Effect of Early Adversity and Childhood Internalizing Symptoms on Brain Structure in Young Men

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Abstract

IMPORTANCE: Early adversity is an important risk factor that relates to internalizing symptoms and altered brain structure.

OBJECTIVE: Toassessthedirecteffectsofearlyadversityandchildinternalizingsymptoms(ie, depression, anxiety) on cortical gray matter (GM) volume, as well as the extent to which early adversity associates with variation in cortical GM volume indirectly via increased levels of internalizing symptoms.

DESIGN, SETTING, AND PARTICIPANTS: A prospective investigation of associations between adversity within the first 6 years of life, internalizing symptoms during childhood and early adolescence, and altered brain structure in late adolescence (age, 18-21 years) was conducted in a community-based birth cohort in England (Avon Longitudinal Study of Parents and Children). Participants from the cohort included 494 mother-son pairs monitored since the mothers were pregnant (estimated date of delivery between April 1, 1991, and December 31, 1992). Data collection for the present study was conducted between April 1, 1991, and November 30, 2010; the neuroimaging data were collected between September 1, 2010, and November 30, 2012, and data analyses for the present study occurred between January 25, 2013, and February 15, 2015. Risk factors were adversity within the first 6 years of the child's life (including prenatal exposure) and the child's internalizing symptoms between age 7 and 13 years.

EXPOSURE: Early childhood adversity.

MAIN OUTCOME(S) AND MEASURE(S): ThemainoutcomewasGMvolumeofcorticalregions previously associated with major depression measured through T1-weighted magnetic resonance images collected in late adolescence.

RESULTS: Among494youngmenincludedinthisanalysis,earlyadversitywasdirectly associated with lower GM volumes in the anterior cingulate cortex ($\beta = -.18$; P = .01) and higher GM volume in the precuneus ($\beta = .18$; P = .009). Childhood internalizing symptoms were associated with lower GM volume in the right superior frontal gyrus ($\beta = -.20$; P = .002). Early adversity was also associated with higher levels of internalizing symptoms ($\beta = .37$; P < .001), which, in turn, were associated with lower superior frontal gyrus volume (ie, an indirect effect) ($\beta = -.08$; 95% CI, −0.14 to −0.01; P = .02).

CONCLUSIONS AND RELEVANCE: Adversityearlyinlifewasassociatedwithhigherlevelsof internalizing symptoms as well as with altered brain structure. Early adversity was related to variation in brain structure both directly and via increased levels of internalizing symptoms. These findings may suggest that some of the structural variation often attributed to depression might be associated with early adversity in addition to the effect of depression.

Introduction

Adversity early in life is associated with both altered brain structure and increased risk of developing internalizing symptoms, namely depression and anxiety.[1-4] Previous studies have shown that childhood adversities including stressful life events, maltreatment, abuse, and domestic violence are associated with structural variation in gray matter (GM) in the brain.[4-9] The effect of early adversity on the brain has long been suggested to relate to neurobiological sequelae associated with excessive stress. For example, there is a large literature linking adversities during childhood (such as poverty and cumulative risk exposures) to later allostatic load, i.e., "the wear and tear" of the body, associated with stress. [10,11] Allostatic load is, in turn, associated with both increased risk of depression,[12] and stress-induced structural remodeling of the brain.[13]

Intriguingly, studies examining structural variation in GM in depressed patients versus normal controls have found that some of the structural variation in depressed patients correlates with experiences of early adversity.[14,15] Hence, it has been suggested that some of the structural brain variation normally attributed to depression may also relate to the effect of early adversity on the brain. In line with this, a recent study found that early maltreatment was indirectly related to altered brain structure via increased psychopathology (not differentiating between externalizing and internalizing symptoms).[9] A limitation of previous adversity-brain research, however, is the use of retrospective reports of early adversity, hindering the examination of prospective and indirect associations.

Present Study. The aim of this study was to examine how adverse experiences – within the first six years of life – relate prospectively to variations in cortical GM volume in adolescent males, both directly and indirectly via increased levels of childhood internalizing symptoms.

Past neuroimaging literature on depression has tended to focus on subcortical structures, such as the hippocampus and amygdala, and it has been suggested that this focus may have placed too much emphasis on subcortical structures in depression relative cortical structures.[16] Recent meta-analyses, applying a whole-brain approach, suggest that cortical regions may be implicated in depression in a more consistent manner than subcortical regions.[16-18] The present study therefore focused on cortical regions, which, in addition, allowed the explorative examination of regional thickness and surface areas measures. The distinction between surface area and thickness is a relatively novel approach that has not been widely applied in the depression and adversity literature. Moreover, it may be important in longitudinal studies as the surface area and cortical thickness are developmentally independent,[19] and may vary in timing of sensitivity towards adverse environments. Studies of non-human primates show that the expansion of the cortical surface area occurs earlier than corresponding changes in cortical thickness.[20] In humans, longitudinal studies have shown a substantial expansion of cortical surface area and GM volume[21,22], and a more moderate increase in cortical thickness[21] within the first two years of life. Longitudinal studies assessing GM development from the age of 5 years show increases in both cortical thickness and surface areas until late childhood/early adolescence.[23] No published research has, to the best of our knowledge, examined the contribution of variation in the surface area and cortical thickness to volumetric effects of adversity before the age of six years. This study focused on adversity during childhood because longitudinal studies, including those cited above, show that cortical GM volume continues to undergo structural development throughout early childhood.[21,22,23]

Methods

Sample

Avon Longitudinal Study of Parents and Children (ALSPAC) is an on-going population-

based study designed to investigate the influence of various risks on the development and health

of children. Pregnant women residing in the former Avon Health Authority in South-West

England who had an estimated date of delivery between April 1991 and December 1992 were

invited to participate, resulting in a cohort of 14,541 pregnancies.[24,25] Ethical approval for the

study was obtained from the ALSPAC Law and Ethics Committee and the Local Research Ethics

Committees. More information on ALSPAC is available online (http://www.bris.ac.uk/alspac/).

Subsample with magnetic resonance images (MRI) of the brain. N= 507 male

participants underwent MR imaging between the ages of 18 and 21 years (Mean ±SD: 235.5

month±10.1). This sample was restricted to male participants because the NIH-funded project,

for which the neuroimaging data was collected, examined associations between axons,

testosterone and mental health. Participants were selected based on their current domicile being

within a 3-hour journey (one-way) from the scanning site and the availability of three blood

samples taken between age 9-17 years for sex-hormone assays[26]. The sample includes the first

507 participants who met these criteria and accepted the invitation to take part in the MR

substudy. We excluded 14 participants due to a failure to pass quality control of the FreeSurfer-

based image-analysis pipeline (see below) leaving n=494 mother-son pairs.

<center>Measures</center>

Early adversity. When the children were 8, 21, 33, 47, 61, and 73 months, their mothers

reported on 37 family adversities including interpersonal loss, family instability, and abuse

towards the child/mother (full list available in eAppendix 1). At each time-point we counted the

number of adversities to create a cumulative index ranging from 0 to 37

Internalizing symptoms in the child. Pre- and early pubertal levels of internalizing

symptoms (depressive/anxiety symptoms) were assessed via maternal reports when the boys

were 7, 10, and 13 years old using the Development and Wellbeing Assessment (DAWBA).[27]

More details available in eAppendix 1.

Sample differences. We tested for differences between the neuroimaging subsample (n=494) and the total sample (n=14541) on the study variables. The number of participants with relevant information ranged from 7278 to 10744 in the full sample, and from 429 to 462 in the brain imaging subsample. Participants in the subsample did not differ from participants in the full sample in terms of early adversity or level of internalizing symptoms at age 7 or 10, but had higher levels of internalizing symptoms at age 13 (OR=1.191; 95% CI 1.04-1.36).

Selection of regions of interest. In order to identify relevant brain regions we employed a meta-analytic technique called activation likelihood estimation (ALE) computed in GingerALE version 2.1.[28] ALE was used to - in a systematic manner - identify regions of interest (ROIs) that show consistently (across multiple studies) lower glucose metabolism (hypometabolism) in depressed patients compared with healthy controls. An ROI-based approach has several advantages: firstly, it limits the analyses to brain regions that are thought to be relevant to depression thereby reducing the risk of false positive and false negatives; secondly, extraction of ROI data permits our complex longitudinal modeling approach.

We examined studies of variation in glucose metabolism at rest, rather than studies of brain structure, because we believe these can provide an unbiased identification of functionally relevant neural substrates of depression. Glucose metabolism at rest can reflect altered neural processing tendencies in depressed patients, in the absence of a task. Such altered neural processing tendencies may, over developmental time or progression of the depression, lead to altered brain structure in the same way that functional recruitment associated to the practice of a new skill (e.g., juggling), leads to altered brain structure.[29] Indeed, previous studies have found overlaps of regions in which alterations in glucose metabolism or cerebral blood flow co-occur with corresponding structural alterations in depression.[30]

The ALE was based on data from 14 ^{18}F-fluorodeoxyglucose Positron Emission

Tomography (^{18}F-FDG-PET) collected at rest. More information about the ALE and details

about inclusion criteria and included studies are available in the eAppendix 2 and eTable 1.

Thirteen studies met inclusion criteria resulting in a sample size of 271 depressive patients and

193 controls. The ALE probability map was thresholded using a minimum cluster of 500 mm[3]

and a false discovery rate of q= 0.5 which resulted in 17 clusters. Large clusters encompassing

multiple local maxima were divided into smaller regions and medial clusters were divided into

separate regions for each hemisphere. This left 30 cortical ROIs (see Table 1 and Figure 1 and

eFigure 1).

MRI acquisition. MR images were acquired on a 3T magnet (GE) using an 8-channel

receiver-only head coil. T1-weighted images were obtained using a 3D fast spoiled gradient-echo

(FSPGR) sequence using the following parameters: oblique-axial orientation (plane passing

through the anterior-posterior commissures), 1-mm isotropic, field of view 256x192x210mm,

TR=7.9 ms, TE=3.0 ms, TI=450ms and Flip angle=20deg.

MRI analysis. For each ROI, we obtained three measures: GM volume, cortical

thickness and surface area. The latter two measures were considered in order to dissect their

relative contribution to cortical GM volume, which served as the primary measure of interest

(GM volume = thickness x surface). All measures were generated using FreeSurfer 5.3.0.[31] More

information about the calculation and extraction of measures of GM volume, cortical thickness

and surface area is available in eAppendice 3.

Control variables. Analyses examining variation in GM volume, surface area or

thickness controlled for prenatal and adolescent adversity (from age 12-16), and duration of

breastfeeding as these factors may affect neural development. We controlled for total brain

volume and total surface area in analyses examining GM volume or surface areas respectively, to

ensure that observed effects were not attributable to individual differences in brain size. As brain

size does not correlate with cortical thickness, no correction was necessary.

Statistical analysis. Prospective associations were estimated in a latent path model. We

used latent variables because latent variables maximize the common variance between the

indicators and minimize the inclusion of error variance.[32] The latent factor for early adversity

was created using factor scores for adversity at age 0-3 years and age 3-6 years as indicators.

These two factors were highly correlated, preventing the association of effects to a specific time-

period (age 0-3 or 3-6 years). The latent factor for child internalizing symptoms was created

using symptom counts at age 7, 10, and 13 years.

Statistical analyses were carried out in Mplus version 7,[33] using full information

maximum likelihood estimation. Mplus includes respondents with missing data because list-wise

deletion of cases with partial complete data can increase sample bias.[34] Model fit was assessed

using the chi-square statistic, which tests the difference between observed and expected

covariance matrices, producing a non-significant value if this difference is close to zero.[35] In the

event of a significant chi-square value we would examine the relative fit indices including the

comparative fit index (CFI) and the Tucker-Lewis index (TLI)[36] and the root mean square error

of approximating (RMSEA)[37]

As a model building strategy we first ran independent models with each ROI as a single

brain outcome. ROIs that were associated with either early adversity or childhood internalizing

symptoms were added to a multivariate model. We applied false discovery rate (FDR)

correction[38] to the multivariate model to correct for multiple comparisons.

Indirect effects were modeled using the MODEL INDIRECT command in Mplus,

bootstrapping 10,000 times with bias corrected 95% confidence intervals to take into account

potential non-normality in the standard errors of indirect pathways.

Results

Descriptive statistics

Seven ROIs showed univariate associations with early adversity or childhood internalizing symptoms and were added to a multivariate model (estimates available in eResults, eTable 2). Only the superior frontal gyrus, the precuneus, and the anterior cingulate cortex (ACC), survived FDR correction and were included in the subsequent analyses.

Correlations among the study variables are shown in Table 2. Early adversity was positively correlated with childhood internalizing symptoms and with precuneus GM volume, but negatively correlated with ACC GM volume. Childhood internalizing symptoms were negatively correlated with superior frontal gyrus GM volume.

(PLEASE INSERT TABLE 2)

The multivariate path model

The model showed good fit to the data as indicated by a non-significant chi-square of $\chi^2(34) = 26.459, p < 0.819$. All estimates and their significance values are available in eResults, eTable 3.

(PLEASE INSERT FIGURE 2)

Direct effects. The path model (Figure 2) showed that early adversity was associated directly with lower GM volume in the right ACC and with greater GM volume in the right precuneus. Childhood internalizing symptoms were associated with lower GM volume in the right superior frontal gyrus. All analyses controlled for total brain volume, breastfeeding and prenatal adversity and adolescent adversity.

Indirect effects. Because early adversity was associated with childhood internalizing symptoms, which were associated with structural variation in the superior frontal gyrus, we tested whether early adversity related to variation in GM volume in the superior frontal gyrus via higher levels

of internalizing symptoms. Early adversity did relate indirectly to lower GM volume in the superior frontal gyrus via child internalizing symptoms (Table 3).

(PLEASE INSERT TABLE 3)

Exploratory follow-up analyses

As can be seen in Figure 2 (Model B), early adversity was associated directly with smaller surface area of the ACC and childhood internalizing symptoms were associated directly with smaller surface area of the superior frontal gyrus, suggesting that volumetric effects in these regions appear to be driven by smaller surface areas. Early adversity was not associated with variation in the surface area of the precuneus, but was associated with greater cortical thickness in this region (Model C). Interestingly, early adversity was also related to lower thickness of the superior frontal gyrus.

Similarly to the previous section we examined whether early adversity associated indirectly with variation in the surface area of the superior frontal gyrus. This indirect effect was not significant (Table 3).

Discussion

This study examined the extent to which adversity within the first six years of life relates to altered cortical brain structure in male youths.

Direct effects

The current study found that adversity within the first six years of life was directly associated with lower GM volume in the ACC, and with greater volume in the precuneus. These findings support previous studies that have found lower GM volume in the ACC in relation to adverse childhood events[7] and harsh parenting.[5] The finding that early adversity associated with larger precuneus GM volume and thickness is somewhat surprising given that another study found lower thickness in the precuneus related to maltreatment.[8] Note, however, that current

study examined the effect of adversity above and beyond internalizing symptoms. Although speculative, the positive association between adversity and precuneus volume could also relate to a 'positive' adaption to adversity.[13] Internalizing symptoms associated with lower GM volume in the right superior frontal gyrus. Associations between depression and reduced cortical frontal lobe volumes have been consistently reported in previous studies and meta-analyses.[14,17,30]

Indirect effects

A novel aspect of the current study is the finding that early adversity was related indirectly to variation in GM volume in the superior frontal gyrus via higher levels of childhood internalizing symptoms. This finding adds to the literature suggesting that volumetric differences in depression may, to some extent, relate to early adverse experiences. Previous studies have shown that lower GM volumes in both cortical and subcortical structures in depressed patients correlate with experiences of childhood adversity[12,14,15] Still, we know of just one study showing that childhood adversity (maltreatment before the age of 12) relates to altered brain structure through increased levels of childhood psychopathology.[9] We extend this finding by showing prospective associations by which early adversity can account for some of the structural variation typically associated with depression, via increased levels of internalizing symptoms. We also examined variation in GM in cortical rather than subcortical regions.

Follow-up analyses of changes in the surface area and cortical thickness

The finding of direct effects whereby early adversity and internalizing symptoms are associated with smaller surface areas of the ACC and the superior frontal gyrus (respectively) are, to the best of our knowledge, novel. Studies in humans and non-human primates have found that early brain development is characterized by an initial expansion of the cortical surface area.[20,21] The expansion of the surface area may be particularly susceptible to early risks

interfering with early brain development. This, however, needs to be tested with longitudinal brain imaging data or in animal models.

Early adversity was also associated with greater thickness of the precuneus, and it appears that more work is necessary to understand factors that relate to structural variation in this region. Finally, early adversity predicted lower thickness of the superior frontal gyrus. This finding did not come of in the volumetric analyses, but fits with the indirect effect of early adversity on GM volume via childhood internalizing symptoms.

Limitations

Results should be seen in light of several limitations. First, we tested the hypothesis that early adversity relates to altered brain structure via childhood internalizing symptoms. Alternative models, e.g., that structural variation may precede early adversity and depression, or that early adversity may predict childhood internalizing symptoms via the effect of adversity on the brain should be examined in future studies. Second, the study was limited to male participants. Third, the study was limited to regions associated with depression identified in our meta-analysis. We cannot rule out the possibility that other cortical and/or subcortical regions could also be associated with internalizing symptoms or adversity. Fourth, cumulative risk indices are statistically sensitive and fit with theoretical and empirical models showing that multiple risks are more harmful than single risks[39]. A limitation, however, is that they give all risks equal weight and do not allow for the separation effects associated with specific risks.[39] Fourth, mothers reported on early adversity and childhood internalizing symptoms introducing the issue of shared method variance and potential reporter bias. Sixth, this study focused on adversity but other factors may also have impacted the participants' brain development.

Conclusions

This study found that adversity within the first six years of life related prospectively to

higher levels of childhood internalizing symptoms and altered brain structure in late adolescence. The association between early adversity and adolescent brain structure worked both directly and indirectly via higher levels of internalizing symptoms. The finding of an indirect effect of early adversity via childhood internalizing symptoms supports previous suggestions that some of the structural variation observed in people suffering from depressed may partially relate to the early risk environment in addition to the effect of depression itself.

The finding that early experiences can affect the brain highlight early childhood as a period of vulnerability, but also as a period of opportunity in which interventions towards adversity might help to prevent children from developing internalizing symptoms and protect against abnormal brain development.

Acknowledgement

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Figure 1. Image Showing the 30 Cortical Regions of Interest (ROIs) on an Inflated Brain After Projection Into FreeSurfer
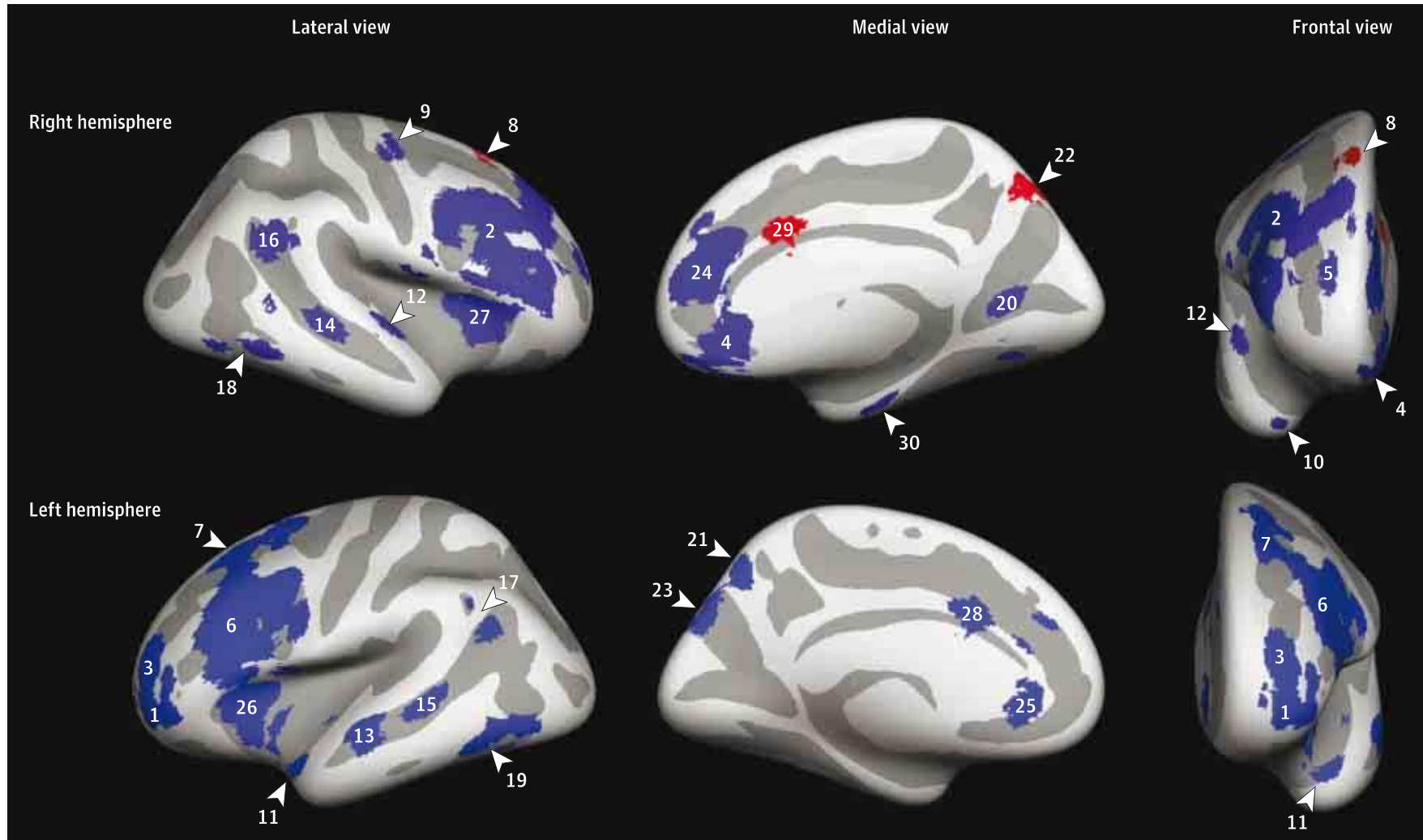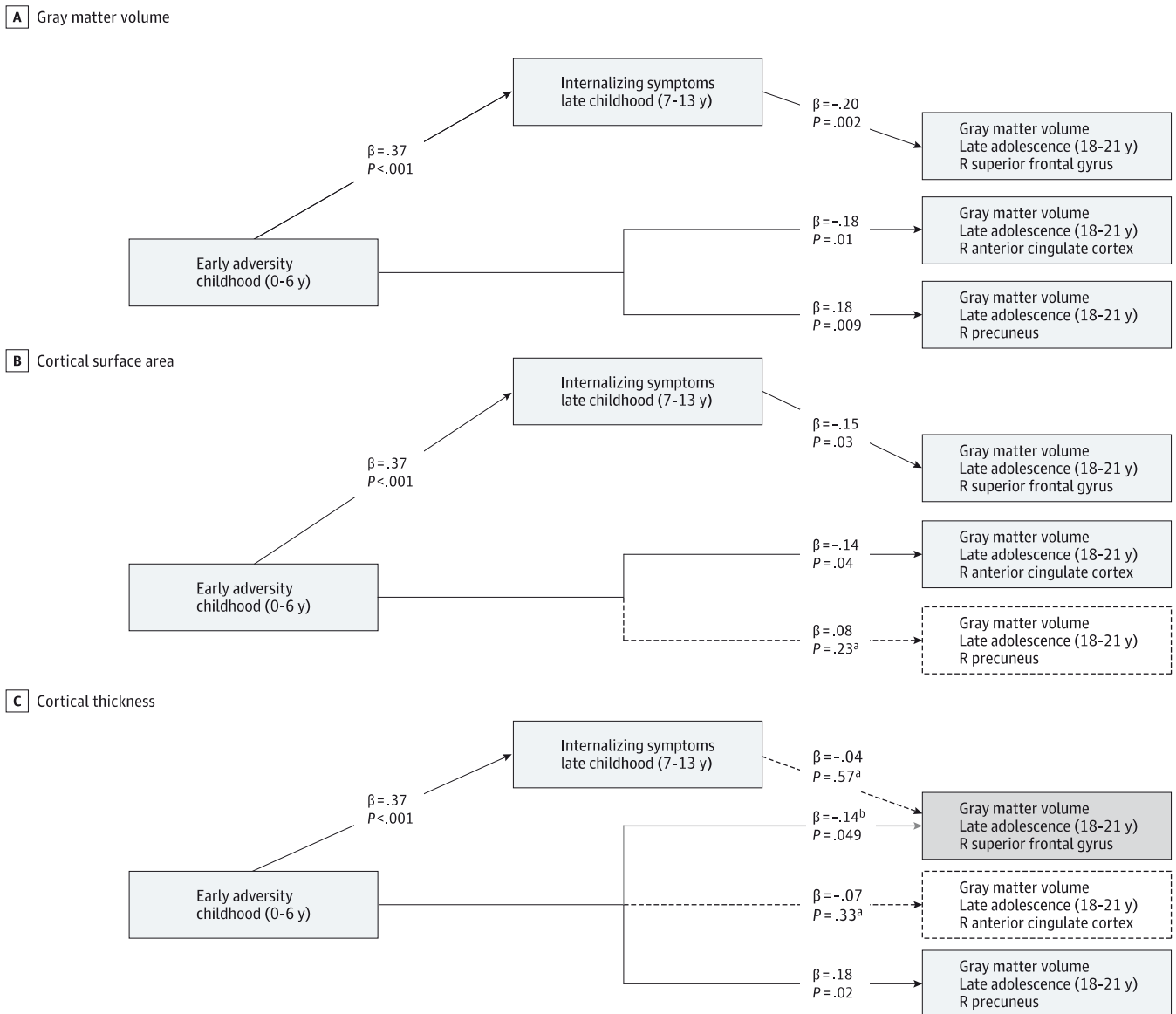
Figure 2. Diagrams Illustrating the Multivariate Path Models of Direct Effects of Early Adversity and Childhood Internalizing Symptoms

Standardized path coefficients for gray matter volume (A), surface area (B) and cortical thickness (C) analyses. Estimates of significant associations are presented in model A. Models B and C indicate whether findings from model A replicated for surface area (B) and thickness (C). Solid lines indicate paths that were replicated; dashed lines indicate paths that were not replicated (ie, it was not significant).a The gray line in model C indicates that this association was unique to model C (ie, it was not significant in model A).b The diagrams do not show control variables (total brain volume, duration of breastfeeding, and prenatal and adolescent adversity). All correlations between regions of interest were included in the model. R indicates right.

Table 1. Cortical ROIs Derived From the ALE of Hypometabolism in Depressed vs. Control Participants

	Cortical Label ROI No.	Roi No.	GM Volume, No. Of voxels	Weighted Center		
				x	y	z
L	frontopolar cortex (lateral)	1	10032	−38	53	−2
R	middorsolateral frontal cortex	2	33208	43	27	23
L	frontopolar cortex (lateral)	3	3064	−26	50	13
R	ventromedial prefrontal cortex	4	5712	7	37	−17
R	frontal medial cortex	5	6560	16	41	39
L	middorsolateral frontal cortex	6	28760	−44	19	26
L	superior frontal sulcus	7	7448	−24	16	52
R	superior frontal gyrus	8	2736	16	20	54
R	frontal precentral sulcus	9	2400	36	−17	60
R	temporal pole	10	2248	29	19	−37
L	temporal pole	11	1952	−43	9	−20
R	superior temporal gyrus	12	2728	56	−8	0
L	superior temporal sulcus (anterior)	13	3040	−55	−16	−8
R	superior temporal sulcus (posterior)	14	2864	47	−35	−7
L	superior temporal sulcus (posterior)	15	2896	−47	−39	0
R	supramarginal/angular gyrus	16	5056	50	−51	26
L	supramarginal/angular gyrus	17	2864	−42	−53	28
R	fusiform gyrus	18	3040	55	−62	−12
L	fusiform gyrus	19	3424	−49	−62	−12
R	lingual gyrus	20	2896	26	−66	1
L	precuneus	21	1712	−5	−68	46
R	precuneus	22	1472	6	−72	45
L	parieto-occipital sulcus	23	3096	−12	−80	33
R	anterior cingulate sulcus (rostral)	24	6900	10	40	16
L	anterior cingulate sulcus (rostral)	25	1248	−2	37	23
L	insula (anterior)	26	5840	−34	17	1
R	insula (anterior)	27	2656	36	22	3
L	anterior cingulate cortex (caudal)	28	2728	−2	16	34
R	anterior cingulate cortex (causal)	29	2352	2	16	34
R	parahippocampal gyrus	30	2016	27	−18	−33

Abbreviations: ALE, activation likelihood estimation; GM, gray matter; L, left, R, right; ROI, region of interest.

Table 2. Correlations among study variables.

	MAIN VARIABLES	1	2	3	4	5	6	7	8	9
				β Correlation Between ROI GM Volumes and Risk Factorsa						
1	Early adversity	1.000b								
2	Childhood internalizing	0.371b	1.000b							
3	GM vol. superior frontal gyrus	0.033	-0.157b	1.000b						
4	GM vol. precuneus	0.111b	0.004	0.171b	1.000b					
5	GM vol. anterior cingulate cortex	-0.102b	0.037	0.194b	0.136b	1.000b				
	CONTROL VARIABLES									
6	Prenatal adversity	0.579b	0.181b	0.072	0.005	-0.029	1.000b			
7	Adolescent adversity	0.253b	0.170b	0.017	0.012	-0.038	0.218b	1.000b		
8	Duruation breastfeeding	-0.118b	-0.017	-0.076	-0.021	-0.089b	-0.038	0.039	1.000b	
9	Total GM brain vol.	0.038	0.030	0.339b	0.376b	0.271b	0.049	-0.063	-0.103b	1.000b

Abbreviations: GM, gray matter; NA, not applicable; ROI, region of interest.
a Numbers refer to the numbered variables.
b Significant 2-tailed probability values at $P < .05$.

Table 3. Indirect Effects of Early Adversity on Brain Structure via Internalizing Symptoms

Child age at time of measurement

	Early childhood (Birth to 73 months)	Childhood (7-13 years)	Late adolescence (18-21 years)	Estimate	p. value	Boostrapped 95% CI
Pathway						
Indirect effect of early adversity on cortical grey matter volume						
Pathway A	Early adversity	Internalizing symptoms	R Superior frontal gyrus	-0.076	0.023	-0.141 to -0.010
Indirect effect of early adversity on cortical surface area						
Pathway B	Early adversity	Internalizing symptoms	R Superior frontal gyrus	-0.057	0.076	-0.119 to 0.006

Abbreviations: GM, gray matter; L, left; R, right.