Effects of childhood poverty and chronic stress on emotion regulatory brain function in adulthood

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Childhood poverty has pervasive negative physical and psychological health sequelae in adulthood. Exposure to chronic stressors may be one underlying mechanism for childhood poverty–health relations by influencing emotion regulatory systems. Animal work and human cross-sectional studies both suggest that chronic stressor exposure is associated with amygdala and prefrontal cortex regions important for emotion regulation. In this longitudinal functional magnetic resonance imaging study of 49 participants, we examined associations between childhood poverty at age 9 and adult neural circuitry activation during emotion regulation at age 24. To test developmental timing, concurrent, adult income was included as a covariate. Adults with lower family income at age 9 exhibited reduced ventrolateral and dorsolateral prefrontal cortex activity and failure to suppress amygdala activation during effortful regulation of negative emotion at age 24. In contrast to childhood income, concurrent adult income was not associated with neural activity during emotion regulation. Furthermore, chronic stressor exposure across childhood (at age 9, 13, and 17) mediated the relations between family income at age 9 and ventrolateral and dorsolateral prefrontal cortex activity at age 24. The findings demonstrate the significance of childhood chronic stress exposures in predicting neural outcomes during emotion regulation in adults who grew up in poverty.

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Childhood poverty has been linked to emotion dysregulation, which is further associated with negative physical and psychological health in adulthood. The current study provides evidence of prospective associations between childhood poverty and adult neural activity during effortful attempts to regulate negative emotion. Adults with lower family income at age 9 exhibited reduced ventrolateral and dorsolateral prefrontal cortex activity and failure to suppress amygdala activation at age 24. Chronic stressor exposure across childhood mediated the relations between family income at age 9 and prefrontal cortex activity. The concurrent adult income, on the other hand, was not associated with neural activity. The in

Significance

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The authors declare no conflict of interest.

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(36, 37) in adolescence when concurrent levels of poverty exposure were controlled. In these studies, poverty exposure at age 9 was concurrently and prospectively associated with chronic stress exposure at age 9, 13, and 17 (37–39), and elevated chronic stress, in turn, mediated the association between childhood poverty and later outcomes. Furthermore, animal studies and recent human brain imaging studies demonstrate that repeated exposure to chronic stress impacts amygdala and PFC development, potentially leading to impaired emotion regulation (40–43).

Therefore, in this longitudinal study, we investigated whether childhood family income was associated prospectively with adult neural activity in the amygdala and PFC during emotion regulation. We also examined a stress pathway linking childhood poverty and the subsequent neural functions for emotion regulation. The current study used family income assessed at age 9 as a direct measure of childhood poverty exposure. To investigate the developmental timing of poverty and neural functioning, we examined the link between childhood poverty and adult neural functioning after controlling for adult income levels. We used a well-established emotion regulation functional magnetic resonance imaging (fMRI) paradigm (18, 44), in which participants are instructed to experience the natural emotional state (Maintain) or to decrease the intensity of their negative affect by using cognitive reappraisal (Reappraisal) while viewing negative images. We hypothesized that, in the contrast of Reappraisal vs. Maintain conditions, low family income at age 9 would be associated with increased amygdala and decreased PFC activation. The amygdala and PFC activation may also be associated with self-reports of emotion regulation (Materials and Methods). Furthermore, we assessed chronic stress by averaging exposure to multiple physical (i.e., substandard housing, crowding, and noise) and social (i.e., family turmoil, violence, and child–family separation) risk factors across ages 9–17. We hypothesized that the influence of childhood income on amygdala and PFC activity would be mediated by chronic stress exposure throughout childhood.

Results

Descriptive and Behavioral Data. Ratings of negative affective state between two conditions, Reappraisal and Maintain, were significantly different, t(48) = 4.13, P < 0.001. The average ratings decreased from the Maintain (mean = 2.93 ± 0.81) to Reappraisal (mean = 2.48 ± 0.95). However, the success of regulating negative emotions (calculated by subtracting Reappraisal ratings from Maintain ratings) was not significantly associated with family income at age 9, chronic stress exposure across ages 9–17, or current adult income levels at age 24.

Family Income at Age 9 and Neural Emotion Regulation at Age 24. Reappraisal of emotion (compared with maintaining one’s emotional response) produced greater activation in bilateral inferior/middle/superior frontal gyrus, precentral gyrus, striatum, insula, parietal lobe, and temporal gyrus (P < 0.05, corrected for multiple comparisons; Materials and Methods). However, no amygdala activation was detected in the contrast of Reappraisal vs. Maintain using a region of interest (ROI) approach, although bilateral amygdala activation was detected on Reappraisal (vs. Baseline) and Maintain (vs. Baseline) conditions (P < 0.05, corrected).

Enhanced neural activation during Reappraisal was predicted by family income at age 9. In particular, in the contrast of the Reappraisal vs. Maintain, lower family income at age 9 predicted reduced activation in the left DLPFC (Fig. 1A), VLPFC/insula/temporopolar area (Fig. 1B), precentral gyrus, and inferior parietal lobe/superior temporal gyrus (Ps < 0.05, corrected; Table 1; all analyses controlled for current income). No cluster was identified with a significant positive association with the current, adult income level.

Amygdala ROI analysis revealed that activation in the Reappraisal vs. Maintain conditions was negatively associated with childhood income in the left amygdala (r(46) = 2.48, x, y, z = –58, –2, –22; 140 voxels) (P < 0.05, uncorrected) (Fig. 1C), controlling for adult income level. Besides the amygdala activity from ROI analysis, no other cluster showed a negative association with family income at age 9 or current adult income level.

Furthermore, we explored functional connectivity between the left amygdala and VLPFC/DLPFC regions using the psychophysiological interaction (PPI) analysis at P < 0.001, uncorrected, cluster size > 10 voxels (SI Text). The analysis revealed that amygdala activity was positively coupled with the left VLPFC [x, y, z = –58, 18, 8; 58 voxels; r(46) = 0.74; Fig. S1] during Reappraisal among individuals with lower family income at age 9, whereas amygdala activity was negatively coupled with the left VLPFC during Reappraisal among individuals with higher family income at age 9 (Fig. S2). Family income at age 9 was not associated with the amygdala–DLPFC connectivity.

Finally, we calculated the correlation between regulation success scores and the amygdala, VLPFC, and DLPFC activity during Reappraisal. The correlation analysis revealed that Reappraisal success was positively correlated with both DLPFC [r (49) = 0.31; P < 0.05] and VLPFC [r(49) = 0.27; P < 0.05], but not with amygdala activity. Thus, DLPFC and VLPFC activity during Reappraisal was associated with greater success in down-regulating negative emotions. However, the use of everyday reappraisal coping (Materials and Methods) was not associated with the neural activity.
Childhood Chronic Stressor Exposure as a Mediator. We next tested whether exposure to chronic stressors during childhood (ages 9–17) mediated the relations between family income at age 9 and adult DLPFC and VLPFC activity during Reappraisal. Elevated childhood chronic stress exposure mediated the associations between family income at age 9 and increased adult left DLPFC activity during Reappraisal, controlling for concurrent, adult income (Fig. 2A). The addition of childhood chronic stress shrank the beta weight for childhood income 75%, which was no longer significant and suggested full mediation [indirect effect = 0.09, 95% confidence intervals (CIs) = 0.02–0.18].

Because the size of the suprathreshold cluster including the left VLPFC was large and contained other parietal and temporal regions, an ROI approach was used to separate the estimated activity of the left VLPFC from the estimated activity of other regions. We placed an 8 mm radius sphere at the left VLPFC peak (x, y, z = –50, 22, 6) from a meta-analysis of fMRI reappraisal studies (19). We found elevated chronic stress exposure across ages 9–17 mediated the relations between family income at age 9 and increased left VLPFC activity during Reappraisal, controlling for concurrent adult income (Fig. 2B). The addition of childhood chronic stress shrank the beta weight for childhood income 64%, which was no longer significant and suggested full mediation (indirect effect = 0.09, 95% CIs = 0.02–0.16). An analysis performed on amygdala activity did not find a mediation effect.

Discussion

We examined whether childhood poverty was prospectively linked to adult neural activity in the PFC and amygdala, regions centrally involved in emotional regulation. We found a significant relation between childhood income and neural functions. During emotion regulation with cognitive reappraisal, lower family income at age 9 was associated with reduced activity in the adult DLPFC and VLPFC but increased amygdala activity. In contrast to childhood income level, current income level as an adult was not linked to neural activity during emotion regulation. When the individual’s stress history was incorporated into our model, exposure to chronic stressors throughout childhood (i.e., ages 9–17) mediated the links between family income at age 9 and reduced adult DLPFC and VLPFC activity. Reduced PFC and increased amygdala activity among adults who grew up in poverty provides evidence for neural embedding of childhood poverty. Furthermore, the mediating role of chronic stressor exposure in childhood may help account for the link between childhood poverty and adult neural functions, which may contribute to physiological and psychological stress regulation difficulties.

We found that lower family income at age 9 was associated with reduced DLPFC and VLPFC activity in 24-y-olds during emotion regulation using cognitive reappraisal. Both DLPFC and VLPFC are involved in cognitive control and executive functioning and facilitate goal-directed behaviors (45). Furthermore, increased DLPFC and VLPFC activity was associated with greater success in down-regulating negative emotions, further supporting the role of these cortical regions in emotion regulation. In contrast to reduced DLPFC and VLPFC activity, family income at age 9 was associated with increased adult amygdala activity during emotion regulation. More specifically, the data in Fig. 1C suggest that in adults who had higher family income at age 9, the negative values of neural activity suggest less amygdala activity during Reappraisal relative to the Maintain condition. However, in those with lower family income at age 9, the positive values of neural activity suggest greater amygdala activity during Reappraisal than Maintain, indicating potential failure of amygdala regulation using Reappraisal. The functional connectivity findings further suggested altered relations between the amygdala and VLPFC activity in the context of childhood poverty exposure. A negative amygdala–VLPFC coupling among individuals with lower family income at age 9 suggests that higher childhood family income is associated with greater VLPFC activity to suppress amygdala activity during emotion regulation. On the other hand, a positive amygdala–VLPFC coupling during Reappraisal suggests that lower childhood income is associated with ineffective amygdala activity suppression of the VLPFC activity during emotion regulation. Such failure of amygdala regulation, in part by the dampened VLPFC and DLPFC activity, has been suggested as neural deficits in many psychiatric illnesses associated with childhood exposure to chronic stress.

With regard to the amygdala findings, we found no main effect of Reappraisal (vs. Maintain) on diminishing amygdala activity; therefore, the potential interpretation of the reappraisal-related

**Table 1. Brain areas with the positive associations between family income-to-needs ratio at age 9 and neural activity in the Reappraise vs. Maintain contrast at age 24**

<table>
<thead>
<tr>
<th>Area of activation</th>
<th>Brodmann area</th>
<th>Side</th>
<th># voxels</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>t(1, 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorsolateral PFC</td>
<td>9, 46</td>
<td>L</td>
<td>343</td>
<td>–40</td>
<td>12</td>
<td>28</td>
<td>3.99</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>–46</td>
<td>0</td>
<td>48</td>
<td>3.92</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>–42</td>
<td>2</td>
<td>38</td>
<td>3.13</td>
</tr>
<tr>
<td>Ventrolateral PFC</td>
<td>47, 13, 38</td>
<td>L</td>
<td>672</td>
<td>–46</td>
<td>10</td>
<td>–8</td>
<td>4.04</td>
</tr>
<tr>
<td>Insula</td>
<td></td>
<td></td>
<td></td>
<td>–28</td>
<td>14</td>
<td>–14</td>
<td>3.95</td>
</tr>
<tr>
<td>Temporopolar area</td>
<td></td>
<td></td>
<td></td>
<td>–48</td>
<td>22</td>
<td>–2</td>
<td>3.30</td>
</tr>
<tr>
<td>Precentral gyrus</td>
<td>6, 8</td>
<td>R, L</td>
<td>602</td>
<td>0</td>
<td>12</td>
<td>68</td>
<td>4.26</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>8</td>
<td>26</td>
<td>64</td>
<td>4.03</td>
</tr>
<tr>
<td>Superior temporal</td>
<td>22, 40</td>
<td>L</td>
<td>293</td>
<td>–2</td>
<td>20</td>
<td>58</td>
<td>3.20</td>
</tr>
<tr>
<td>gyrus, inferior</td>
<td></td>
<td></td>
<td></td>
<td>–58</td>
<td>48</td>
<td>32</td>
<td>3.60</td>
</tr>
<tr>
<td>parietal gyrus</td>
<td></td>
<td></td>
<td></td>
<td>–56</td>
<td>56</td>
<td>30</td>
<td>3.14</td>
</tr>
</tbody>
</table>

P < 0.05, corrected. L, left; MNI, Montreal Neurological Institute; PFC, prefrontal frontal cortex; R, right.
Growing animal and human evidence suggests exposure to chronic stress in early childhood produces lasting neurobiological changes that may reframe the understanding of childhood SES, poverty, and childhood poverty predicted activity in several other frontal, parietal, and temporal regions of the adult brain, including the precentral gyrus, inferior parietal lobes, superior temporal gyrus, and temporal regions of the adult brain, including the precentral gyrus and inferior parietal lobes, during cognitive reappraisal. In all of these regions, low family income at age 9 predicted reduced activity during cognitive reappraisal. Each of these regions has been shown to be involved in emotion regulation via cognitive reappraisal (18, 19, 44). The precentral gyrus contributes to the top-down control of cognitive and emotional processes through selective attention. Although we did not find a significant association between childhood income and amygdala, it is involved in reappraisal, the precentral gyrus is structurally interconnected and frequently activated with the mPFC as well as lateral PFC during Reappraisal (50). The inferior parietal lobes is a part of the attention system along with the DLPCF (51). Thus, the activity in the precentral gyrus and inferior parietal lobes may contribute to reappraisal by selectively monitoring information. Previously, adult retrospective reports of childhood SES have been associated with lower activity in the inferior partial lobe during monetary reward processing (52). Temporopolar area and superior temporal gyrus are related to the representation of perceptual and semantic information that likely assists in the reappraisal process (18). Thus, the significant associations between childhood family income and neural activity in these regions uncovered herein may reflect the pervasive effects of childhood SES disparities on neural functions across multiple regions involved in emotional regulation.

We also tested the hypothesis that exposure to chronic stressors across ages 9–17 would help explain the relations between childhood poverty and reduced DLPCF and VLPFC activity during emotion regulation (Chorpita) 

The current study revealed that childhood poverty is related to reduced activity in the VLPFC and DLPFC and increased activity in the amygdala during emotion regulation among young adults. Furthermore, in both the DLPCF and VLPFC, childhood chronic stress exposure mediated the relations between childhood poverty and increased activity during emotion regulation. The current study demonstrates the significance of childhood family income and stress exposure in predicting neural outcomes in young adults during emotion regulation. Greater knowledge about the developmental timing of risk exposures and brain development would be extremely valuable for informing interventions. Thus, future longitudinal studies should examine the timing of childhood poverty, stressor exposures, and brain development, ideally from conception throughout childhood.

Materials and Methods

Participants. Participants were initially recruited for a longitudinal study on rural poverty and child development (mean age, 9.2 y) in rural counties in the Northeastern United States from public schools, the Cooperative Extension...
Procedure. In the longitudinal study, a pair of trained researchers visited children’s homes at each wave of data collection, independently interviewing the participant and his/her mother. Only one child per household was eligible for the study. Demographic information, measures of mental health, and chronic stress exposure were assessed during the home visits. In the fMRI study, participants visited the University of Michigan’s neuroimaging center, where trained researchers administered training and fMRI sessions.

Measures. Income-to-needs. The ratio of family income-to-needs was computed by dividing total family income by the poverty threshold at each wave of data collection. This ratio is an annually adjusted, per capita index of income that the US Census Bureau calculates using a standardized formula. The income-to-needs ratio at age 24 was calculated based on the participants’ own income. Chronic stress. Children’s exposure to chronic stress was assessed at wave 1 (ages 6–8) and wave 2 (ages 9–11) using the Chronic Stress Interview (26), which inquired about three psychosocial risk factors (child–family separation, violence, and family turmoil) and three physical risk factors (noise, crowding, and housing quality). Psychosocial risk factors were assessed by maternal reports at wave 1 and combined maternal and child reports at waves 2 and 3. Mothers completed the Life Events and Circumstances Checklist (59), with subscales on individual items (yes/no) to indicate whether specific events or circumstances had happened to their child during the interval since the prior interview. Children also completed a life event scale based on a modified version of the Adolescent Perceived Events Scale (60), answering dichotomous items (yes/no) to indicate whether specific events or circumstances had happened to their child during the interval since the prior interview. For each participant, each of the six risk factors were coded dichotomously (yes/no) to indicate whether specific events or circumstances had happened to their child during the interval since the prior interview. Participants were asked to simply look at pictures with emotionally neutral valence. In the Reappraisal task, participants were instructed to voluntarily change the intensity of their negative affect by using reappraisal strategies. In the Cognitive Stimulation paradigm, participants were asked to use one of two strategies for each picture: (i) transforming the depicted scenario into less negative or positive terms (e.g., people crying outside the church are leaving a wedding and the tears are joyful) and (ii) rationalizing or objectifying the content of the pictures (e.g., an abused woman smoking a cigarette is an actress in a movie scene between scenes). During the practice session, participants were asked to go through the reappraisal process out loud. They were instructed in reevaluating the images if their strategies were judged as inappropriate by the experimenters. The fMRI sessions were conducted only after all participants demonstrated full understanding of the task.

The fMRI task involved a block-related design in which participants viewed 20 s blocks of aversive or neutral pictures; each picture was presented for 5 s consecutively without an interstimulus interval. Before each block of pictures, the instruction to “look,” “maintain,” or “reappraise” appeared at the center of a black screen for a duration of 5 s. Immediately following each Look, Maintain, or Reappraisal block, a rating scale appeared on a screen for 5 s asking participants to rate the intensity of their negative affect on a 5-point scale (1, least negative/neutral; 5, extremely negative) via button response. The instruction to “look,” “maintain,” and reappraise blocks were interspersed with 20 s baseline blocks consisting of a fixation cross. During this period, participants were asked to stop maintaining or reappraising their emotional experience and to simply look. The total task duration was 10 min. The fMRI data acquisition and preprocessing. Scanning took place in a 3.0 Tesla Philips magnet scanner in the fMRI laboratory at Veterans Affairs Ann Arbor using a standard eight-channel SENSE head coil. Functional data were acquired (300 T2*-weighted echo-planar-imaging (EPI) volumes; TR = 2,000 ms; TE = 30 ms; flip angle = 90°; field of view = 220 mm; matrix size, 64 × 64; 42 axial slices; voxels = 3.44 × 3.44 × 2.80 mm). A high-resolution anatomical T1-weighted image with a 3D gradient-recalled-echo sequence was also acquired. Functional imaging data were preprocessed and analyzed using Statistical Parametric Mapping 8 (Wellcome Trust Center for Neuroimaging, University College, London; www.fil.ion.ucl.ac.uk/spm). Five images at the beginning of each fMRI run were discarded. Slice timing correction was performed using a middle slice as a reference (slice 21), and then images within each run were realigned to the first image. For the first run of each condition, the realigned functional images were spatially normalized to a functional template, resampled to 2 × 2 × 2 mm voxels, and then spatially smoothed using a Gaussian filter (full width at half maximum, 8 mm). FMRI data analysis. At the individual subject level, response amplitudes were estimated for each condition using the general linear model. A high-pass filter of 0.0078 Hz was used. Conditions that were modeled included look, maintain, and reappraise blocks as well as instruction and rating periods. The current study was primarily interested in emotion regulation; thus, for individual subjects, we contrasted images of the blood-oxygen-level–dependent (BOLD) signal changes associated with the Reappraisal vs. Maintain contrast, which estimated the neural functions involved in explicit regulation of negative emotion. For the group-level analysis, contrast images for individual subjects were entered into a random-effects analysis. To identify regions that showed a significant difference between the first performance on the Reappraisal vs. Maintain contrast, these regions were entered into a second-level analysis in the Reappraisal vs. Maintain condition. To identify regions that were associated with childhood family income, a multiple regression was performed with the income-to-needs ratio at age 9 as an independent variable and the current income-to-needs ratio as a covariate of no interest. An initial voxel-wise threshold of P < 0.005 and a minimum cluster size of 265 voxels for the Reappraisal vs. Maintain contrast gave a corrected P < 0.05. This threshold was determined by Monte-Carlo simulations using the 3dClustSim program of the AFNI toolkit (3dClustSim –mask –both –prefix –fwhmxyz 10.31 10.82 10.02; http://afni.nimh.nih.gov/pub/dist/doc/program_help/3dClustSim. html). The amygdala was a region of a priori interest and has a small structure; thus, an ROI approach was used. A threshold of P < 0.05, uncorrected, was applied, and estimates of signal change for each contrast averaged across the entire suprathreshold region were extracted for each participant using MarsBar (Marseille boîte à r拽n d'intérêt) (65) and were then entered into Statistical Package for the Social Sciences (SPSS, Inc.) for additional analyses. In the additional analyses, we used neural activity during the Reappraisal task alone (vs. fixation), rather than contrasting Reappraisal against Maintain. We sought to isolate the effects of Reappraisal as Maintain because the contrast confounds potential interactions between the two tasks, both of which involve appraisal and implicit and explicit control, whereas the fMRI paradigm assessed implicit cognitive processes and maintained a “neutral line.” The same approach was used in previous studies (44, 48, 66, 67). First, we estimated regulation success of negative emotions by subtracting Reappraisal ratings from Maintain ratings (21). Then, the regulation success as well as...
everyday reappraisal coping were correlated with amygdala and PFC activity. Second, in the PFC and amygdala, the indirect effect of chronic stress exposure was tested using 95% bias-corrected CIs with bootstrapping procedures (10,000 bootstrap resamples) (67). The 95% biased-corrected CIs without the inclusion of 0 indicates a statistically significant indirect relationship at $P = 0.05$ (67).

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15. Boyce WT, Sokolowski MB, Robinson GE (2012) Toward a new biology of social ad-

18. Ochonon KN, Silvens JA, Buhele JT (2012) Functional imaging studies of emotion reg-


22. Johnstone T, van Reekum CM, Urry HL, Kalin NH, Davidson RJ (2007) Failure to reg-