the parent and/or child.

Global Health Outcomes
We used the GPH subscale of the McArthur Health and Behavior Questionnaire to assess GPH problems at outcome (T3) based on parent report of the child’s medical problems. This 5-item composite score assesses indicators of poor health and difficulties stemming from physical health problems (eg, missing school) with higher scores indicating worse physical health. Parents were asked to answer questions such as “In general, would you say your child’s physical health is excellent, good, fair, or poor?” and “How often in an average month does your child stay home or come home from school or childcare because of illness?”

Magnetic Resonance Imaging Acquisition
Structural images were collected as part of a longer scan session that also included acquisition of task-based and functional connectivity data. Imaging data were collected using a scanner (3-T Tim Trio system; Siemens). Time 1-weighted structural images were acquired in the sagittal plane using an magnetization-prepared rapid gradient-echo 3-dimensional sequence (repetition time = 2400 milliseconds; echo time = 3.16 milliseconds; flip angle = 8°; slab = 176 mm; 176 slices; matrix size = 256 × 256; field of view = 256 mm; voxel size = 1 × 1 × 1 mm).

Volumetric Segmentation and Regional Calculations
FreeSurfer version 5.1.0 software (http://surfer.nmr.mgh.harvard.edu/) was used to segment each participant’s anatomical image using the atlas by Destrieux et al, allowing estimation of gray matter volume for 5 PFC subregions. The white and pial FreeSurfer surfaces were visually inspected and were regenerated with manual intervention to correct errors when necessary. Overall PFC volume comprised 5 smaller subregions that were calculated from the Destrieux cortical atlas: (1) superior frontal volume = combined left and right superior frontal; (2) middle frontal volume = left and right rostral middle frontal + caudal middle frontal; (3) inferior frontal gyrus = left and right parsopercularis + pars triangularis + pars orbitalis; (4) orbital frontal volume = left and right lateral orbitofrontal + medial orbitofrontal; and (5) frontal pole volume = the sum of left and right frontal pole volumes. Whole-brain volume (total gray + cortical white matter volume) was also obtained from FreeSurfer.

Data Analysis
A multivariate regression with dependent variables (subregions of the PFC) superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus (IFG), orbital cortex, and frontal pole volume and independent variables ACEs, sex, and age at scan was run to determine which PFC regions were significantly associated with early ACEs. Two separate sequential mediation models were analyzed using the PROCESS macro for SAS (model 6) with 1 model testing depression severity as the outcome and the other model testing GPH as the outcome. PROCESS calculates a bias-corrected and accelerated bootstrapped confidence interval (10 000 resamples) for the size of each indirect effect, with significant mediation indicated by a confidence interval that does not contain 0. PROCESS model 6 tests all indirect and direct pathways included in the model (Figure 1). The a paths are the associations between the independent variable and the mediator variables. The b paths are the associations between the mediator variables and the dependent variable. The d path is the association between the 2 mediators, and the c’ path is the direct effect of the independent variable on the dependent variable. These sequential models included covariates to control for age, sex, whole-brain volume, and preexisting depression severity (when GPH is the dependent variable) or GPH and preschool depression severity (when depression severity is the dependent variable).

Results
Association Between ACEs and PFC Subregions
The multivariate regression that included the PFC subregions superior frontal gyrus, middle frontal gyrus, IFG, orbital cortex, and frontal pole volume was significant overall (Wilks’ λ = 0.896; F5,133 = 3.09; P = .01). Only 1 significant association between early ACEs and IFG volume was found (model parameter estimate = −0.223; SE = 0.071; t = −3.14; P = .002), which survived multiple comparison correction after covarying for sex and age (eTable in the Supplement). Thus, IFG volume was used in the following analyses.

Risk Trajectory From Early ACEs to Depression Severity
Mean (SD) and correlations for focal variables as well as covariates used in the mediation analyses are provided in Table 1 and Table 2. All independent variables were mean centered. The overall model explained 18% of the variance in depression severity (Figure 2). As expected and consistent with prior research, there was a significant total effect from early ACEs to depression severity (T3) (model parameter estimate = 0.11, P = .03). The total effect remained significant when age, sex, GPH (from the preceding wave T2), depression severity in early childhood, and whole-brain volume were included as covariates. Next we examined whether IFG volume and poorer emotion awareness would operate sequentially to mediate the association between early ACEs and depression severity, which it did (model parameter estimate = 0.03, 95% CI, 0.002-0.086). Higher early ACEs scores predicted decreased IFG volume (a1: model parameter estimate = −0.22, P = .005), which predicted poorer emotional awareness (d2: model parameter estimate = −0.58, P = .006), which predicted higher depression severity (b2: model parameter esti-
Table 2. Correlations of Variables Used in Mediation Models

<table>
<thead>
<tr>
<th>Variables by No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Early ACEs</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2. IFG volume, cm³ (S1)</td>
<td>-0.25*</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Emotion awareness (T2)</td>
<td>0.08</td>
<td>-0.25*</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>4. Global physical health (T3)</td>
<td>0.28*</td>
<td>-0.17</td>
<td>0.25*</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>5. Depression severity (T3)</td>
<td>0.29*</td>
<td>-0.23*</td>
<td>0.25*</td>
<td>0.35*</td>
<td>1.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Age, y (S1)</td>
<td>0.15</td>
<td>-0.08</td>
<td>0.04</td>
<td>0.11</td>
<td>0.10</td>
<td>1.0</td>
<td></td>
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</tr>
<tr>
<td>7. Whole-brain volume, cm³ (S1)</td>
<td>-0.15</td>
<td>0.63*</td>
<td>-0.22*</td>
<td>-0.07</td>
<td>0.05</td>
<td>0.07</td>
<td>1.0</td>
<td></td>
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</tr>
<tr>
<td>8. Global physical health (T2)</td>
<td>0.24*</td>
<td>-0.12</td>
<td>0.19*</td>
<td>0.53*</td>
<td>0.18</td>
<td>0.09</td>
<td>-0.00</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Depression severity (PS)</td>
<td>0.31*</td>
<td>-0.15</td>
<td>0.20*</td>
<td>0.13</td>
<td>0.22*</td>
<td>0.10</td>
<td>-0.01</td>
<td>0.25*</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>10. Depression severity (T2)</td>
<td>0.18</td>
<td>-0.08</td>
<td>0.23*</td>
<td>0.21*</td>
<td>0.35*</td>
<td>0.15</td>
<td>0.16</td>
<td>0.21*</td>
<td>0.22*</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Abbreviations: ACEs, adverse childhood experiences; IFG, inferior frontal gyrus; PS, preschool; S1, scan 1; T2, time 2; T3, time 3.
* P < .05.
† P < .01.
‡ Used in models as covariates.

Figure 2. Sequential Mediation Model Depicting Analysis of Mediating Associations Between ACEs and MDD Severity

Mediation model with parameter estimates was based on maximum likelihood procedures. ACEs indicates adverse childhood events; GPH, global physical health; MDD, major depressive disorder; PS, preschool; S1, scan 1; T2, time 2; T3, time 3; WBV, whole-brain volume. a1 Represents the association between early ACEs and inferior frontal gyrus volume; a2, the association between inferior frontal gyrus volume and MDD severity; b1, the association between inferior frontal gyrus volume and poor emotional awareness; b2, the association between early ACEs and depression severity; c′, the direct effect between early ACEs and depression severity; d1,2, the association between inferior frontal gyrus volume and poor emotional awareness.

P = .08). Early childhood adverse childhood events did not uniquely predict impaired emotion awareness (a2: model parameter estimate = 0.008, P = .97) and poorer emotional awareness did not significantly mediate the association between early ACEs and depression severity without IFG volume in the model (model parameter estimate = 0.0004; 95% CI, −0.017 to 0.022). However, poorer emotion awareness did uniquely predict depression severity (b2: model parameter estimate = 0.05, P = .04). Thus, poorer emotion awareness helped to explain the association between IFG volume to depression but was not a direct mediator of the associations between early ACEs and greater depression severity in early adolescence.

Risk Trajectory From Early ACEs to Global Physical Health

As shown in Figure 3, the overall model explained 16% of the variance in GPH. As expected and consistent with prior research, there was a significant total effect from early ACEs to GPH (T3) (c: model parameter estimate = 0.03, P = .03). The total effect remained significant when age, sex, depression severity (from the preceding wave T2) and whole-brain volume were included as covariates. An increase from 0 to 3 in early ACEs was associated with a 25% increase in children's GPH problems. Next, we examined whether IFG volume and impaired emotion awareness would operate sequentially to mediate the association between early ACEs and GPH problems. Higher early ACEs scores predicted decreased IFG volume (a1; β = −0.19, P = .02), which predicted poorer emotional awareness (d1,2: α = −0.59, P = .006), which predicted higher GPH problems (b2: β = 0.01, P = .04). Thus, results indicated the 3-path serial mediation with 4 covariates was significant (model parameter estimate = 0.002; 95% CI, 0.0002-0.0056).

When we decomposed the sequentially mediated effect, results indicated that only the indirect sequential effect was significant. That is, there were no significant indirect effects of early ACEs on GPH when tested using only IFG as a mediator or when using poor emotion awareness as a mediator.

Although health records were not obtained and the variance in health problems reported by parents was low, the poly-
Figure 3. Sequential Mediation Model Depicting Analysis of Mediating Associations Between Early ACEs and GPH Problems

| Mediation model with parameter estimates was based on maximum likelihood procedures. ACEs indicates adverse childhood events; GPH, global physical health; MDD, major depressive disorder; S1, scan 1; T2, time 2; T3, time 3; WBV, whole-brain volume. a1 represents the association between early ACEs and inferior frontal gyrus volume; a2, the association between early ACEs and poor emotional awareness; b1, the association between inferior frontal gyrus volume and GPH problems; b2, the association between poor emotional awareness and GPH problems; c′, the direct effect between early ACEs and GPH problems; d1, the association between inferior frontal gyrus volume and poor emotional awareness. *P < .05. **P < .01.

Discussion

These study findings elucidate 1 possible contributing mechanistic neurodevelopmental pathway by which early ACEs confers risk for later depressive symptoms and physical health problems in adolescence. A sequential mediation was found where early ACEs predicted the volume of the IFG, a structure known to be associated with impulse control, emotion processing, and regulation, and IFG volume in turn predicted emotion awareness. The finding that the IFG emerged as the only region negatively affected by ACEs (that survived multiple comparisons) is of interest and could suggest this is a region uniquely sensitive to the effects of early adversity. One rationale for the sensitivity of IFG to early adversity/stress is suggested by nonhuman primate data showing a high density of glucocorticoid receptors in this region. However, future work is needed to investigate any drivers of regional sensitivity to stress in the PFC in humans.

These factors sequentially mediated the risk between early ACEs and later depression severity. This model suggests the possibility that early ACEs have a specific deleterious effect on the development of the IFG, a subregion of the PFC involved in inhibitory control and emotion function, resulting in deficits in emotion development, which then contribute to risk for increased depressive symptoms. These findings build on the extant literature where associations between these variables separately have been reported, bringing these factors together in a plausible neurodevelopmental risk trajectory.

A similar model (with weaker effects) was evident for the risk trajectory to physical health problems. This finding was notable given that the patient sample had only reached adolescence when health outcomes were measured, a developmental period prior to the time typically associated with higher risk for health problems in prior work on ACEs. To date and to our knowledge, most studies that establish links between ACEs and later health problems have been conducted in middle-aged and older adults. Although a measure of documented health problems would be ideal, these data were not available in the current dataset. However, it was notable that this effect remained even when controlling for prior depression and was moderately correlated with parent report of chronic medical conditions, suggesting it is not merely somatization due to mental health problems. Future studies that assess verifiable health problems are needed to confirm this finding. However, current findings suggest that these effects can be detected earlier in development during the adolescent period and provides a mechanistic framework to understand the risk trajectory. It will be important to continue to follow health outcomes in this sample into later adulthood when a variety of chronic health problems are more likely to arise and more powerful effects might become evident.

Limitations and Strengths

A limitation of the study was that the sample was enhanced for preschoolers with symptoms of depression, although our findings remained significant when early childhood depression severity was controlled as noted above. Thus, the findings should be replicated in community samples to ascertain whether the same process can be identified in the general population. The assessment of physical health based on parent report rather than medical record is a limitation of the design, and future investigations would benefit from access to clinical records of physical health outcomes. In addition, the sample size is relatively small for the analyses conducted, and these findings should be replicated in larger samples. It should be noted that the ACEs variable used included income-to-needs, which is not a standard component of other reports on ACEs. Although we feel this is a strength of the analysis, it should be considered when comparing these findings with the extant literature. The main strengths of the study include the prospective longitudinal design that started in the preschool period and includes neuroimaging and detailed measures of emotion functioning and mental health.

Conclusions

The finding that similar risk factors emerged linking early ACEs to both increased depression severity and physical health problems is intriguing. This suggests that a common biological embedding process may operate linking early adversity and poor emotional and physical health outcomes. This finding is globally consistent with the model proposed by Miller et al., although the role of immune factors proposed in that model have
yet to be investigated in relation to emotional health outcomes. Future studies that address the specific biological and physiological processes on an epigenetic, immune, and neurobiological level are needed to further examine the mechanisms of this risk trajectory so that opportunities for more effective prevention can be targeted.

ARTICLE INFORMATION
Accepted for Publication: July 18, 2017.
Published Online: October 30, 2017.

Author Contributions: Dr Luby had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Luby, Barch, Belden.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Luby, Whalen, Tillman, Belden.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Barch, Whalen, Tillman, Belden.
Obtained funding: Luby, Barch, Belden.
Administrative, technical, or material support: Luby, Barden.
Supervision: Luby, Barch.
Conflict of Interest Disclosures: Dr Luby receives royalties from Guilford Press. Dr Barch consults for Uphser-Smith, Pfizer, and Amgen on work unrelated to this article. No other disclosures were reported.
Funding/Support: Drs Luby, Barch, Whalen, and Belden were funded by the National Institute of Mental Health.
Role of the Funder/Sponsor: The National Institute of Mental Health had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.
Additional Contributions: We thank the families participating in the Preschool Depression Study.

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