## ORIGINAL ARTICLE

# An epigenetic mechanism links socioeconomic status to changes in depression-related brain function in high-risk adolescents

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Identifying biological mechanisms through which the experience of adversity emerges as individual risk for mental illness is an important step toward developing strategies for personalized treatment and, ultimately, prevention. Preclinical studies have identified epigenetic modification of gene expression as one such mechanism. Recent clinical studies have suggested that epigenetic modification, particularly methylation of gene regulatory regions, also acts to shape human brain function associated with risk for mental illness. However, it is not yet clear whether differential gene methylation as a function of adversity contributes to the emergence of individual risk for mental illness. Using prospective longitudinal epigenetic, neuroimaging and behavioral data from 132 adolescents, we demonstrate that changes in gene methylation associated with lower socioeconomic status (SES) predict changes in risk-related brain function. Specifically, we find that lower SES during adolescence is associated with an increase in methylation of the proximal promoter of the serotonin transporter gene, which predicts greater increases in threat-related amygdala reactivity. We subsequently demonstrate that greater increases in amygdala reactivity moderate the association between a positive family history for depression and the later manifestation of depressive symptoms. These initial results suggest a specific biological mechanism through which adversity contributes to altered brain function, which in turn moderates the emergence of general liability as individual risk for mental illness. If replicated, this prospective pathway may represent a novel target biomarker for intervention and prevention among high-risk individuals.

## INTRODUCTION

Although specific stressors including exposure to traumatic events or the experience of childhood maltreatment and neglect have been associated with increased risk for mental illness,[1] non-specific, relatively common risk factors, such as low socioeconomic status (SES), account for a large proportion of psychiatric morbidity in the population.[2] Low SES may confer risk through a variety of mechanisms, including higher levels of perceived and objective stress and cumulative environmental risk such as poor housing quality, noise pollution and exposure to violence.[3] Lower SES has been associated with a host of negative outcomes including poorer general health and increased risk for mental illness including depression, anxiety and addiction.[2,4,5] Given the insidious nature of low SES, it is at best difficult to directly mitigate these associated risks. An alternative strategy is to identify specific biological processes mediating the association between lower SES and individual risk thereby creating possible targets through which risk may be buffered.

One candidate biological process through which the environment may be exerting its influence is epigenetics, which encompasses molecular mechanisms mediating the effects of extrinsic factors on intrinsic functions through the modulation of gene expression.[6] In particular, experience-dependent methylation of gene regulatory regions such as proximal promoter sites has been proposed as one epigenetic mechanism through which stress may drive risk for future mental illness.[6] Generally, relatively increased DNA methylation of gene promoters, which is most often associated with decreased gene expression, has been associated with exposure to both specific[7] and non-specific stressors including lower SES.[8] These epigenetic changes in gene expression subsequently impact risk-related brain function and behavior.[9]

Recent clinical studies have specifically implicated DNA methylation of the proximal promoter region of the serotonin transporter gene (*SLC6A4*) as a potential epigenetic mechanism of increased risk for mental illness. For example, the experience of specific (that is, child abuse)[10] and non-specific (that is, lower SES)[11] stressors is associated with increased methylation of multiple CpG sites within *SLC6A4*, including the proximal promoter, and these patterns of methylation have been associated with higher depressive symptoms.[12] Moreover, we have demonstrated that relatively increased *SLC6A4* proximal promoter methylation is associated with increased threat-related amygdala reactivity, which not only has a central role in stress responsiveness but also is implicated in the etiology and pathophysiology of stress-related disorders including depression.[13,14] Collectively, these epigenetic findings are consistent with the important modulatory role of the serotonin transporter on stress physiology, amygdala function and mood.[15]

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Despite these findings, cross-sectional data collected at one point in time do not allow for examination of dynamic changes in DNA methylation. Thus, it is unclear whether the experience of stress is associated with a *change* in *SLC6A4* methylation and, if so, how this manifests as a *change* in risk-related brain function. Here, we use longitudinal epigenetic, neuroimaging and behavioral data to construct a prospective indirect effects model examining whether lower SES predicts increased future risk for depression via increased *SLC6A4* proximal promoter methylation and resulting sensitization of threat-related amygdala reactivity. We test this model in adolescents at high and low risk for depression due to presence or absence of a family history of depression, respectively.

In prior analyses of this cohort, we have found that either a positive family history of depression or exposure to stressful life events predicts greater increases in the reactivity of the left amygdala to fearful facial expressions from Wave 1 to Wave 2.[16] Thus, we first examined whether adversity-related changes in *SLC6A4* proximal promoter methylation may, in part, explain this sensitization of amygdala reactivity. We modeled the effect of three types of stressors previously associated with risk for depression, including childhood maltreatment, stressful life events, and low SES, on changes in methylation. We hypothesized that exposure to these stressors would be associated with an increase in *SLC6A4* proximal promoter methylation from Wave 1 to Wave 2, and that this increase would be associated with sensitized amygdala reactivity to threat over the same time period.

Although a positive family history is one of the strongest predictors of the future development of depression, not all individuals with this risk factor will become depressed.[17,18] Thus, we next examined the extent to which greater increases in threat-related amygdala reactivity associated with differential *SLC6A4* methylation predicted individual risk for depression in adolescents and whether this risk was specific youth with a positive family history of depression. Prior studies have found that threat-related amygdala reactivity predicts greater psychological vulnerability to future trauma,[19,20] and we recently demonstrated in a large sample of young adults that a baseline measure of threat-related amygdala reactivity predicts the likelihood of experiencing anxiety and depression symptoms following subsequent exposure to stressful life events several years later.[14] Accordingly, we hypothesized that increases in amygdala reactivity from Wave 1 to Wave 2 would predict greater increases in depressive symptoms from Wave 2 to Wave 3, approximately 1 year later.

## MATERIALS AND METHODS

### Participants

In line with our prior work,[13] analyses focused on the subset of 183 Caucasian, non-Hispanic participants from the Teen Alcohol Outcomes Study[16] in order to avoid potential population stratification due to differences in ancestry (see Supplementary Table 1 for full sample demographics). We used genetic ancestry[21] to confirm self-report of race/ethnicity (see Supplementary Methods).

Participants were 11–15 years old at Wave 1, 13–18 years old at Wave 2 and 14–19 years old at Wave 3. After complete description of the study to the participants, parents provided written informed consent and participants provided assent following procedures approved by the Institutional Review Board at the University of Texas Health Sciences Center San Antonio. Twenty participants (19 positive for a family history of depression (FH+) and 1 negative for a family history (FH −)) had an anxiety disorder diagnosis at study entry or developed an anxiety disorder between Waves 1 and 2. Anxiety diagnosis (dummy-coded) was included as a covariate in analyses run in the full sample, but removed as a covariate in multi-group analyses given the single diagnosis in the FH − group. Seven FH+ participants developed a diagnosis of major depression between Waves 1 and 2 and two FH+ participants developed a diagnosis between Waves 2 and 3. We did not include depression diagnosis as a covariate since depressive symptoms at Wave 2 were included as a covariate in all analyses. There were 21 pairs of siblings included in this sample. Recruitment procedures, attrition and exclusion of participants for

functional magnetic resonance imaging quality control at Waves 1 and 2 have been reported previously.[16] We also examined characteristics of attrition from Wave 1 to 3. Fewer FH+ participants ($n = 33$) completed the Wave 3 follow-up compared with FH − participants ($n = 46$), $\chi^2(1) = 5.12$, $P = 0.024$. There were no differences in attrition based on gender, age, CTQ emotional neglect scores, stressful life events, SES or depressive symptoms assessed at Wave 1.

### Environmental risk factors

Consistent with our prior research,[22] emotional neglect was assessed at Wave 1 with the emotional neglect subscale of the Childhood Trauma Questionnaire.[23] To assess SES at Wave 1, parents reported education levels and income for themselves and their spouses (if married). Consistent with prior research,[24] a composite SES indicator was calculated by averaging the standardized values of these variables (Supplementary Table 2). Stressful life events occurring the year before the first functional magnetic resonance imaging scan were assessed at Wave 1 with the Stressful Life Events Schedule.[25] As reported in our prior research,[16] objective threat ratings for each life event were squared, summed and averaged to obtain a mean level of objectively-rated stressful life events occurring the year before the first wave.

### SLC6A4 methylation

Details regarding acquisition and analysis of *SLC6A4* methylation have been reported previously for the first wave of the study.[13] Procedures were identical for obtaining methylation levels at the second wave of the study. In line with prior research,[13] data from the 20 CpG sites proximal to the transcription start site of *SLC6A4* measured at Wave 1 and Wave 2 were entered into a principal components analysis. Consistent with our prior research conducted with Wave 1 data,[13] the principal components analysis including Wave 1 and Wave 2 data resulted in five components with eigenvalues greater than 1, and scores for the first component (representing 24.1% of the total variance) were extracted for each individual (Supplementary Table 3). Similar to our prior work in this sample,[16] residualized change scores were calculated as a measure of changes greater or less than expected at Wave 2 based on Wave 1 values. Methylation data were available for 178 participants at Wave 1 and 136 participants at Wave 2; residualized change scores (that is, for those participants that provided valid data at both Wave 1 and Wave 2) were available in 132 participants.

### Amygdala reactivity

Details regarding acquisition, pre-processing and analysis of functional magnetic resonance imaging data have been reported previously.[16] All analyses were conducted with mean parameter estimates extracted from functional clusters significant at $P < 0.05$ family-wise error corrected within amygdala regions of interest. We focused analyses on values extracted from the left amygdala for the contrast of Fearful Faces > Shapes, based on our prior finding that left amygdala reactivity to fearful faces increased from Wave 1 to Wave 2 in adolescents at higher risk for depression.[16] To examine specificity of effects to the basolateral or centromedial amygdala, we also extracted values for the contrast of Fearful Faces > Shapes using probabilistic regions of interest based on cytoarchitectonic mapping[26] and corrected for multiple comparisons by applying a Bonferroni-corrected threshold of $P < 0.025$. Similar to the procedure with *SLC6A4* methylation, we calculated a residualized change score. Imaging data were available for 139 participants at Wave 1 and 107 participants at Wave 2; change scores were available in 87 participants.

### Depressive symptoms

Adolescents completed the Youth Self Report[27] at each wave of the study. To assess depressive symptoms, we used Affective Problems scores from the DSM-oriented scales,[28] which have been shown to correspond to DSM-IV major depressive disorder symptoms.[29] Residualized change scores were calculated to assess the changes in symptoms from Wave 2 to 3. Symptom scores were available in 136 participants at Wave 2 and 79 participants at Wave 3; residualized change scores were available in 79 participants.

### Covariates

We included the following as covariates on all paths of the model: age at Wave 1, time (in years) between waves, gender (dummy-coded: 0 = Male, 1 = Female), anxiety diagnosis (except in multi-group models) and the risk

factors (CTQ emotional neglect, SES and stressful life events at Wave 1). Note that the risk factors were predictors of interest in the first path and that they were then carried forward as covariates on all other paths of the model. Family history (dummy-coded: 0 = negative family history, 1 = positive family history) was also included as a covariate in analyses conducted in the full sample; this was removed as a covariate when conducting multi-group analyses to test for moderation by family history. As described in detail elsewhere,[13] a subset of participants ($n = 103$) were genotyped for the serotonin transporter-linked polymorphic region (5-HTTLPR) and rs25531. Genotype (dummy-coded: $0 = L_AL_A$; $1 = L_A/S$, $L_A/L_G$, $S/S$, $L_G/L_G$, $S/L_G$) was included as a covariate on all paths. Genotype distribution did not deviate from Hardy–Weinberg equilibrium for the 5-HTTLPR, $\chi^2(1) = 0.001$, $P = 0.97$, or rs25531, $\chi^2(1) = 0.44$, $P = 0.51$, genotypes. Finally, to ensure that changes in methylation and amygdala reactivity between Wave 1 and Wave 2 emerged before the onset of depressive symptoms, we also included YSR Affective Problems scores at Wave 2 as a covariate in all analyses. The one exception was in the final path (predicting residualized change in Affective Problems scores from Wave 2 to 3) because YSR Affective Symptoms at Wave 2 are implicitly controlled for using residualized change as an outcome. We also examined gender as a moderator of all paths of the analysis (reported in Supplementary Information).

## Statistical analyses

All statistical analyses were conducted using MPlus v7 software (Muthén & Muthén, Los Angeles, CA, USA) with full information maximum likelihood estimation, which provides unbiased estimates in the presence of missing data. Each path was first estimated in the full sample including all covariates described above. All predictors were mean centered to aid in interpretation of the results, and the variance and covariance of all predictors was modeled. Next, multi-group analyses were conducted to test for moderation by family history. Moderation was assessed using $\chi^2$ difference tests; if constraining parameter estimates to be equal between groups leads to a significant decrease in model fit, then one can conclude that the effect is significantly moderated by family history. Additional tests to examine the robustness of these effects are reported in the Supplementary Information.

After testing each path individually, we then constructed an indirect effects model to test the indirect effect of environmental risk factors on changes in depressive symptoms, mediated by changes in SLC6A4 methylation and amygdala reactivity to fear. On the basis of results from testing paths individually, we constrained the paths from environmental risk to SLC6A4 methylation and from SLC6A4 methylation to amygdala reactivity to be equal across family history groups, but allowed the final path (change in amygdala reactivity to change in symptoms) to be free across the positive family history and negative family history groups given evidence for moderation. We also freed each parameter in the model individually and tested whether allowing parameter estimates for any of the covariates or variances to vary by family history improved the fit of the model. None of the covariates were significantly moderated by family history; therefore, all parameters except that path were constrained to be equal in the model. The 5-HTTLPR genotype covariate was removed from this model due to poor model fit; removing this covariate from each path resulted in a significant improvement in model fit, $\Delta\chi^2(4) = 50.22$, $P < 0.001$. To provide a measure of general effect size for the indirect effect, we report the product of coefficients $\alpha\beta$ statistic. We also provide boot-strapped confidence intervals, which use a Monte Carlo simulation (1000 draws), which do not assume normality of the distribution of indirect effects to assess significance.

## RESULTS

### Lower SES at Wave 1 predicts greater increases in SLC6A4 proximal promoter methylation at Wave 2

We first tested whether stressors previously associated with risk for depression predicted changes in SLC6A4 methylation. Consistent with our hypothesis, lower SES measured at Wave 1 prospectively predicted greater increases in SLC6A4 proximal promoter methylation 2 years later at Wave 2, $B = -0.33$, s.e. = 0.1, Beta = $-0.24$, $P = 0.02$, $\Delta r^2 = 0.05$ (Figure 1). In fact, SES was the only measure of environmental stress that predicted changes in SLC6A4 proximal promoter methylation (Supplementary Table 4).
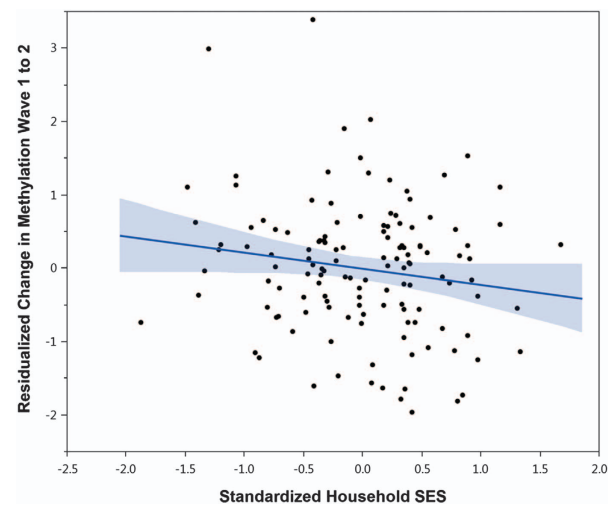


**Figure 1.** Lower socioeconomic status (SES) at Wave 1 predicts greater increases in SLC6A4 methylation from Wave 1 to 2. Standardized household SES was calculated by obtaining the mean of standardized scores of parents' education and income levels, as well as spouses' education and income levels if reporting parent was married. Lower SES at Wave 1 was associated with greater increases in methylation at Wave 2, $B = -0.33$, s.e. = 0.1, Beta = $-0.24$, $P = 0.02$, $\Delta r^2 = 0.05$. Shaded area represents 95% confidence intervals.

Although SES significantly varied as a function of familial risk in the expected direction (that is, lower in those with a positive family history), the effect of SES on SLC6A4 methylation was not moderated by family history for depression, $\Delta\chi^2(1) < 0.001$, $P > 0.99$. In other words, lower SES predicted an increase in SLC6A4 proximal promoter methylation over time to the same degree in adolescents with or without a positive family history of mental illness.

### Increases in SLC6A4 proximal promoter methylation from Wave 1 to Wave 2 predict greater increases in threat-related amygdala reactivity over the same time period

Having identified that lower SES is associated with an increase in SLC6A4 proximal promoter methylation over time, we next asked whether this change in methylation was associated with the change in left amygdala reactivity to fearful facial expressions previously noted in this cohort.[16] We found that greater increases in SLC6A4 proximal promoter methylation from Wave 1 to Wave 2 were associated with greater increases in reactivity during the same time window, $B = 0.09$, s.e. = 0.04, Beta = 0.21, $P = 0.04$, $\Delta r^2 = 0.05$. Subsequent analysis by amygdala subregion revealed that this effect was driven by increases in centromedial but not basolateral amygdala reactivity, $B = 0.10$, s.e. = 0.04, Beta = 0.26, $P = 0.01$, $\Delta r^2 = 0.08$ (Figure 2; Supplementary Table 5). As observed for SES effects on methylation, the association between SLC6A4 methylation and reactivity was not moderated by familial risk, $\Delta\chi^2(1) = 1.02$, $P = 0.31$. Thus, increases in SLC6A4 proximal promoter methylation predict increases in threat-related centromedial amygdala reactivity independently of family history of depression.

### Increases in threat-related amygdala reactivity from Wave 1 to Wave 2 predict future increases in depressive symptoms from Wave 2 to Wave 3 one year later

Analyses revealed a significant moderating effect of familial risk on the association between increases in amygdala reactivity and future depressive symptoms, $\Delta\chi^2(1) = 5.92$, $P = 0.01$. In adolescents with a positive family history, greater increases in reactivity from Wave 1 to Wave 2 prospectively predicted greater increases in
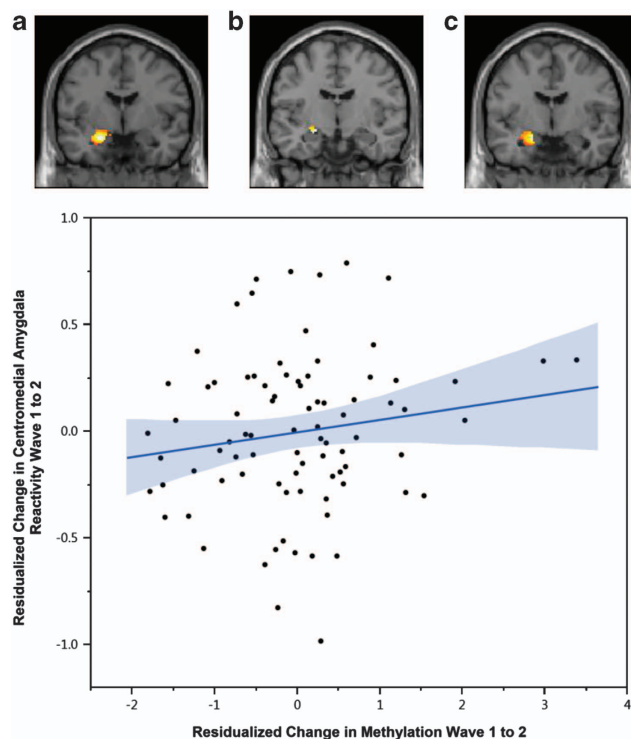
Figure 2. Greater increases in *SLC6A4* methylation are associated with greater increases in centromedial amygdala reactivity to fearful facial expressions from Wave 1 to Wave 2. Mean parameter estimates were extracted from functional clusters activated at both Waves 1 and 2 within the whole left amygdala (**a**), the left centromedial amygdala (**b**) and the left basolateral amygdala (**c**) for the contrast of Fearful Faces > Shapes. Greater increases in *SLC6A4* methylation were associated with greater increases in centromedial amygdala reactivity, $B = 0.10$, s.e. $= 0.04$, Beta $= 0.26$, $P = 0.01$, $\Delta r^2 = 0.08$.
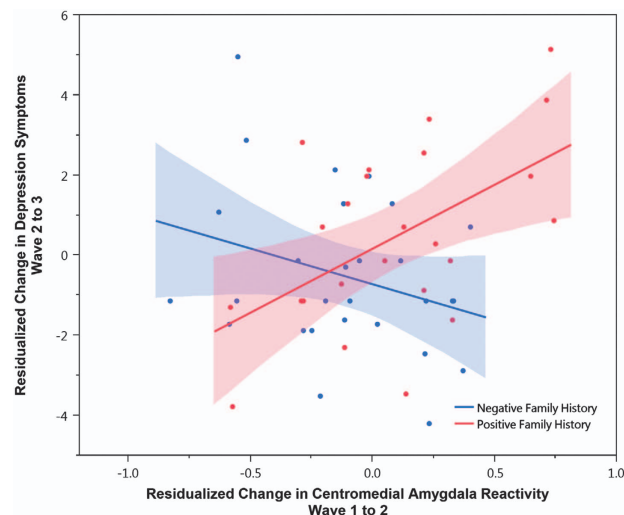


Figure 3. Greater increases in centromedial amygdala reactivity to fearful faces from Wave 1 to Wave 2 predict greater increases in depressive symptoms from Wave 2 to Wave 3 in adolescents with a positive family history of depression. Residualized change scores were calculated with symptoms from the Youth Self Report (YSR) Affective Problems scale at Waves 2 and 3. Greater increases in centromedial amygdala reactivity predicted greater increases in symptoms 1 year later in the positive family history group, $B = 2.71$, s.e. $= 1.1$, Beta $= 0.46$, $P = 0.02$, $\Delta r^2 = 0.21$.

depressive symptoms from Wave 2 to Wave 3, $B = 2.71$, s.e. $= 1.1$, Beta $= 0.46$, $P = 0.02$, $\Delta r^2 = 0.21$ (Figure 3; Supplementary Table 6). There was no such relationship in adolescents without a family history of depression, $B = -0.95$, s.e. $= 1.3$, Beta $= -0.17$, $P = 0.47$, $\Delta r^2 = 0.02$.

### Lower SES in adolescence has an indirect effect on future changes in depressive symptoms via increased methylation and threat-related amygdala reactivity

The above analyses separately established effects between lower SES and increases in *SLC6A4* proximal promoter methylation, increases in methylation and increases in amygdala reactivity, and increases in reactivity and future depressive symptoms. Finally, we constructed an indirect effects model to simultaneously examine the indirect effect of lower SES measured at Wave 1 on changes in depressive symptoms from Wave 2 to Wave 3, via changes in *SLC6A4* methylation and threat-related amygdala reactivity. The path from amygdala reactivity to changes in symptoms was freed to vary between the family history groups given the finding of significant moderation. All other paths were constrained to be equal across groups. The indirect effect was estimated by generating bias-corrected 95% confidence intervals with 1000 bootstrapped samples; confidence intervals that do not include 0 indicate a significant indirect effect. The final model had a good fit, $\Delta \chi^2 (38) = 28.87$, $P = 0.86$, root mean square error of approximation $= 0.00$, comparative fit index $= 1.00$, standardized root mean square residual $= 0.07$. As expected, SES had an indirect effect on

changes in depressive symptoms in the positive family history group only, $\alpha\beta = -0.06$, s.e. $= 0.05$, 95% confidence intervals $[-0.21, -0.002]$ (Figure 4). This negative indirect effect indicates that lower SES predicts greater than expected increases in *SLC6A4* methylation and centromedial amygdala reactivity, which in turn predicts greater than expected increases in future depressive symptoms. In contrast, this indirect effect was not significant for the negative family history group, $\alpha\beta = 0.03$, s.e. $= 0.05$, 95% confidence intervals $[-0.02, 0.17]$.

## DISCUSSION

Our results provide initial evidence for a prospective biological pathway through which a common stressor, namely lower SES, may increase risk for future depression in high-risk adolescents. Specifically, lower SES predicted residualized change in *SLC6A4* proximal promoter methylation, which in turn predicted residualized change in threat-related reactivity of the centromedial amygdala, which drives a number of autonomic responses to stress including activation of the hypothalamic pituitary adrenal axis. These findings extend our earlier observation identifying a cross-sectional relationship between methylation and amygdala reactivity in two separate cohorts,[13] and suggest that relative methylation status of the *SLC6A4* proximal promoter region is a reliable predictor of amygdala reactivity across time. Because SES was on average lower among adolescents with a positive family history of depression, and this pathway is uniquely associated with the emergence of depressive symptoms in these adolescents, this may partially explain our prior finding that these same adolescents show greater increases in amygdala reactivity over time.[16]

Our results further demonstrate that an increase in risk-related brain function prospectively predicts an increase in depression symptoms approximately 1 year later particularly among high-risk adolescents. Notably, we found that sensitized amygdala reactivity only predicted increases in depressive symptoms among adolescents with a positive family history of depression. It is possible that these high-risk adolescents experience additional forms of chronic
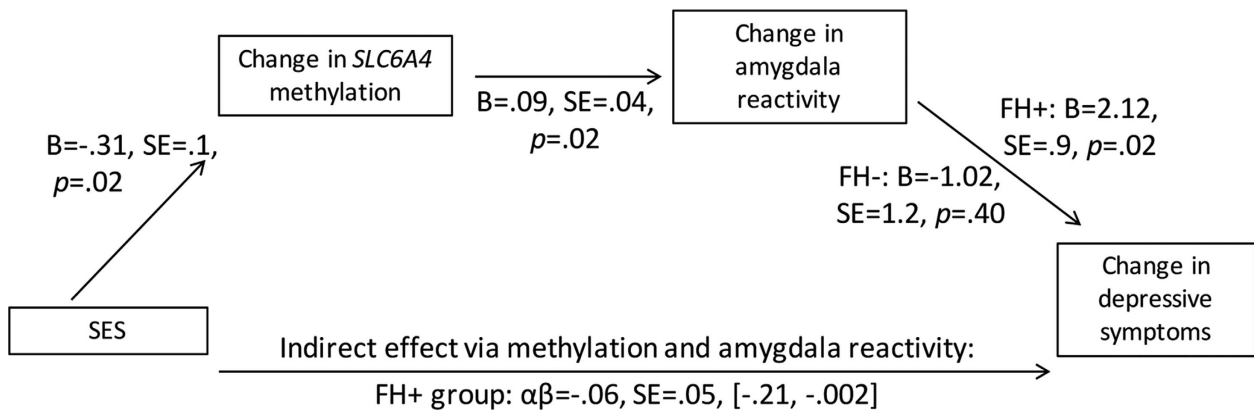
**Figure 4.** Indirect effects model examining the indirect effect of SES on future changes in depressive symptoms, via changes in *SLC6A4* methylation and centromedial amygdala reactivity to fear. Not shown in figure: covariates included on each path were age, gender, emotional neglect, stressful life events, SES, time between waves and depressive symptoms at Wave 2 (except on the final path). 95% confidence intervals for the indirect effect were obtained by requesting 1000 bootstrapped samples using Mplus v7. FH+ = positive family history; FH− = negative family history; SES = socioeconomic status assessed at Wave 1.

adversity such as parental neglect or familial discord uncommon among their low-risk counterparts, and that this additional exposure is necessary to trigger symptoms of depression. This is consistent with our finding in an independent sample of young adults that increased amygdala reactivity to threat only predicts future internalizing symptoms in response to higher levels of stress.[14]

As our follow-up measure of depressive symptoms was limited to self-report, however, it is unclear whether this pathway predicts clinically significant levels of dysfunction. Of course, we did not have access to brain-derived DNA and were limited to assays of *SLC6A4* methylation in DNA derived from peripheral tissues. But, there is evidence that methylation of *SLC6A4* may be conserved across DNA derived from multiple tissue types including blood, saliva and brain.[13] These limitations notwithstanding our results identify a specific biological pathway through which broader environmental adversity may act to drive individual vulnerability for depression among at-risk adolescents.

In addition to increased chronic stress experienced by parents and their offspring, lower SES is further associated with a range of environmental risk factors that may bias developmental changes in DNA methylation, including poor nutrition and smoking.[30,31] Identifying specific environmental mechanisms contributing to the effects of SES on methylation observed here will help narrow targets for possible intervention. Moreover, preventive interventions such as training in mindfulness-based techniques may be effective in lowering threat-related amygdala reactivity in adolescents identified as high risk due to increased *SLC6A4* methylation.[32] Isolation of family process factors (for example, high family conflict) that help explain why higher amygdala reactivity predicts depressive symptoms only in adolescents with a positive family history of depression will help further focus on targets for prevention within a family context. Thus, if replicated, the risk pathway identified here could represent a discrete biomarker that could be targeted by novel strategies for personalized treatment and prevention.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## AUTHOR CONTRIBUTIONS

ARH and DEW designed the study; DEW oversaw analysis of DNA methylation; ARH and JRS oversaw analysis of functional imaging data; JRS conducted the statistical analyses and drafted the manuscript; all authors edited and approved the final manuscript.

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Supplementary Information accompanies the paper on the Molecular Psychiatry website (http://www.nature.com/mp)