

Original Investigation

Early Childhood Depression and Alterations in the Trajectory of Gray Matter Maturation in Middle Childhood and Early Adolescence

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IMPORTANCE The trajectory of cortical gray matter development in childhood has been characterized by early neurogenesis and volume increase, peaking at puberty followed by selective elimination and myelination, resulting in volume loss and thinning. This inverted U-shaped trajectory, as well as cortical thickness, has been associated with cognitive and emotional function. Synaptic pruning-based volume decline has been related to experience-dependent plasticity in animals. To date, there have been no data to inform whether and how childhood depression might be associated with this trajectory.

OBJECTIVE To examine the effects of early childhood depression, from the preschool age to the school age period, on cortical gray matter development measured across 3 waves of neuroimaging from late school age to early adolescence.

DESIGN, SETTING, AND PARTICIPANTS Data were collected in an academic research setting from September 22, 2003, to December 13, 2014, on 193 children aged 3 to 6 years from the St Louis, Missouri, metropolitan area who were observed for up to 11 years in a longitudinal behavioral and neuroimaging study of childhood depression. Multilevel modeling was applied to explore the association between the number of childhood depression symptoms and prior diagnosis of major depressive disorder and the trajectory of gray matter change across 3 scan waves. Data analysis was conducted from October 29, 2014, to September 28, 2015.

MAIN OUTCOMES AND MEASURES Volume, thickness, and surface area of cortical gray matter measured using structural magnetic resonance imaging at 3 scan waves.

RESULTS Of the 193 children, 90 had a diagnosis of major depressive disorder; 116 children had 3 full waves of neuroimaging scans. Findings demonstrated marked alterations in cortical gray matter volume loss (slope estimate, -0.93 cm^3 ; 95% CI, -1.75 to -0.10 cm^3 per scan wave) and thinning (slope estimate, -0.0044 mm ; 95% CI, -0.0077 to -0.0012 mm per scan wave) associated with experiencing an episode of major depressive disorder before the first magnetic resonance imaging scan. In contrast, no significant associations were found between development of gray matter and family history of depression or experiences of traumatic or stressful life events during this period.

CONCLUSIONS AND RELEVANCE This study demonstrates an association between early childhood depression and the trajectory of cortical gray matter development in late school age and early adolescence. These findings underscore the significance of early childhood depression on alterations in neural development.

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Longitudinal studies of childhood structural brain development using magnetic resonance imaging in healthy children have begun to map the normative pattern of development of gray matter from school age through adolescence.¹ Although development of gray matter begins in utero, there has been much interest in its trajectory during the school-age and early adolescent period.² The specific cellular processes that underlie gray matter change during this period in humans remain to be elucidated. In contrast with white matter, which shows linear increases in volume, findings suggest a pattern of rapid neurogenesis and related increases in gray matter volume during early childhood, peaking in early puberty followed by a process of selective elimination and myelination, resulting in volume loss and thinning.³⁻⁵ The inverted U-shaped trajectory of the development of cortical and subcortical gray matter regions is influenced by sex, pubertal status, IQ, and genetic and psychosocial factors.^{6,7} The characteristics of this inverted U-shaped trajectory for gray matter have been associated with function across several domains.⁵ More important, associations between cortical thickness, mood regulation, and executive functioning have been demonstrated in cross-sectional analyses.^{8,9} There is some evidence that this synaptic pruning-based volume decline is associated with experience-dependent plasticity.¹⁰⁻¹² The notion that the rate of decline of cortical gray matter in humans could vary based on history of experience has powerful public health implications.

Building on advances in mapping the normative trajectory of gray matter development, there has been escalating interest in whether symptoms of childhood psychiatric disorders and/or genetic predisposition to psychiatric disorders alter this trajectory. As many major psychiatric disorders are thought to be neurodevelopmental, investigations of whether and how childhood mood and emotional functioning might alter this trajectory is of great interest and represents a critical gap in the literature on developmental neuroscience. Alterations in maturation of gray matter have been detected in some childhood psychiatric disorders.¹³⁻¹⁵ A pattern of loss of cortical gray matter during adolescence, consistent with the normative process but at an accelerated rate, has been observed in children with schizophrenia and bipolar disorder.^{16,17} This pattern of accelerated loss of gray matter may be interpreted as reflecting synaptic pruning taking place earlier in development, before being fully informed by the effects of broader experience.

Numerous cross-sectional neuroimaging studies report decreased cortical gray matter in depressed adults compared with healthy adults.¹⁸ These findings have been interpreted as a pattern of premature brain aging.¹⁹ However, to date, there have been very few data on longitudinal imaging to inform whether childhood depression is also associated with alterations in development of gray matter. Given the known cognitive and emotional impairments in children with depression, accelerated reductions in cortical gray matter development are hypothesized.²⁰

In one of the only available longitudinal imaging studies in which adolescents at high and low risk for depression underwent neuroimaging twice, volumetric changes in the hippocampus, putamen, and amygdala were found, but no

changes in cortical gray matter were reported.²¹ In contrast, in a cross-sectional study of the 6- to 54-year-old offspring of depressed parents, cortical gray matter thinning across the lateral surface of the right hemisphere was reported in high-risk participants vs controls and was associated with current symptom severity.⁹ The lack of longitudinal imaging data in child samples represents a critical gap in the literature given the rapid changes in cortical gray matter during this developmental period.

This gap is important given that depression has been shown to have an onset as early as the preschool period, with validity evidenced by numerous neurobehavioral markers, including alterations in the function and structure of key brain regions involved in emotion processing.²²⁻²⁵ More important, depression that begins at preschool age exhibits continuity with depression in later childhood that meets *DSM-5* criteria, suggesting that it is an early manifestation of the well-validated childhood and adolescent disorder.²⁶ Our current investigation uses data from an ongoing 11-year longitudinal study of early childhood depression to examine the effects of childhood depression on the trajectory of cortical gray matter development, accounting for sex, age, IQ, poverty, family history of depression, and adverse experiences. Cortical gray matter volume was the primary variable because it is the most global metric. Significant volume findings were followed up by separate analyses of thickness and surface area, as they can have differential developmental trajectories, genetic influences, and patterns of impairment across neuropsychiatric conditions.²⁷⁻²⁹

In addition to behavioral data across 8 annual (and numerous semiannual) waves, 3 waves of neuroimaging during school age and early adolescence were obtained. Neuroimaging was initiated in this sample (first scan) just past the age of peak cortical growth for most children and maps the downward slope of the inverted U-shaped curve during pruning and myelination, both key processes contributing to volume reduction and thinning as assessed in human neuroimaging studies.^{30,31} The available data allow an unprecedented investigation into the association of childhood depression with the trajectories of cortical gray matter development across late school age and early adolescence.

Methods

Two hundred eleven children participated in a longitudinal study of preschool depression from September 22, 2003, to December 13, 2014, comprising 3 waves of neuroimaging. Healthy children and those with a history of depression were invited to participate and undergo neuroimaging (see eFigure 1 in the Supplement for exclusion criteria). One hundred ninety-three children had useable IQ data and neuroimaging data at 1 or more waves. Before and at the time of the first scan, children participated in behavioral assessments comprising 1 to 7 annual (and 1-4 semiannual) waves. These assessments included parent and child report using age-appropriate psychiatric interviews (Preschool Age Psychiatric Assessment [PAPA], ages 3-7 years, parent-only report; Child and Adolescent Psy-

chiatric Assessment [CAPA], age 8 years, parent-only report and ages ≥ 9 years, parent and child report).^{32,33} The validity and reliability of the major depressive disorder (MDD) module in the PAPA to identify depression in preschool-aged children (using a 6-month primary period) have been previously established.^{34,35} In addition, demographic, psychosocial (including stressful and traumatic life events assessed using the PAPA or CAPA), and developmental characteristics were also assessed (life events detailed in eTable 1 in the Supplement).³⁴ To examine the effect of socioeconomic status on structural brain outcomes, we used a ratio of income to needs, defined as the income level of the family divided by the federal poverty line by family size. A childhood depression symptom number score that spanned the preschool-age through school-age period (P-SA-MDD) was calculated for each participant by taking the mean number of core symptoms of MDD endorsed at all behavioral assessment waves using the PAPA and/or CAPA before and concurrent with and including the first scan. During this period, participants completed a mean (SD) of 5.48 (2.80) (range, 1-11) behavioral assessments. We also created categorical groups based on history of diagnoses of MDD in the same period. The Child Depression Inventory (CDI) parent and child reports were completed at the time of neuroimaging. In addition, the Family Interview for Genetic Studies was used to assess for family history of depression in first- and second-degree relatives.³⁶ All study methods were reviewed and approved by the Washington University School of Medicine Institutional Review Board. Written informed consent and assent were obtained from all study participants. Data analysis was conducted from October 29, 2014, to September 28, 2015.

Participants underwent neuroimaging with a magnetic resonance imaging scanner (model 3.0-T Tim Trio; Siemens Healthcare GmbH). The 2 results of magnetization-prepared rapid acquisition gradient echo scans were assessed visually, and the best one was selected for further processing by blinded raters. The selected magnetization-prepared rapid acquisition gradient echo image for each wave was processed using the longitudinal stream in FreeSurfer software package, version 5.3 (surfer.nmr.mgh.harvard.edu).³⁷ Several processing steps, such as skull stripping, Talairach transformations, and atlas registration, as well as spherical surface maps and parcellations, were initialized with common information from an unbiased within-patient template. This longitudinal stream reduces the bias that would otherwise be present in selecting a single scan result as baseline, and significantly increases reliability and statistical power.³⁸ Further details of FreeSurfer methods are available in eAppendix 1 in the Supplement.

The longitudinal multilevel linear model (MLM) was implemented in SAS, version 9.3 (PROC MIXED; SAS Institute, Inc). The growth curve model included both random intercept and random slope components (with an unstructured covariance matrix between the 2 components). Time was coded as wave number. All models included the following covariates: age at first neuroimaging scan (centered at mean = 10.3 years), quadratic age at first neuroimaging scan, sex (male, 1; female, 0), ratio of income to needs at first neuroimaging scan (centered at mean = 1.74), and IQ (centered at 105.6). We also considered an MLM that included an autoregressive estimate of co-

variance between neuroimaging waves in the model residuals. However, this model had convergence problems with default settings, and even after achieving convergence via more lenient convergence parameters, the model fit statistics (Akaike t_j ; 3 information criterion, Akaike information criterion corrected for infinite sample sizes, Bayesian information criterion) favored the simpler growth-curve only model. Degrees of freedom calculations used the method of Kenward and Roger.³⁹

Results

Participant characteristics at each neuroimaging scan are provided in Table 1. Of the 193 participants, 90 had lifetime MDD. eFigure 1 in the Supplement details the study flow, including dropout rates and reasons. The P-SA-MDD score was significantly different in depressed participants than in those without depression (eAppendix 2 in the Supplement).

A longitudinal MLM was conducted to examine the effect of P-SA-MDD symptom scores (centered at mean = 2.2) on initial values and change in global cortical gray volume. Growth trajectories (intercept, reflecting initial values, and linear change across time) were estimated for each participant. The P-SA-MDD symptom scores were used to predict variation in intercept and linear change over time (defined as neuroimaging scan number). Quadratic models were considered but the quadratic term was nonsignificant, indicating linear trajectories across time.

The longitudinal growth model result for gray matter volume is shown in Table 2. There was a main effect of time (B , -7.80 ; SE , $= 0.61$; t , $= -12.73$; $P < .001$), indicating that youths' cortical gray volume decreased significantly across neuroimaging scan waves, consistent with normative gray matter reduction seen at the age range studied. In addition, male sex, higher ratio of income to needs, and higher IQ scores were significantly associated with larger volume. More important, there was a significant interaction between the P-SA-MDD symptom score and time, indicating that global cortical gray volume decreased faster for those with higher P-SA-MDD symptom scores (eFigure 2 in the Supplement). Specifically, children with a mean P-SA-MDD score of 5 (the number of symptoms needed for a diagnosis of MDD and almost 2 SDs above the mean) had a 1.81 times greater decrease in global cortical volume from the first neuroimaging scan to the third compared with children with a mean MDD severity of 0 (-3.65% vs -2.02%). Figure 1 shows individually estimated gray matter volume slopes as a function of P-SA-MDD symptom score.

To better understand the association of P-SA-MDD symptom score with gray matter decline, we conducted MLMs for global (mean) cortical thickness and global cortical area of the gray and white matter surface to determine which of these factors was contributing to the volume changes. As shown in Table 2, we saw a significant interaction between P-SA-MDD symptom score and time for global cortical thickness (Figure 2 and eFigure 2 in the Supplement), such that children with a P-SA-MDD symptom score of 5 had a 1.69 times greater decrease in cortical thickness from the first neuroimaging scan

Table 1. Characteristics of the Sample^a

Characteristic	Value ^b		
	First Scan (n = 174)	Second Scan (n = 161)	Third Scan (n = 140)
Sex			
Female	85 (48.9)	79 (49.1)	70 (50.0)
Male	89 (51.1)	82 (50.9)	70 (50.0)
Race			
White	96 (55.2)	80 (49.7)	65 (46.4)
African American	58 (33.3)	65 (40.4)	59 (42.1)
Other	20 (11.5)	16 (9.9)	16 (11.4)
Age, y			
6	1 (0.6)	0	0
7	6 (3.4)	0	0
8	21 (12.1)	0	0
9	49 (28.2)	13 (8.1)	0
10	39 (22.4)	28 (17.4)	4 (2.9)
11	41 (23.6)	48 (29.8)	26 (18.6)
12	17 (9.8)	46 (28.6)	42 (30.0)
13	0	21 (13.0)	45 (32.1)
14	0	5 (3.1)	18 (12.9)
15	0	0	5 (3.6)
Parental educational level at neuroimaging scan			
High school diploma	13 (7.5)	12 (7.5)	10 (7.1)
Some college	75 (43.1)	69 (42.9)	58 (41.4)
4-y College degree	40 (23.0)	34 (21.1)	28 (20.0)
Graduate education	46 (26.4)	42 (26.1)	32 (22.9)
Psychotropic medication use			
Yes	31 (17.8)	36 (22.4)	35 (25.0)
No	143 (82.2)	125 (77.6)	105 (75.0)
Family history of MDD			
Lifetime MDD diagnosis	135 (77.6)	127 (78.9)	111 (79.3)
Current MDD diagnosis	73 (42.0)	71 (44.1)	69 (49.3)
Preschool onset MDD diagnosis	26 (14.9)	10 (6.2)	10 (7.1)
Age, mean (SD), y	55 (31.6)	49 (30.4)	44 (31.4)
Ratio of income to needs, mean (SD)	10.28 (1.30)	11.81 (1.21)	12.98 (1.14)
IQ score, mean (SD)	1.72 (0.96)	1.74 (0.96)	1.69 (0.97)
Traumatic and stressful life events by time of neuroimaging scan, mean (SD), No.	106.1 (15.0)	105.0 (14.8)	104.8 (15.1)
Prior assessments with MDD diagnosis, mean (SD), %	18.8 (35.5)	21.3 (37.2)	27.0 (42.4)
	17.5 (26.3)	13.3 (19.4)	13.8 (18.7)

Abbreviation: MDD, major depressive disorder.

^a There were 116 children with the 3 full waves of usable neuroimaging scans, 50 with 2 usable scans, and 27 with only 1 usable scan. The children with 1 scan did not differ from those with 2 or 3 scans by sex ($P = .44$), age at first scan ($P = .78$), ratio of income to needs at first scan ($P = .27$), or mean severity of MDD up to the first scan ($P = .57$).

^b Data are presented as number (percentage) of patients unless otherwise indicated.

to the third compared with those with a mean MDD score of 0 (-3.93% vs -2.33%). No evidence was found for an effect of MDD symptom score on change in global cortical surface area (Table 2). However, main effects of time, sex, and IQ score indicated that the surface area decreased with time and that males and those with higher IQ scores had greater surface areas. Additional MLMs conducted separately for the left and right brain hemisphere indicated a significant interaction of P-SA-MDD symptom score with time in gray matter volume in the left hemisphere ($P = .02$), a marginally significant interaction in gray matter volume in the right hemisphere ($P = .05$), and significant interactions in both hemispheres for gray matter thickness (eTable 2 in the Supplement). These effects for volume and gray matter thickness were substantively identical and significant for trend level when the analyses were run sepa-

rately for males and females, even though these analyses each had approximately half the sample size (eTable 3 and eTable 4 in the Supplement).

To aid in clinical interpretation, the models were run again using the dichotomous variable of MDD diagnosis before or concurrent with the first neuroimaging scan. The interaction between MDD and time was significant for volume (B, 2.84; SE, 1.24; t , 2.29; $P = .02$) and thickness (B, 0.0132; SE, 0.0049; t , 2.70; $P = .008$) but not surface area (B, 1.45; SE, 1.52; t , 0.96; $P = .34$), as was seen in the models of P-SA-MDD symptom scores.

When child-reported CDI score was used in the model, the interaction between CDI total T score and time was significant for volume (B, -0.26; SE, 0.10; t , -2.46; $P = .02$) and thickness (B, -0.0013; SE, 0.0004; t , -3.27; $P = .001$) but not

Table 2. Multilevel Mixed Models of Global Volume, Thickness, and Surface Area of Cortical Gray Matter

Characteristic	Estimate	SE	t Test	P Value
Global Cortical Gray Volume^a				
Intercept	555.38	1.83	95.31	<.001
Age	-2.77	2.63	-1.05	.29
Age squared	2.24	1.74	1.29	.20
Sex (male, 1; female, 0)	44.64	6.74	6.62	<.001
Ratio of income to needs	8.28	3.82	2.17	.03
IQ score	0.96	0.25	3.89	.001
Time ^b	-7.80	0.61	-12.73	<.001
P-SA-MDD severity	0.48	2.60	0.18	.86
P-SA-MDD severity × time	-0.93	0.42	-2.21	.03
Global Cortical Thickness^c				
Intercept	2.7688	0.0114	243.28	<.001
Age	-0.0270	0.0048	-5.68	<.001
Age squared	0.0004	0.0031	0.13	.90
Sex (male, 1; female, 0)	0.0133	0.0122	1.10	.28
Ratio of income to needs	0.0048	0.0069	0.69	.49
IQ score	0.0006	0.0004	1.35	.18
Time	-0.0415	0.0024	-17.26	<.001
P-SA-MDD severity	0.0080	0.0055	1.46	.15
P-SA-MDD severity × time	-0.0044	0.0016	-2.72	.007
Global Cortical Surface Area^d				
Intercept	1775.34	18.58	95.53	<.001
Age	12.12	8.64	1.40	.16
Age squared	7.74	5.69	1.36	.18
Sex (male, 1; female, 0)	145.89	22.17	6.58	<.001
Ratio of income to needs	21.01	12.54	1.68	.10
IQ score	2.93	0.81	3.61	<.001
Time	-6.16	0.75	-8.19	<.001
P-SA-MDD severity	-2.87	7.99	-0.36	.72
P-SA-MDD severity × time	-0.48	0.52	-0.93	.35

Abbreviation: P-SA-MDD, depression symptom number score that spanned the preschool-age through school-age period.

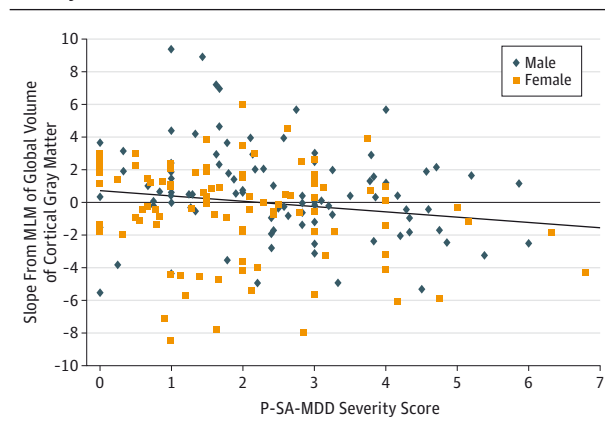
^a Estimates are in cubic centimeters.

^b Defined as neuroimaging scan number.

^c Estimates are in millimeters.

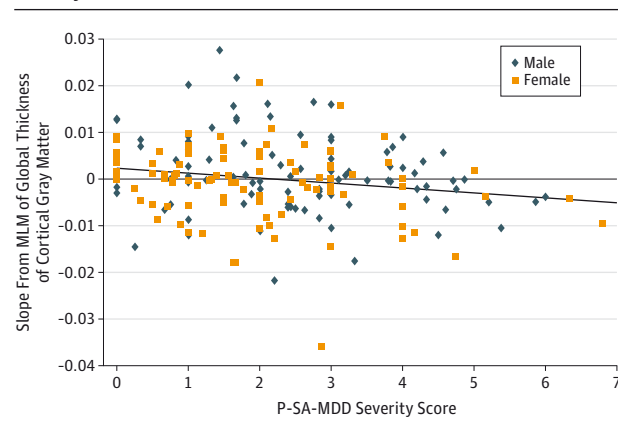
^d Estimates are in square centimeters.

Figure 1. Association Between Individually Estimated Slopes Over Time for Global Volume of Cortical Gray Matter as a Function of P-SA-MDD Severity Score



Individual slopes were significantly correlated with P-SA-MDD severity score (-0.156; $P = .03$). MLM indicates multilevel linear model; P-SA-MDD, depression symptom number score that spanned the preschool-age through school-age period.

Figure 2. Association Between Individually Estimated Slopes Over Time for Global Thickness of Cortical Gray Matter as a Function of P-SA-MDD Severity Score



Individual slopes were significantly correlated with P-SA-MDD severity score (-0.189; $P = .008$). MLM indicates multilevel linear model; P-SA-MDD, depression symptom number score that spanned the preschool-age through school-age period.

surface area ($B, -0.11$; $SE, 0.13$; $t, -0.81$; $P = .42$). Results for parent-reported CDI score were going in the same direction (eAppendix 2 in the Supplement).

To further investigate the specificity of this effect for depression (vs psychotropic exposure), models were rerun removing participants with any lifetime psychotropic medication use, resulting in a sample size of 156. Despite this reduced sample size and elimination of some of the children with the most severe depression who received medication (mean P-SA-MDD symptom score before the first neuroimaging scan, 3.74 vs 1.85 for those with and without medication exposure, respectively; $t, 8.27$; $df, 191$; $P < .001$), similar results to those in the models with all children were found (eAppendix 2 in the Supplement).

Childhood depression is frequently comorbid with externalizing disorders, which are also associated with alterations in volume and/or thickness of gray matter.⁴⁰ To determine whether patterns of gray matter change held when accounting for comorbid externalizing disorders, we reran the models including the presence of externalizing disorder (attention-deficit/hyperactivity disorder, oppositional defiant disorder, or conduct disorder) before the first neuroimaging scan and its interaction with time as additional covariates. The estimates, SEs, and significance of the interactions of P-SA-MDD symptom score with time were similar to those in the models that did not include externalizing disorders, again demonstrating greater declines in global volume of cortical gray matter ($B, -1.09$, $SE, 0.51$; $t, -2.15$; $P = .03$) and global thickness of cortical gray matter ($B, -0.0044$; $SE, 0.0020$; $t, -2.22$; $P = .03$) for those with higher P-SA-MDD symptom scores.

To explore whether the association between P-SA-MDD symptom score and cortical gray matter development might reflect the influence of the early experience of depression vs a familial or genetically influenced outcome, we included family history of depression (a potential marker of genetic risk) and its interaction with time as covariates in the models and found that the interaction of P-SA-MDD symptom score and time remained significant for global volume of cortical gray matter ($B, -1.04$; $SE, 0.42$; $t, -2.44$; $P = .02$) and global thickness of cortical gray matter ($B, -0.0050$; $SE, 0.0017$; $t, -3.00$; $P = .003$) and remained nonsignificant for global surface area of cortical gray matter ($B, -0.53$; $SE, 0.53$; $t, -1.01$; $P = .32$). To investigate whether the effect was specific to experiences of depression or based on more general forms of adversity, additional models included experiences of traumatic and stressful life events and their interaction with time as model covariates. Again, the interaction of P-SA-MDD symptom score and time remained significant for volume of cortical gray matter ($B, -0.95$; $SE, 0.43$; $t, -2.19$; $P = .03$) and thickness of cortical gray matter ($B, -0.0046$; $SE, 0.0017$; $t, -2.75$; $P = .007$) and remained nonsignificant for surface area of cortical gray matter ($B, -0.46$; $SE, 0.53$; $t, -0.86$; $P = .39$).

Additional MLMs were run to test for effects of P-SA-MDD symptom score over time in specific regions of the brain (eAppendix 2 in the Supplement). There were no significant interactions of P-SA-MDD symptom score with time after correction for multiple comparisons. Effect sizes were calculated by taking the correlation of P-SA-MDD symptoms score

with participants' individual slope estimates. Effect sizes for all regions tested are in eTable 5 in the Supplement.

Discussion

These longitudinal findings demonstrate marked bilateral decreases in thickness of cortical gray matter and in volume of the right hemisphere (with marginal significance on the left hemisphere) associated with mean level of depression symptom scores and MDD diagnosis experienced from preschool to school age. Children with depression symptom scores 2 SDs above the mean had reduction in volumes of gray matter at almost twice the rate of those with no childhood depression symptoms. Similarly, cortical thickness also decreased more rapidly at almost the same rate. To our knowledge, these findings provide the first longitudinal neuroimaging data showing increases in rates of volume reduction and cortical thinning related to number of childhood depression symptoms and diagnosis during the preschool-age to school-age period.

The absence of lateralized findings for thickness and the marginally significant finding on the left hemisphere for volume is notable given that much of the extant literature on MDD has discussed the right hemisphere.^{9,41,42} In addition, the lack of specific findings in regions that regulate the emotions is also notable given that these more specific volume reductions have been reported in depression.^{16,43-46} These more global findings in children suggest a relatively generalized process that may be operative at earlier developmental stages. While we did see thinning in some candidate regions, none survived multiple comparison correction. The whole-brain effects likely arise from the aggregation of thinning across several regions. Such global volumetric and thickness alterations are also consistent with reports of large-scale structural network anomalies of gray matter in depressed adults.⁴⁷ Furthermore, significant effects of sex and ratio of income to needs on the trajectory of volume and thickness of cortical gray matter were also found and are worthy of further follow-up. The finding of differences in thickness and volume without differences in surface area has been reported in several neuropsychiatric conditions.^{48,49}

The study findings from this population enriched for early childhood depression and followed up into middle childhood and early adolescence provide the first data, to our knowledge, demonstrating depression-related alterations in volume and thickness of cortical gray matter evident as early as middle childhood. These findings add to a growing body of neuroimaging data in children and adolescents with depression reporting structural alterations in frontal cortical areas.^{42,46,50,51} The study findings provide support for the notion that cortical thinning evident in depression begins in childhood, as speculated by Peterson et al.⁹ A limitation of the study is that it was not possible to separate developmental timing effects. Future studies designed to compare patients with early childhood depression during the preschool period vs those without preschool depression with onset of depression at school age are needed to clarify whether there are effects of timing of childhood depression on brain change.

We speculate that changes in cortical gray matter related to childhood depression may reflect experience-dependent neuroplasticity. However, the study was not designed to definitively inform whether the cortical changes were related to depression-based experience-dependent plasticity vs other genetic or psychosocial processes. Nonetheless, the current findings are consistent with an experience-dependent process given the fact that a family history of depression, a putative marker of family genetic risk, was not related to trajectories of cortical gray matter. Furthermore, the finding that dimensional and categorical measures of MDD as well as ratio of income to needs predicted cortical change, and that the experience of stressful and traumatic life events during this same period was not related to cortical change, suggests that the finding may be more specifically related to certain types of negative experience rather than a more general effect of stressful events. While an experimental design with neuroimaging prior to depression would be needed to test this hypothesis, the findings highlight the potential unique importance of the experience of childhood depression in the developmental trajectory of cortical gray matter.

The functional and depression-specific clinical implications of the increased rate of volume reduction and thinning of the cerebral cortex found in this study are not clear from these data. Such alterations in other psychiatric disorders have been interpreted as accelerated maturation, which may be seen as maladaptive given that pruning may be strongly informed

by early negative disorder-related experience rather than more developmentally normative positive experiences later. Furthermore, our study cannot inform the cellular processes that underlie the alterations in gray matter development and whether they are related to increased rates of myelination and/or cell loss owing to pruning.^{30,31} In addition, since the neuroimaging scans began after the cortical peak, it is not possible to determine whether early or premature and/or accelerated pruning is taking place.

Conclusions

Of critical importance is that childhood depressive symptoms were associated with decline in volume and thickness of cortical gray matter even after accounting for other key factors known to affect this developmental process. These findings of markedly increased rates of cortical volume loss and thinning across the entire cortex underscore the importance of attention to childhood depression as a marker of altered childhood cortical brain development. Whether these early alterations serve as an endophenotype of risk for later depressive episodes or chronic course is a question of interest as the study sample is followed up through adolescence. The study findings signal the need for greater public health attention and screening for depression in young children.⁵²

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