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Brain Structure Relations With Psychopathology Trajectories in the ABCD Study

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Objective: A general psychopathology (p) factor captures shared variation across mental disorders. Structural neural alterations have been associated with the *p* factor concurrently, but less is known about whether these alterations relate to within-person change in the *p* factor over time, especially during preadolescence, a period of neurodevelopmental changes.

Method: This study examined whether baseline brain structure was prospectively related to the trajectory of the *p* factor and specific forms of psychopathology over 2 years in 9,220 preadolescents (aged 9-10 at baseline) from the Adolescent Brain Cognitive Development Study (ABCD). Longitudinal multilevel models were conducted to determine whether baseline brain structure (volume, surface area, thickness) was associated with between-person differences and within-person change in the *p* factor (from a higher-order confirmatory factor model) and internalizing, externalizing, neurodevelopmental, somatization, and detachment factor scores (from a correlated factors model) over 3 study waves.

Results: Smaller global volume and surface area, but not thickness, were associated with higher between-person levels of the *p* factor scores, which persisted over time. None of the brain structure measures were related to within-person change in the *p* factor scores. Lower baseline cortical thickness was associated with steeper decreases in internalizing psychopathology, which was driven by lower thickness within sensorimotor and temporal regions.

Conclusion: These novel results identify specific brain structure features that might contribute to transdiagnostic psychopathology development in preadolescence. Children with smaller total brain volume and surface area may be vulnerable to persistent general psychopathology during preadolescence. Cortical thinning reflective of pruning and myelination in sensorimotor and temporal brain regions specifically may protect against increases in internalizing, but not general psychopathology, during preadolescence.

Key words: brain structure; general psychopathology; longitudinal; *p* factor; transdiagnostic

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Factor analytic models have identified a general psychopathology factor (*p* factor), which captures shared variation across mental disorder categories.[1,2] The *p* factor accounts for comorbidity and severity of psychopathology and has been identified in a range of samples across the life span.[3,4] People who are high in *p* experience greater life impairment and distress (ie, psychiatric hospitalizations, social welfare benefits, violence convictions),[1,2] history of childhood maltreatment,[1,2] and future psychopathology[2,5] and suicidality[2,6] compared with people who are low in *p*. However, the psychological and neurobiological mechanisms underlying general psychopathology are not yet well established.

Neuroimaging research has identified global patterns of structural alterations in cortical volume, surface area (SA), and cortical thickness (CT) distributed throughout the brain in people high in *p*, but the type of alteration differed in youth vs adult studies. Prior research in children (aged 9-10) from the Adolescent Brain Cognitive Development (ABCD) Study[7,8] and children and youth (aged 8-23) from the Philadelphia Neurodevelopmental Cohort[9] revealed that global patterns of smaller brain volume and/or SA, but not CT, were associated with higher levels of the *p* factor. Adolescent studies also reported widespread negative deviations from normative models of brain volume and SA, with minimal deviations in CT, associated with transdiagnostic psychopathology.[10,11] Alternatively, research in midlife adults (aged 45) from the Dunedin Longitudinal Study[12] found that pervasive patterns of cortical thinning, but not smaller SA, were associated with higher *p* factor scores. These studies largely have described similar patterns of brain structural alterations associated with both general and specific forms of psychopathology, with a few exceptions (eg, fear symptoms specifically related to lower CT[9]).

However, abnormalities within different features of cortical mantle structure associated with transdiagnostic psychopathology dimensions suggest that differences in developmental stage are important for understanding the structural neural mechanisms underlying general psychopathology.

Cortical volume is the product of SA and thickness. SA and CT develop at different rates throughout the life span and are evolutionarily, genetically, and cellularly distinct.[13] CT increases from birth to early childhood and then decreases linearly throughout childhood and adolescence.[13-16] Alternatively, volume and SA tend to follow an inverted U–shaped developmental trajectory, peaking during preadolescence before plateauing and slightly decreasing throughout adolescence into early adulthood.[13-15] As CT and SA follow different neurodevelopmental trajectories, they may relate to transdiagnostic psychopathology dimensions differently throughout the life span.

Much of the research examining the structural neural correlates of general and specific psychopathology factors has been cross-sectional, which, by design, cannot establish the temporal precedence between brain structure and psychopathology. Some studies have examined relations between change in brain structure over 2 time points and mental disorder symptoms[17] or whether symptoms were prospectively related to change in brain structure.[18-20] Few studies have examined whether brain structure is associated with change in psychopathology over time,[11,21] however, and no known prospective longitudinal investigations of relations between brain morphology and the *p* factor have been conducted. As a result, we cannot know whether childhood brain structural alterations relate to future levels of or rates of change in *p* over time. It is especially important to conduct such prospective longitudinal studies during preadolescence, a time marked by extensive neurodevelopmental changes,[13,13–15] before the onset of most mental disorders in adolescence and young adulthood.[22]

Based on cross-sectional studies of the relations between brain structure and general and specific psychopathology dimensions,[7-9,12] 3 primary questions emerge about the role of brain morphology in transdiagnostic psychopathology development in preadolescence: First, do previously identified inverse cross-sectional relations between brain structure and the *p* factor persist over time? Second, does childhood brain morphology prospectively relate to rates of change in *p* or specific psychopathology factors over time? Third, if so, which brain structure components (ie, volume, SA, or CT) are associated with these psychopathology trajectories? Determining childhood brain structural alterations that prospectively relate to levels and/or rates of change in general and specific forms of psychopathology has implications for early identification of children who may be vulnerable to developing comorbid and severe forms of disorders in adolescence.

In the current study, we used 3 waves of clinical data and the first wave of structural magnetic resonance imaging (MRI) data from 9,220 preadolescents (aged 9-10 at baseline) from the ABCD Study to test whether baseline brain structure is prospectively related to between-person differences and within-person changes in transdiagnostic psychopathology dimensions during preadolescence. We tested whether between-person differences and within-person changes in the *p* factor over time were associated with structural alterations in volume, SA, or CT. As some forms of psychopathology may develop at different rates than others, we also tested whether baseline brain structure was prospectively associated with the trajectories of externalizing, internalizing, neurodevelopmental, somatization, and detachment symptoms rather than the *p* factor.

To this end, we calculated unstandardized factor scores from previously identified higher-order and correlated factors confirmatory factor models of the structure of psychopathology using the same clinical scales at each wave.[23] Using longitudinal multilevel modeling, we tested whether baseline brain structure (volume, SA, CT) was related to the intercept (between-person differences) and slope (within-person rate of change) of the psychopathology factor scores over 3 waves (2-year time frame). Baseline brain structure may reflect the extent of volume, SA, and CT maturation that has occurred before the child's age at the baseline MRI. Consistent with prior cross-sectional studies using ABCD Study data,[7,8] we hypothesized that reduced volume and SA, but not CT, would be associated with higher between-person *p* factor scores. We considered analyses examining whether brain structure relates to within-person trajectories of *p* factor scores over time to be exploratory, as no known studies have investigated this question. Finally, we hypothesized that the prospective relations between brain structure and the intercept and slope of psychopathology factor scores would generalize across the specific forms of psychopathology.

METHOD

Participants

The ABCD Study sample consists of 11,875 children who participated in a major collaboration between 22 US sites. Complete recruitment details can be found elsewhere.[24] Exclusion criteria included not being fluent in English, having a parent not fluent in English or Spanish, major medical or neurological conditions, gestational age <28 weeks or birth weight <1200 g, contraindications to MRI

scanning, history of traumatic brain injury, current schizophrenia diagnosis, moderate/severe autism spectrum disorder, intellectual disability, or alcohol/substance use disorder. Institutional review board approval was obtained for each site before data collection. All parents provided written informed consent, and children provided assent.

Demographic, clinical, and structural MRI data were accessed from the National Institute of Mental Health Data Archive (NDA). The current study is based on 9,856 unrelated children (randomly selecting one child per family when more than one child in a family participated) from the ABCD Data Release 4.0 (DOI 10.15154/1523041), including data collected between September 1, 2016, and February 15, 2021. In response to coronavirus disease 2019 (COVID-19) restrictions, the ABCD Study team pivoted to remote or hybrid in-person/remote visits when in-person testing was not feasible from March 2020 on, affecting wave 3 (Supplement 1, available online). Participants with missing demographic information, with complete nonresponse on clinical data, or who did not pass structural MRI quality assurance measures (Figure S1, available online) were excluded (baseline wave 1: n = 9,220; 1-year follow-up wave 2: n = 8,660; 2-year follow-up wave 3: n = 8,017).

Psychopathology. Child psychopathology at each wave was assessed with the Child Behavior Checklist (CBCL) age 6-18 form,[25] a 119-item parent rating scale describing child behaviors and emotions. Parents rate which behaviors were characteristic of their child over the past 6 months on a scale of 0 ("Not True [as far as you know]"), 1 ("Somewhat or Sometimes True"), or 2 ("Very True or Often True") (see Supplement 2, available online, for details on measures).

Covariates. Parents/guardians reported their child's sex assigned at birth and age (in months). MRI scanner was dummy-coded into Prisma, Discovery, Achieva, and Ingenia variables (Prisma Fit = reference group).

MRI Data Acquisition, Processing, and Quality Control. MRI acquisition and scanning parameters, processing, and quality assurance procedures are described elsewhere[26,27] (Supplement 3, available online). Briefly, brain data were collected on 3T MRI scanners (MAGNETOM Prisma and Prisma Fit [Siemens Health Care, Erlangen, Germany], Discovery MR750 [GE Healthcare, Waukesha, Wisconsin], Achieva dStream and Ingenia [Philips Healthcare, Andover, Massachusetts]). T1 images were corrected for gradient nonlinearity distortions using scanner-specific, nonlinear transformations. The ABCD Data Analysis, Informatics, and Resources Center (DAIRC) performed cortical reconstruction and volumetric segmentation using FreeSurfer v7.1.1 (https://surfer.nmr.mgh.harvard.edu/).[28] We used postprocessed volume, SA, and CT data mapped to 34 cortical parcellations per hemisphere based on the Desikan-Killiany brain registration atlas[29] and volume of 19 subcortical segmentations.[30] The DAIRC employed automated and manual approaches to review datasets for quality before sharing data.

Statistical Analyses

Confirmatory Factor Analyses. Previously, higher-order and correlated factors models of CBCL item-level data[31] from the ABCD Data Release 3.0 were fit at each of the 3 waves[23] (Supplement 4, available online). These factor models were found to be metric invariant (ie, equivalent factor loadings across waves).[23] Thus, we used unstandardized factor loadings from those baseline factor models to calculate unstandardized *p* factor scores (from the higher-order model) and externalizing (EXT), internalizing (INT), neurodevelopmental (ND), somatization (SOMAT), and detachment (DETACH) factor scores (from the correlated factors model) (see Tables S1-S3, available online, for baseline factor loadings). We calculated factor scores by multiplying each CBCL item by its unstandardized factor loading and then summing the weighted items for each factor.

Longitudinal Multilevel Modeling. We conducted 3-level linear growth models to control for nesting within ABCD Study sites. Level 1 accounted for the within-subject trajectory of psychopathology factor scores; level 2 accounted for within-site, between-subject differences; and level 3 accounted for between-site differences. We included site- and subject-specific random intercepts and slopes for time. Time was coded as wave number (baseline wave 1 = 0; wave 2 = 1; wave 3 = 2).

Analyses were performed in R version 4.1.1 (http://www.r-project.org/) using the lme4 package.[32] First, we conducted unconditional 3-level linear growth models to determine factor score trajectories over wave and the extent of variability in site and subject intercepts and slopes. Second, we examined whether 4 global brain structure measures (total cortical volume, subcortical volume, cortical SA, mean CT) were associated with site- and subject-level intercepts and slopes of the factor scores over wave, resulting in 24 conditional 3-level growth models tested. Baseline brain structure measures were included as time-invariant covariates (TICs). We mean-centered site means for each brain structure variable to capture between-site effects. We

site-mean-centered brain structure variables for subjects to capture within-site, between-subjects effects. Sex, age, and MRI scanner model were included as level 2 TICs.

The conditional 3-level growth models were conducted using the following fixed effects formula: psychopathology factor scores = $\beta_1 \times$ wave + $\beta_2 \times$ age + $\beta_3 \times$ sex + $\beta_4 \times$ MRI scanner dummies + $\beta_5 \times$ site brain structure + $\beta_6 \times$ subject brain structure + $\beta_7 \times$ site brain structure × wave + $\beta_8 \times$ subject brain structure × wave. As we were interested in subject-level effects of brain structure on psychopathology factor scores, we report only those relevant regression coefficients here (see Table S4, available online, for site-level results). We assumed that the missing data mechanism was missing at random and the likelihood of the growth models based on the observed data was sufficient for inference on the associations of interest. Therefore, all subjects with at least one observation across waves were included in the models.

Third, if any global brain structure measures were associated with the subject-level intercept or slope, we performed follow-up parcel-wise analyses to determine whether results were driven by structural alterations within specific brain regions. Parcel-wise analyses were conducted with the 68 cortical parcellations derived from the surface-based atlas procedure[29] and the 19 subcortical regions derived by the automated labeling procedure.[30] The volume, area, or thickness of each region, hereinafter referred to as parcels, were centered and included in the 3-level growth models as TICs just as described in the global analyses above. We conducted these parcel-wise analyses both with and without the global brain structure measures included as TICs to evaluate specificity of relations between each parcel and the psychopathology trajectories.

We corrected for multiple comparisons by using a false discovery rate (FDR) procedure[33] ($q < .05$) for the 48 global tests in one set and follow-up parcel-wise tests in a second set. Analysis code is available at https://github.com/Ageyr13/ABCD_brain_structure_MLM.git. Relations between brain structure and intercepts would indicate that baseline brain structure is associated with psychopathology at baseline, whereas relationships with slope would indicate that within-person psychopathology trajectories differ as a function of baseline brain structure. If there were significant relations between brain structure and intercepts, but not slopes, we tested whether these relations remained at waves 2 and 3.

Sensitivity Analyses. We conducted 5 sensitivity analyses. First, we included parental education and total combined family income (over past 12 months) as TICs in the growth models as measures of socioeconomic status that may influence brain structure and psychopathology. Second, we controlled for the effects of baseline psychotropic medication use (over past 2 weeks) by including this as an additional TIC that may influence brain structure and psychopathology. Third, we controlled for the wave 3 visit setting to ensure that results were not partially driven by remote/hybrid vs in-person setting. Fourth, we conducted the analyses using factor scores derived from a bifactor model, which imposes an orthogonal structure between the general and specific factors (see Supplement 4 and Table S3, available online, for more details). Fifth, as we randomly selected one sibling per family for inclusion in the main analyses, we subsequently randomly sampled one sibling per family and ran the growth models 100 times to evaluate the robustness of the associations across different combinations of included siblings (one per family).

RESULTS

Descriptive Statistics

Table 1 shows descriptive statistics and missingness information for all study variables (see Table S5 for variable intercorrelations, available online). Of the 9,220 included participants at baseline, 1,405 (15.31%) had missing CBCL data at waves 2 or 3. Of the 1,405 participants with missing CBCL data, 1,047 were missing at waves 2 or 3, and 358 were missing at both follow-up waves. Baseline differences in all study variables between participants with any missing CBCL data (n = 1,405) vs participants with no missing follow-up data (n = 7,815) were tested. The sample with no missing follow-up data had a significantly greater proportion of non-Hispanic White participants; a smaller proportion of Black participants and participants categorized as other race; higher parental education and family income; larger volume and SA; and lower baseline p, EXT, and ND factor scores than participants with missing CBCL data. As there are differences between participants with and without missing data on baseline factor scores, we conducted an additional sensitivity analysis by removing 358 participants with completely missing CBCL follow-up data.

Unconditional 3-Level Linear Growth Model

Fixed effects indicated a significant decreasing trend of p, EXT, INT, ND, and SOMAT factor scores over the waves, whereas there was a significant increasing trend of DETACH factor scores (Table 2). Not surprisingly, random effects indicated that there was more intraindividual (ie, wave within subject) and interindividual (ie, subject within site) variability

TABLE 1 Descriptive Statistics of Study Variables and Comparisons of Participants With and Without Missing Follow-up Data

	Baseline wave 1 sample				No missing data sample		Missing data sample			
	n	Min	Max	Mean (SD) or %	n	Mean (SD) or %	n	Mean (SD) or %	χ^2/t	*p*
Demographic covariates										
Age, months	9,220	107	132	118.95 (7.40)	7,815	118.97 (7.43)	1,405	118.84 (7.26)	0.57	.569
Sex, female	9,220	—	—	47.7	7,815	47.5	1,405	49.2	1.39	.238
Non-Hispanic White	9,220	—	—	51.3	7,815	53.9	1,405	36.6	142.87	< .001
Black	9,220	—	—	17.7	7,815	15.7	1,405	28.8	140.40	< .001
Asian	9,220	—	—	4.9	7,815	4.9	1,405	4.7	0.12	.729
Hispanic	9,220	—	—	12.0	7,815	11.9	1,405	12.7	0.75	.388
Other[a]	9,220	—	—	14.2	7,815	13.6	1,405	17.2	12.86	< .001
Parent education[b]	9,207	1	8	5.22 (1.65)	7,805	5.33 (1.60)	1,402	4.63 (1.77)	13.78	< .001
Family income[c]	8,413	1	10	7.21 (2.43)	7,199	7.36 (2.32)	1,214	6.32 (2.82)	12.12	< .001
Psychotropic medication use	9,220	—	—	8.8	7,796	8.7	1,405	9.8	2.03	.154
Global brain structure										
Cortical volume	9,220	394,785	832,508	597,704.74 (55,937.30)	7,815	599,547.00 (55,424.72)	1,405	587,457.49 (57,622.22)	7.28	< .001
Subcortical volume	9,220	36,446	80,975	59,971.95 (4,871.54)	7,815	60,058.99 (4,839.50)	1,405	59,487.80 (5,020.34)	4.05	< .001
Cortical surface area	9,220	127,160	275,078	189,473.85 (17,987.90)	7,815	190,007.18 (17,823.60)	1,405	186,507.28 (18,605.13)	6.53	< .001
Cortical thickness	9,220	2.42	3.06	2.73 (0.08)	7,815	2.73 (0.08)	14,05	2.72 (0.08)	2.43	
	All waves				No missing data sample		Missing data sample			
	n	Min	Max	Mean (SD)	n	Mean (SD)	n	Mean (SD)	χ^2/t	*p*
Factor scores										
p1	9,220	0	57.15	7.42 (7.68)	7,815	7.29 (7.54)	1,405	8.13 (8.42)	3.50	< .001
p2	8,660	0	50.63	7.16 (7.40)	—	—	—	—	—	—
p3	8,017	0	65.72	6.73 (7.27)	—	—	—	—	—	—
EXT1	9,220	0	40.89	3.84 (4.91)	7,815	3.76 (4.81)	1,405	4.31 (5.40)	3.58	< .001
EXT2	8,660	0	39.03	3.57 (4.67)	—	—	—	—	—	—
EXT3	8,017	0	38.84	3.29 (4.55)	—	—	—	—	—	—
INT1	9,220	0	14.18	1.34 (1.80)	7,815	1.34 (1.79)	1,405	1.34 (1.85)	0.06	.952
INT2	8,660	0	12.92	1.37 (1.82)	—	—	—	—	—	—
INT3	8,017	0	13.67	1.25 (1.78)	—	—	—	—	—	—
ND1	9,220	0	17.89	2.65 (3.00)	7,815	2.59 (2.95)	1,405	2.99 (3.24)	4.28	< .001
ND2	8,660	0	17.89	2.56 (2.95)	—	—	—	—	—	—
ND3	8,017	0	18.27	2.42 (2.86)	—	—	—	—	—	—
SOMAT1	9,220	0	8.12	0.77 (1.10)	7,815	0.77 (1.09)	1,405	0.78 (1.18)	0.08	.937

(*continued*)

TABLE 1 Continued

	All waves				No missing data sample		Missing data sample			
	n	Min	Max	Mean (SD)	n	Mean (SD)	n	Mean (SD)	χ^2/t	*p*
SOMAT2	8,660	0	9.17	0.76 (1.11)	—	—	—	—	—	—
SOMAT3	8,017	0	8.15	0.73 (1.07)	—	—	—	—	—	—
DETACH1	9,220	0	7.31	0.45 (0.82)	7,815	0.45 (0.81)	1,405	0.48 (0.89)	1.46	.144
DETACH2	8,660	0	7.31	0.49 (0.83)	—	—	—	—	—	—
DETACH3	8,017	0	7.31	0.54 (0.92)	—	—	—	—	—	—

Note: *Comparisons were made by χ^2 tests for categorical variables and independent samples t tests for continuous variables. All p values are unadjusted; p values that survived false discovery rate correction for the 20 tests (q < .01) are indicated in boldface. Slight variations in sample size reflect missing data in some variables. 1 = baseline wave 1; 2 = 1-year follow-up wave 2; 3 = 2-year follow-up wave 3; DETACH = detachment factor scores; EXT = externalizing factor scores; INT = internalizing factor scores; ND = neurodevelopmental factor scores; p = general psychopathology factor scores; SOMAT = somatization factor scores.*

[a] *"Other" refers to individuals identifying as American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or mixed race.*

[b] *Mean parental education of 5.22 is equivalent to an associate degree.*

[c] *Mean combined family income of 7.21 is equivalent to between $50,000 and $75,000 income over the past 12 months.*

than between-site variability in the intercept and slope of the factor scores over time. Random effects also showed that there was more interindividual variability in the intercepts than the slopes, with minimal variability in the slopes of the factor scores over time. The intrasubject correlations for each of the psychopathology factor scores over wave were as follows: p = 0.745; EXT = 0.728; INT = 0.649; ND = 0.747; SOMAT = 0.523; DETACH = 0.568.

Global Brain Structure Associations With Psychopathology Trajectories

Smaller baseline total cortical volume, subcortical volume, and SA, but not mean CT, were significantly associated with higher *p* factor scores at baseline (intercept) after FDR correction (Table 3), which remained significant at waves 2 and 3 (Table S6, available online). These findings are largely consistent across factors except for INT. None of the baseline global brain structure measures was associated with the slope of the psychopathology factor scores over wave, apart from INT factor scores. Specifically, baseline mean CT was estimated to have a positive slope over the waves for the INT factor scores, which remained significant even after controlling for *p* factor scores ($\beta = .010$, $p = .008$). We estimated simple slopes at 1 SD below the mean, the mean, and 1 SD above the mean using the R interactions package[34] to illustrate this interaction. We found that children with lower baseline mean CT had significantly steeper decreases in INT factor scores over wave ($\beta = -.03$, SE = 0.01, $p < .001$), followed by children with average mean CT ($\beta = -.02$, SE = 0.01, $p = .02$). Children with higher mean CT did not show a significant change in INT factor scores over wave ($\beta = -.01$, SE = 0.01, $p = .52$) (Figure 1).

Parcel-wise Analyses

Based on results from the global brain structure analyses, we conducted parcel-wise analyses of associations of 68 cortical volume, 68 SA, and 19 subcortical volume parcels with the intercept of *p* factor scores and associations of 68 CT parcels with the slope for INT factor scores. Parcel-wise analyses were conducted with and without global brain structure included as a covariate. FDR correction was employed for all 446 parcel-wise tests simultaneously.

The association between baseline global volume and SA and the intercept of *p* factor scores was distributed throughout the brain with 66 cortical volume, 68 SA, and 19 subcortical volume parcels demonstrating significant associations with intercepts (Figure 2A-C). These parcel-wise relations largely were no longer significant after controlling for global brain structure (see Table S7, available online, for a few exceptions). Alternatively, the association between mean CT and the slope

TABLE 2 Unconditional Linear 3-Level Growth Models of Psychopathology Factor Scores Over 3 Waves

	p		EXT		INT		ND		SOMAT		DETACH	
	β	SE	β	SE	β	SE	β	SE	β	SE	β	SE
Fixed effects												
Intercept	7.33***	0.25	3.78***	0.16	1.32***	0.05	2.64***	0.09	.77***	0.02	.45***	0.02
Wave	−.28***	0.06	−.24***	0.04	−.03*	0.01	−.09***	0.02	−.02*	0.01	.04***	0.01
	Variance	**SD**	**Variance**	**SD**	**Variance**	**SD**	**Variance**	**SD**	**Variance**	**SD**	**Variance**	**SD**
Random effects												
Level 1 residual	12.04	3.47	5.10	2.26	1.02	1.01	1.94	1.39	0.54	0.74	0.27	0.52
Level 2 intercept	46.13	6.79	18.67	4.32	2.24	1.50	7.04	2.65	0.68	0.82	0.42	0.64
Level 2 covariance	−0.33	—	−0.38	—	−0.24	—	−0.31	—	−0.26	—	−0.09	—
Level 2 slope	2.26	1.50	0.99	0.99	0.12	0.34	0.26	0.51	0.03	0.17	0.05	0.23
Level 3 intercept	1.22	1.11	0.48	0.69	0.04	0.20	0.16	0.40	0.01	0.09	0.00	0.06
Level 3 covariance	−0.81	—	−0.94	—	−0.70	—	−0.63	—	−0.91	—	−1.00	—
Level 3 slope	0.07	0.26	0.02	0.15	0.00	0.05	0.01	0.10	0.00	0.01	0.00	0.00

Note: *Unstandardized estimates are shown. DETACH = detachment factor scores; EXT = externalizing factor scores; INT = internalizing factor scores; Level 1 = intraindividual variability (within-subject repeated measures); Level 2 = interindividual variability (within-site); Level 3 = intersite variability (between-site); ND = neurodevelopmental factor scores; p = general psychopathology factor scores; SD = standard deviation; SE = standard error; SOMAT = somatization factor scores.*
**p < .05; ***p < .001.*

for INT factor scores was driven by 16 of the 68 CT parcels and remained significant after controlling for global CT. Baseline CT within the bilateral paracentral lobule, left precentral gyrus, bilateral postcentral gyrus, bilateral superior parietal lobule, left inferior temporal gyrus, left middle temporal gyrus, bilateral parahippocampal gyrus, right cuneus, bilateral lateral occipital cortex, and bilateral lingual gyrus parcels significantly predicted the slope for INT factor scores over wave (Figure S2 and Table S8, available online).

Sensitivity Analyses

The above results were largely unchanged after controlling for parental education and family income, psychotropic medication use, visit setting, employing factor scores from a bifactor model, and excluding participants with completely missing follow-up data (Tables S9-S13, available online). Exceptions were due to slight changes in unadjusted *p* values, which either no longer met the FDR significance threshold ($q < .05$) or now met this threshold, despite effect sizes remaining similar (Supplement 5, available online). Critically, we also found that the above estimates were stable across inclusion of 100 different combinations of randomly selected siblings (Figure S3, available online).

DISCUSSION

In this study of preadolescents from the ABCD Study, we examined prospective relations between baseline brain structure and transdiagnostic psychopathology trajectories over a 2-year period. Consistent with prior research using ABCD Study participants,[7,8] we found that smaller global baseline volume and SA, but not CT, were associated with higher between-person *p* factor scores and now show that these relations persisted over wave, independent of sex, age, scanner, site, socioeconomic status, psychotropic medication, visit setting, type of confirmatory factor model, and inclusion of different randomly selected siblings. Between-person effects largely generalized across all forms of psychopathology except for INT. None of the brain structure measures were prospectively related to within-person trajectories of *p* factor scores. However, lower baseline mean CT was associated with steeper declines in INT factor scores over time, driven by lower CT within visual, somatomotor, and temporal regions.

We found that smaller volume and SA were associated with between-person levels of the *p* factor. These findings both replicate and extend prior research with ABCD Study participants, which found that global patterns of smaller volume and/or SA was cross-sectionally associated with higher *p*.[7,8] This internal replication is particularly of note given that each of these investigations, including the present study, used different combinations of psychopathology measurements (ie, diagnostic interview vs CBCL) and confirmatory factor models (ie, bifactor vs higher-order/correlated factors). Our results further show that these inverse relations between volume and SA and the *p* factor are stable during preadolescence.

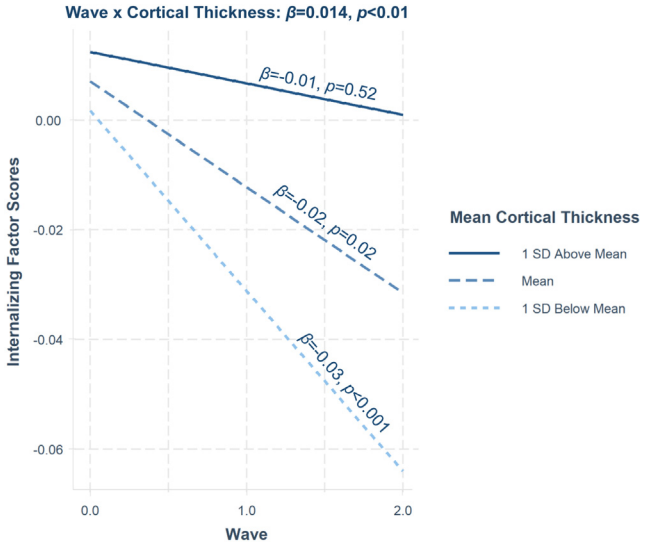
TABLE 3 Global Brain Structure Relations With Intercept and Slope of the Psychopathology Factors Over Wave

	p		EXT		INT		ND		SOMAT		DETACH	
Global brain structure	**Std. β**	**[95% CI]**	**Std. β**	**[95% CI]**	**Std. β**	**[95% CI]**	**Std. β**	**[95% CI]**	**Std. β**	**[95% CI]**	**Std. β**	**[95% CI]**
Total cortical volume												
Intercept	**−.098*** **	[−0.120, −0.076]	**−.105*** **	[−0.128, −0.083]	−.003	[−0.024, 0.019]	**−.104*** **	[−0.126, −0.082]	−.022*	[−0.043, −0.000]	**−.048*** **	[−0.069, −0.027]
Slope	.008	[−0.000, 0.016]	.005	[−0.004, 0.013]	.009	[−0.001, 0.018]	.009*	[0.001, 0.017]	.010	[−0.001, 0.021]	−.001	[−0.012, 0.010]
Total subcortical volume												
Intercept	**−.078*** **	[−0.100, −0.056]	**−.080*** **	[−0.103, −0.058]	−.003	[−0.025, 0.018]	**−.089*** **	[−0.111, −0.067]	−.010	[−0.032, 0.011]	**−.036** **	[−0.057, −0.016]
Slope	.003	[−0.006, 0.011]	.003	[−0.006, 0.011]	.001	[−0.008, 0.010]	.003	[−0.005, 0.012]	.004	[−0.007, 0.015]	−.006	[−0.017, 0.005]
Total cortical surface area												
Intercept	**−.103*** **	[−0.126, −0.081]	**−.113*** **	[−0.136, −0.091]	−.006	[−0.028, 0.017]	**−.106*** **	[−0.129, −0.084]	−.022*	[−0.044, −0.001]	**−.043*** **	[−0.064, −0.022]
Slope	.006	[−0.003, 0.014]	.006	[−0.003, 0.014]	.003	[−0.007, 0.012]	.006	[−0.002, 0.014]	.006	[−0.005, 0.017]	−.003	[−0.014, 0.007]
Mean cortical thickness												
Intercept	−.003	[−0.023, 0.018]	.002	[−0.018, 0.023]	.005	[−0.015, 0.025]	−.010	[−0.030, 0.011]	.002	[−0.018, 0.022]	−.019	[−0.038, 0.000]
Slope	.005	[−0.003, 0.014]	−.002	[−0.011, 0.006]	**.014** **	[0.004, 0.023]	.007	[−0.001, 0.015]	.009	[−0.002, 0.020]	.008	[−0.003, 0.019]

Note: *n = 25,897 observations over 3 waves. Three-level linear growth models were run (level 1 = within-subject repeated measures of psychopathology factor scores; level 2 = within-site, between-subject differences; level 3 = between-site differences). Intercept effects can be interpreted as the main effect of baseline brain structure on between-person differences in the psychopathology factor scores. Slope effects can be interpreted as interactions between baseline brain structure and wave. Site-level intercepts and slopes and covariates age, sex, and scanner (dummy-coded) are not shown here (see Table S5, available online). Standardized estimates are shown. Estimates in boldface survived false discovery rate correction (q < .05) for the 48 tests. DETACH = detachment factor scores; EXT = externalizing factor scores; INT = internalizing factor scores; ND = neurodevelopmental factor scores; p = general psychopathology factor scores; SOMAT = somatization factor scores; Std. = standardized.*

**unadjusted p < .05; **unadjusted p < .01; ***unadjusted p < .001.*

FIGURE 1 Mean Cortical Thickness Relations With Rate of Change of Internalizing Factor Scores Over Wave



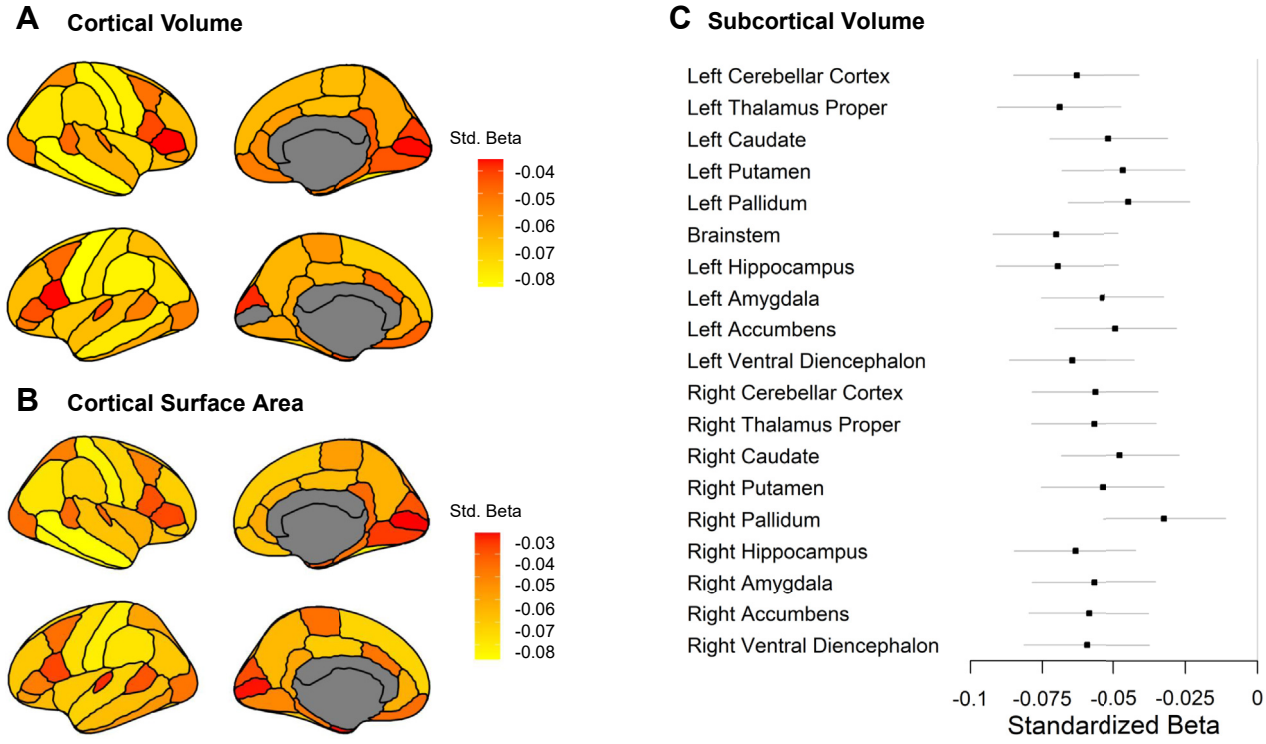
Note: *The interaction between mean cortical thickness and wave (slope) for internalizing factor scores is shown. Simple slopes analysis revealed that children with higher mean cortical thickness (1 SD above the mean) showed no change in internalizing factor scores over the study waves. Children with lower mean cortical thickness (1 SD below the mean) showed the steepest declines in internalizing factor scores over the waves followed by children with average levels of mean cortical thickness. Standardized estimates are shown.*

However, we did not find evidence of prospective relations between brain structure and within-person rates of change in the *p* factor or specific psychopathology factors except for INT. Lower average CT (ie, thinner cortex) was associated with within-person rates of change in INT factor scores over time. This finding is consistent with prior cross-sectional research in the Philadelphia Neurodevelopmental Cohort, which found that CT was associated with fears but not *p* factor scores.[9] Cortical thinning is thought to reflect myelination (ie, increasing proportion of myelinated axons) and pruning (ie, synapse, dendrite, or cell body loss/remodeling).[35,36] Baseline CT may reflect the degree to which pruning and myelination have occurred thus far in development. Therefore, the CT by wave interaction can be interpreted as children with thinner cortices at ages 9 to 10 (putatively reflecting greater pruning and myelination) showed the steepest decrease in INT symptoms during preadolescence. This interaction was driven by CT within visual, somatomotor, and temporal regions involved in sensation-, perception-, and action-related processes. Why might this interaction be driven by these specific regions? Developmental neuroimaging studies have shown that cortical maturation occurs on a gradient from lower-order, unimodal sensorimotor cortices to higher-order, heteromodal association cortices (ie, prefrontal and parietal regions).[16] Sensorimotor brain regions show peak volume and thickness first and thin more rapidly at an earlier age in childhood than heteromodal association cortices.[16,35,37] As a result, these sensorimotor and temporal regions should have undergone extensive thinning by ages 9 to 10. Thus, our findings suggest that children who have undergone normative age-related thinning in sensorimotor and temporal brain regions at ages 9 to 10 may be most protected from developing INT symptoms, as opposed to children with thicker sensorimotor and temporal regions.

Variability in cortical maturation may be due to some combination of genetic, molecular, and environmental processes. Although speculative, our results suggest that childhood environments optimized for sensorimotor and temporal cortical maturation may protect children from developing INT symptoms. For example, Rosen *et al.*[38] posit that early cognitive stimulation from caregivers supporting maturation of visual sensory cortices may scaffold healthy prefrontal cortex and executive function skills development, which is dysfunctional in most mental disorders, and has been shown to prospectively predict later psychopathology in the ABCD sample.[23] Results from cross-sectional adult studies have shown that smaller visual association cortex volume (specifically within lingual gyrus), which supports executive functioning through its prefrontal cortex connections, is associated with higher levels of *p* and specific factors, including INT.[39-41] Although often overlooked, it is important to consider the role of sensorimotor cortices in psychopathology risk in addition to typically studied heteromodal association cortices.

Why having thinner sensorimotor and temporal cortices might protect against development of INT psychopathology, but not general psychopathology, is less clear. Although speculative, given that lower global CT is associated with higher levels of general psychopathology in adulthood,[12] one hypothesis is that alterations in CT may first be associated with change in specific INT psychopathology in preadolescence before generalizing to all forms of psychopathology (ie, *p* factor) over the course of development. This interpretation would be consistent with a dynamic mutualism theory, which proposes that symptom comorbidity and severity, as captured by the *p* factor, may increase over time.[42] In other words, childhood alterations in cortical thinning could initially relate to the trajectory of INT psychopathology, but as symptom comorbidity and severity increase throughout youth development, CT may predict the trajectory of the *p* factor. As

FIGURE 2 Parcel-wise Cortical Volume, Surface Area, and Subcortical Volume Relations With the Intercept of *p* Factor Scores



Note: *(A and B) Statistical parametric maps from parcel-wise analyses are shown to illustrate significant negative associations of (A) cortical volume and (B) cortical surface area with the intercept of p factor scores. (C) Forest plot of significant negative associations between subcortical volume parcels and the intercept of p factor scores. All associations shown are false discovery rate corrected for all parcel-wise tests (q < .05). Color bars reflect effect sizes (standardized β values). Std. = standardized.*

this finding was not hypothesized in advance, it will be important to determine its replicability in other studies. Nevertheless, the current findings suggest that prospective relations between childhood levels of CT and subsequent within-person change in psychopathology do not generalize across all forms of disorder during preadolescence.

It is also possible that brain structure may not have been associated with within-person trajectories of the *p* factor because the waves occurred over a short 2-year time frame during preadolescence, before the onset of most mental disorders in adolescence.[22] Consequently, there was not much change or interindividual variability in the slopes observed in the psychopathology dimensions over the waves. Effect sizes of relations between brain structure and psychopathology factors over time were small (but not smaller than is typical[43]), possibly because the influence of brain structure on future psychopathology may increase with time as psychopathology emerges in later years. A second possibility is that a static brain structure measure at one time point may not provide enough information to relate to within-person psychopathology change. One study found that longitudinal relations between brain structure and youth EXT symptoms were driven by change in brain structure rather than structure at one time point.[19] Third, although brain structural abnormalities often are conceptualized as preceding the onset of symptoms, it is possible that they may be a consequence of the *p* factor rather than a prospective predictor of changes in *p*. Indeed, a prospective youth longitudinal study found that INT and EXT symptoms were associated with changes in brain structure, but not the other way around.[21] Fourth, brain connectivity alterations may be more likely to relate to within-person psychopathology trajectories than brain morphology. Cross-sectional research with ABCD Study participants has shown concurrent relations between general and specific psychopathology factors and alterations in structural[44] and functional connectivity.[45-47] Future ABCD studies should investigate these questions as these children are followed into adolescence.

Interestingly, we found that the trajectories of p, EXT, INT, ND, and SOMAT factor scores decreased, whereas the trajectory of DETACH factor scores

increased over the waves. Child psychopathology may truly decrease during this preadolescent period before the rise of many forms of psychopathology in adolescence.[22] Anxiety and impulse-control disorders typically manifest in preadolescence and then begin to decline before the onset of substance use, mood, and thought disorders in adolescence and young adulthood.[48] It is less clear why DETACH symptoms (ie, being withdrawn, underactive, low energy) increased over the waves. Wave 3 occurred during the COVID-19 pandemic, so parents may have rated their children as more withdrawn and underactive because the children were spending most of their time at home, not in school. However, one might expect the effects of the COVID-19 pandemic to similarly lead to increases in other forms of psychopathology, given that recent studies have found that rates of anxiety and depression increased from before to during the pandemic.[49] Regardless, it will be important to continue to examine psychopathology trajectories in later adolescent time points.

Our study has several limitations. First, approximately 15% of the included sample had missing follow-up data, and there were significant differences between participants with complete data vs participants with missing data. However, sensitivity analyses that removed participants with completely missing follow-up data yielded the same results as the main analyses. Second, there were only 3 waves of data available at the time of analysis, which limited our analysis approach to tests of linear changes in the transdiagnostic psychopathology dimensions over time. Third, our clinical assessments relied on parent reports of child symptoms, which could be subject to reporting biases. However, maternal psychopathology was not found to bias parent reporting of child symptoms in the ABCD Study.[50]

Despite these limitations, this study is the first to examine prospective relations between brain structure and between-person differences and within-person changes in the *p* factor and specific psychopathology factors over time in the large ABCD Study sample of preadolescents aged 9-10 followed for 2 years. Our novel findings identified specific brain structure features that might contribute to transdiagnostic psychopathology development in preadolescence. Smaller total brain volume and cortical SA may be risk markers for future persistent preadolescent levels of general psychopathology. Future studies should continue to investigate whether cortical thinning reflective of pruning and myelination in sensorimotor and temporal brain regions may specifically protect against increases in INT psychopathology, but not general psychopathology, during preadolescence.

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Dr. Ren served as the statistical expert for this research.

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Data curation: Romer
Formal analysis: Romer, Ren
Resources: Pizzagalli
Supervision: Pizzagalli
Visualization: Romer
Writing — original draft: Romer
Writing — review and editing: Ren, Pizzagalli

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