Dimensional Psychopathology and Neurostructural Variation during Development: A Multi-Method Investigation

By

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1. Introduction

Psychopathology has been traditionally conceptualized and studied as a series of discrete categories. These categories are typically operationalized as diagnoses, which are often derived from the Diagnostic and Statistical Manual of Mental Health Disorders (DSM 5). Accordingly, the majority of research surrounding psychopathology and its mechanisms has employed case-control designs in which healthy controls are compared to persons who meet criteria for a categorically-defined disorder. Investigations of psychopathology through this lens are widespread, but highly problematic. A categorical approach to the classification of symptoms, such as the one presented in the DSM-5, poses substantial constraints on our ability to understand the full spectrum of psychopathology as it manifests in reality. Specifically, measuring psychopathology with a categorical approach introduces biases in comparisons and needs to be complemented by population-based studies (Lee et al., 2007), and does not adequately capture the continuous variation in symptoms (Krueger et al., 2018).

An additional important limitation of the categorical, case-control approach to studying psychopathology is that it often does not allow for naturally occurring comorbidity. Mental health disorders are characterized by a substantial degree of comorbidity and there are many psychopathology symptoms that are transdiagnostic (Grisanzio et al., 2018; Kessler et al., 2005). However, case-control study designs often exclude participants that meet criteria or have symptoms of additional disorders beyond the particular disorder or diagnosis of focus for that study. Studies only including individuals that either 1. meet criteria for one categorically-defined diagnosis or 2. are deemed to be healthy or normal due to a reported absence of any diagnoses discount the many individuals that do not perfectly fit into these arbitrarily defined categories. In other words, such an approach does not capture the full continuum of psychopathology and its common comorbidities.

An alternative approach to conceptualizing psychopathology that helps to address the limitations of a categorical approach is one that attends to and accounts for the dimensional and continuous nature of psychopathology. An early study from Krueger (1999) used factor analysis to provide evidence that certain psychopathology symptoms group together, and, more specifically, that internalizing symptoms and externalizing symptoms cluster together into two separate factors or dimensions (Krueger, 1999). Since then, research has continued to show that psychopathology is characterized by symptoms that are continuous (Kotov et al., 2017), highly correlated (Conway et al., 2019), and hierarchically organized (Caspi & Moffitt, 2018; Conway et al., 2019; Kotov et al., 2017; Lahey et al., 2017; Zald & Lahey, 2017). Additionally, psychopathology dimensions have been found to be more reliable and valid than psychopathology categories (Markon et al., 2011). Thus, studying psychopathology through a dimensional perspective, rather than with a categorical design, can be an effective way to capture the true nature of psychopathology and its naturally occurring comorbidity.

Researchers have suggested a variety of ways to statistically model this dimensional nature of psychopathology. More specifically, some have demonstrated a conceptualization of psychopathology that consists of a hierarchy of correlated symptom domains (Caspi et al., 2014; Kotov et al., 2017; Lahey et al., 2011, 2017). With the use of a variety of methods (Lahey et al., 2020), this type of conceptualization illustrates a structural hierarchy consisting of one general psychopathology factor representing the shared variance across all measured symptoms and disorders, in addition to multiple specific factors representing the variance in specific symptom domains (i.e. internalizing, externalizing). Furthermore, prior studies have shown that a bifactor model, in which all measured psychopathology symptoms load onto both a general psychopathology factor and one orthogonal specific factor, can be a useful model for investigating the distinct and shared features associated with dimensions of

psychopathology because it identifies multiple phenotypes that are uncorrelated (Lahey et al., 2017; Moore et al., 2020). Bifactor models have been utilized and replicated in both youth (Hankin et al., 2017; Laceulle et al., 2015; Moore et al., 2020) and adult samples (Caspi et al., 2014; Lahey et al., 2012, 2018).

Multivariate analytical approaches are also useful methods for studying psychopathology and its dimensionality (Kaczkurkin et al., 2020). Much of the existing literature on psychopathology and associated mechanisms or outcomes relies on univariate analytical approaches in which each variable of interest (i.e. symptom, disorder, underlying mechanism) is tested independently. However, this approach does not allow for the simultaneous examination of multiple dimensional, correlated variables. Multivariate approaches, such as partial least squares (PLS) analysis or canonical correlation analysis (CCA), help to address that limitation (Kaczkurkin et al., 2020). These are data-driven approaches which allow for the mutual examination of associations among multiple variable sets, and which are capable of characterizing statistical variation among multiple modalities in the same subjects (Kaczkurkin et al., 2020; McIntosh & Mišić, 2013; Xia et al., 2018; Zhuang et al., 2020). Thus, such methods can facilitate the delineation of complex relationships between two different dimensional datasets. A growing body of literature has employed these multivariate techniques to the study of psychopathology and neural mechanisms (Berman et al., 2014; Drysdale et al., 2017; Kaczkurkin et al., 2020; Kebets et al., 2019; Lin et al., 2018; Mihalik et al., 2019; Moser et al., 2018; Rodrigue et al., 2018; Stout et al., 2018; Sui et al., 2013; Supekar et al., 2019). However, much of this work focuses on particular disorders or symptoms groups (i.e. schizophrenia or psychosis), rather than on more broadly defined psychopathology dimensions.

Importantly, there is research to suggest that the dimensional, comorbid nature of psychopathology is also manifested in the patterns of neural mechanisms underlying

psychopathology as well. In particular, it has been found that multiple mental health disorders share similar neural mechanisms (Kaczkurkin et al., 2020). For example, a meta-analysis demonstrated common variations in gray matter volume (GMV) in the bilateral insula and the dorsal anterior cingulate across six disorders: depression, anxiety, bipolar disorder, addiction, schizophrenia, and obsessive-compulsive disorder (Goodkind et al., 2015). Additionally, from a more dimensional perspective, prior studies have demonstrated inverse associations between GMV and dimensions of psychopathology (i.e., greater loadings on psychopathology dimensions being associated with smaller GMVs) (Kaczkurkin, Park, et al., 2019; Moore et al., 2019; Romer et al., 2017; Snyder et al., 2017).

There are several limitations of the prior research in this area that are important to note. First, many prior studies on relationships between brain volume and psychopathology have focused on adults, rather than children, which is a limitation for several reasons. For one, it is important to build a more accurate understanding of the associations between dimensional psychopathology and neurostructural variation during development, as childhood is a time during which many forms of psychopathology first manifest (Roza et al., 2003). Further, the emergence of psychopathology symptoms during development has been found to be a substantial risk factor for psychopathology during adulthood (Reef et al., 2010). Additionally, there are substantial levels of brain development (Giedd et al., 1999) and neural plasticity (Sale et al., 2014) during childhood. As a result of this enhanced neural plasticity, childhood is a time of heightened susceptibility to environmental influences that are likely to influence the development of psychopathology (Sale et al., 2014). Therefore, the identification of neural mechanisms underlying childhood psychopathology is a vital step towards the advancement of early risk-identification, prevention, and intervention.

A second important limitation of much of the prior work surrounding dimensional psychopathology and brain volume is a reliance on univariate analyses, in which each

psychopathology dimension or brain region is tested separately. While this is a useful method, it does not allow for identifying which regions cluster together with which symptoms. A third limitation is a focus on samples with age ranges that are quite broad. Given that psychopathology dimensions may change considerably over the course of development, a large sample of children with a narrowly defined age range may be useful. Finally, previous findings surrounding associations between dimensional psychopathology and brain volume during development are in need of replication in order to further assess their validity and robustness (Ioannidis, 2005).

The aim of the current project was to address these limitations and build upon prior work in order to further delineate the neurostructural substrates of psychopathology during development. To accomplish this, associations between regional GMV and dimensions of psychopathology, as defined by a bifactor model, were investigated through two different statistical approaches and with a large sample of children with a narrowly defined age range (children 9 to 10 years old from the Adolescent Brain and Cognitive Development (ABCD) Study). More specifically, we examined associations between regional GMVs and four dimensions of psychopathology representing general psychopathology, internalizing symptoms, ADHD symptoms, and conduct problems through both a structural equation modeling (SEM) approach (Study 1) and a partial least squares (PLS) approach (Study 2). Study 1 aimed to test the relationships between the GMV of each particular brain region and the four psychopathology dimensions using SEM. Study 2 aimed to identify which regional GMVs cluster with which psychopathology dimensions using PLS analysis. We controlled for demographic factors such as age, sex, and race/ethnicity in all analyses.

In line with prior findings (Kaczkurkin, Park, et al., 2019), we hypothesized that Study 1 would demonstrate general psychopathology associated with smaller regional GMVs throughout many regions of the brain. We hypothesized that results of Study 2 would be

consistent with those of Study 1 in demonstrating a global relationship between general psychopathology and GMV even when accounting for multivariate, simultaneous associations and variance. More specifically, in considering that a substantial portion of genetic variance in psychopathology is shared across disorders and that genetics show non-specific associations with the brain (Zald & Lahey, 2017), we predicted a global pattern for GMV and psychopathology, rather than a focal one. These findings together would provide compelling evidence that the relationship between psychopathology and smaller GMV is both global and evident early on in the course of development. Additionally, this study provides a baseline measure for longitudinal analyses of the ABCD dataset in the future. Given that adolescence is a time of exponential increase in mental disorders (Roza et al., 2003), longitudinal follow-up analyses will allow for a better understanding of how these brain-behavior relationships change throughout development, as well as for delineation of their clinical implications.

2. Methods

2.1 Participants

The current study used data from Wave 1 (release 2.0.1) of the Adolescent Brain and Cognitive Development (ABCD) Study (Volkow et al., 2018). The Vanderbilt University institutional review board approved the use of the dataset. The ABCD study Wave 1 includes data from 11,875 children between 9 and 10 years old. Recruitment strategies for the ABCD Study is detailed elsewhere (Casey et al., 2018; Garavan et al., 2018). To summarize, data for the ABCD Study were collected at 21 sites across the United States. Researchers engaged in

probability sampling of schools within catchment areas for each study site, and then children eligible for the study within each of the sample schools were recruited to participate. Age, gender, race/ethnicity, socio-economic status, and urbanicity were the primary sociodemographic factors considered during sample recruitment. Target numbers for these factors were based on the American Community Survey (ACS), which is conducted annually by the U.S. Census Bureau, and on the National Center for Education Statistics student enrollment data. The study sites themselves are not exactly representative of the general U.S. population. However, each site implemented the same unbiased recruitment strategy. Additionally, the researchers of the ABCD Study provide post-stratification weights, which can be used to adjust the sample and make it more representative of the general U.S. population for the purpose of analysis.

2.1.1 Final sample for Study 1

Participants were excluded for missing data or for failing to pass quality assurance measures (see Supplementary Figure 1). After such exclusions, the final sample size included in Study 1 was N = 9,607. Details of the exact methods for imaging data exclusions can be found elsewhere (Hagler et al., 2019). In comparing those excluded (N = 2,268) to the final included sample, the final sample was older in age, had a lower proportion of racial/ethnic minority status individuals, had higher income, had a higher proportion of females, and had more parental education (p-values $\leq .001$). The demographic characteristics of the analyzed sample are summarized in Table 1.

Table 1. *Summary of demographic characteristics of the final Study 1 sample (N = 9,607)*

	Mean	*SD*
Age (months)	119.16	7.47
	N	*%*
Gender		
Female	4,686	48.78
Male	4,921	51.22
Race-Ethnicity		
White	5,127	53.37
Hispanic	1,961	20.41
African American	1,365	14.21
Other	1,154	12.01
Household Annual Income		
< $5,000	320	3.33
$5,000-$11,999	323	3.36
$12,000-$15,999	220	2.29
$16,000-$24,999	411	4.28
$25,000-$34,999	520	5.41
$35,000-$49,999	735	7.65
$50,000-$74,999	1,219	12.69
$75,000-$99,999	1,301	13.54
$100,000-$199,999	2,753	28.66
≥ $200,000	1,003	10.44
Missing	802	8.35
Parental Education		
No degree	468	4.87
Highschool degree/GED	1,147	11.94
Some college	1,572	16.36
Associate's degree	1,228	12.78
Bachelor's degree	2,721	28.32
Master's degree	1,867	19.43
Professional/Doctoral degree	591	6.15
Missing	13	0.14

Note. The "Other" Race-Ethnicity category includes those who were identified by their parent as American Indian/Native American, Alaska Native, Native Hawaiian, Guamanian, Samoan, Other Pacific Islander, Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, Other Asian, or Other Race.

2.1.2 Final Sample for Study 2

The same exclusions for missing data or failing to pass quality assurance measures (see Supplementary Figure 1) were completed in Study 2. An additional 1,389 same-family participants were excluded from the PLS analysis in order to include only one participant per family in the analyses. One participant from each family was randomly selected to be included in the analyses and other family member participants were excluded. This was necessary to control for non-independence between twins and siblings. See the statistical analysis section of this manuscript for more details. The final sample size used for the PLS analysis was N = 8,218. This sample was split into a training sample (N = 4,138) and a replication sample (N = 4,080) that had similar demographics (i.e. age, education level, income, and race/ethnicity breakdown). There were also no significant differences in psychopathology scores for the four psychopathology dimensions (general, internalizing, conduct problems, and ADHD) between the two groups. These two groups were created in order to have a subsample to use to test whether the PLS analysis results would replicate. A summary of the demographic characteristics of the sample included in the PLS analysis can be found in Table 2.

Table 2. *Summary of demographic characteristics of the final Study 2 sample*

	Overall (N = 8,218)		Training (N = 4,138)		Replication (N = 4,080)		Training vs. Replication
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*p*
Age (months)	119.01	7.42	119.05	7.42	118.96	7.39	.588
	N	*%*	*N*	*%*	*N*	*%*	*p*
Gender							.344
Female	3,985	48.49	2,028	49.01	1,957	47.97	
Male	4,233	51.51	2,110	50.99	2,123	52.03	
Race-Ethnicity							.987
White	4,289	52.19	2,160	52.20	2,129	52.18	
Hispanic	1,754	21.34	897	21.68	857	21.01	
African American	1,182	14.38	583	14.09	599	14.68	
Other	993	12.08	498	12.04	495	12.13	
Household Annual Income							.793
< $5,000	282	3.43	146	3.53	136	3.34	
$5,000-$11,999	288	3.51	144	3.48	144	3.53	
$12,000-$15,999	197	2.40	103	2.49	94	2.30	
$16,000-$24,999	360	4.38	180	4.35	180	4.41	
$25,000-$34,999	465	5.66	223	5.39	242	5.93	
$35,000-$49,999	631	7.68	312	7.54	319	7.82	
$50,000-$74,999	1026	12.49	519	12.54	507	12.43	
$75,000-$99,999	1121	13.64	589	14.23	532	13.04	
$100,000-$199,999	2303	28.01	1,137	27.48	1,165	28.55	
≥ $200,000	839	10.21	420	10.15	419	10.27	
Missing	707	8.60	365	8.82	342	8.38	
Parental Education							.486
No degree	412	5.01	215	5.20	197	4.83	
Highschool degree/GED	1000	12.17	501	12.11	499	12.23	
Some college	1358	16.53	655	15.83	703	17.23	
Associate's degree	1050	12.78	513	12.40	537	13.16	
Bachelor's degree	2279	27.73	1,182	28.56	1,097	26.89	
Master's degree	1587	19.31	794	19.19	793	19.44	
Professional/Doctoral degree	521	6.34	270	6.52	251	6.15	
Missing	11	0.13	8	0.19	3	0.07	

Note. The "Other" Race-Ethnicity category includes those who were identified by their parent as American Indian/Native American, Alaska Native, Native Hawaiian, Guamanian, Samoan,

Other Pacific Islander, Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese, Other Asian, or Other Race.

2.2 Measures of Psychopathology

Psychopathology symptoms were measured with parent reports on the Child Behavior Checklist (CBCL) for school-aged children (Achenbach, 2009). The CBCL contains 119 items that describe emotions and behaviors in children that may be concerning, and items were rated on a 3-point scale (0 = not true (as far as you know), 1 = somewhat or sometimes true, and 2 = very true or often true). Only one of the child's parents or guardians responded to the CBCL items. Internal consistency for the CBCL items included in the present analyses was excellent in the current sample (α = .94).

2.3 Image Acquisition, Processing, and Quality Assurance

The imaging protocol for the ABCD Study was developed by the ABCD Data Analysis and Informatics Center (DAIC) and the ABCD Imaging Acquisition Workgroup, and the protocol was harmonized for all scanner platforms. The scanning took place in either one or two sessions and included 3D T1- and 3D T2-weighted images of brain structure. As previously detailed elsewhere (Casey et al., 2018), the collection of imaging data occurred at 21 different sites using several models of 3 tesla (3T) scanners from three vendors: Siemens, Phillips, and General Electric. The specific scanner models used are General Electric Discovery MR750, Siemens Prisma, Siemens Prisma Fit, Phillips Achieva dStream, and Phillips Ingenia. Additional details about the parameters for imaging are as follows: TR (repetition time) 2400 to 2500 ms; TE (echo time) 2 to 2.9 ms; FOV (field of view) 256 × 240 to 256; FOV phase of 93.75% to 100%; matrix 256 × 256; 176 to 225 slices; TI

(inversion delay) 1060 ms; flip angle of 8°; voxel resolution of 1×1×1×mm; total acquisition time from 5 minutes 38 seconds to 7 minutes 12 seconds.

Full descriptions of the procedures for processing and analyzing the ABCD Study brain data can be found elsewhere (Hagler et al., 2019). In summary, DAIC conducted centralized processing and analysis of the neurostructural data using a series of processing steps within the Multi-Modal Processing Stream (MMPS). MMPS is a software package developed and maintained at the Center for Multimodal Imaging and Genetic (CMIG) at the University of California, San Diego (UCSD). Briefly, the pipeline consisted of: 1) preprocessing (correction for gradient nonlinearity distortions, intensity scaling and inhomogeneity correction, registration to an averaged reference brain in standard space, and manual quality control (QC)); 2) brain segmentation (cortical surface reconstruction and subcortical segmentation performed based on automated, atlas-based, segmentation procedures in FreeSurfer v5.3); 3) derivation of morphometric measures (calculation of average volume in each cortical parcel of the standard FreeSurfer Desikan parcellation scheme (Desikan et al., 2006) and in each subcortical region (Fischl et al., 2002)); and finally, 4) post-processing QC (manual review by trained technicians for motion, intensity inhomogeneity, white matter underestimation, pial overestimation, and magnetic susceptibility artifact). See Supplementary Figure 1 for additional details about QC exclusion thresholds.

2.4 Bifactor Modeling of Psychopathology Dimensions

Psychopathology factors were modeled using Mplus version 8.4 (Muthén & Muthén, 2017). Exploratory factor analyses of the CBCL data from a random half of the ABCD Study sample (N = 5,932) was conducted by Moore et al. (2020) and yielded 3 correlated

dimensions of psychopathology (internalizing, ADHD, and conduct problems). This exploratory analysis also helped to reduce the number of CBCL items to reflect those most associated with psychopathology at the age of this sample. The final analyses included 66 items. The following are the primary reasons for item elimination: some items do not reflect psychopathology symptoms (i.e. constipation and finger nail biting), some items are not age-appropriate for this sample (i.e. substance use questions), some items had little endorsement (rating above 0) within this sample, and some items were very similar to another item (composites were created in these cases). Each item that was included in the final model has a factor loading on both the general psychopathology factor and a single specific factor (conduct, internalizing, or ADHD). For example, the item, "cruel to animals", loads onto the general factor and the specific conduct factor. The item, "feels has to be perfect", loads onto the general factor and the internalizing factor. The item, "can't sit still, restless, or hyperactive" loads onto the general factor and the specific ADHD factor.

Moore et al. (2020) then performed a confirmatory bifactor analysis with the second half (N = 5,934) of the ABCD Study data, which defined a general psychopathology factor, which is reflective of the shared symptoms across all participants, as well as specific factors for internalizing, ADHD, and conduct problems (see Figure 1). These four factors are orthogonal to each other and their psychometric properties met the standards for construct reliability and factor determinacy that are recommended for bifactor models (Bornovalova et al., 2020). Additionally, Moore et al. (2020) used additional variables from the ABCD Study data, that held theoretical and clinical relevance, as external criterion measures to investigate the bifactor model's criterion validity. The factors all showed adequate criterion validity, as they had significant associations with the external criterion measures. For additional details about the particular calculation procedures and results of this bifactor modeling process, as

well as the validity and reliability of the psychopathology dimensions, see Moore et al. (2020).

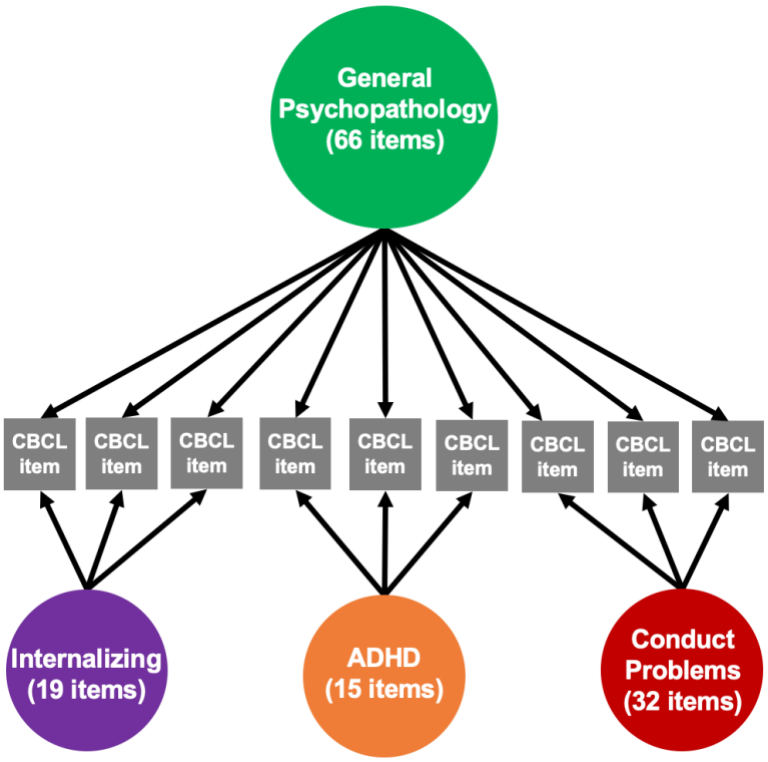

Figure 1. Bifactor analyses delineate general and specific factors. A confirmatory bifactor model of the CBCL data defined four orthogonal psychopathology factors: general psychopathology, which represents symptoms across all domains, in addition to specific factors for internalizing symptoms, ADHD symptoms, and conduct problems.

2.5 Statistical Analyses

2.5.1 Study 1: Structural Equation Modeling

Associations between psychopathology and GMV were examined using the four latent psychopathology factors identified by Moore et al. (2020). We conducted analyses with

68 cortical brain regions derived from the surface-based atlas procedure developed by Desikan et al. (2006), in addition to 19 subcortical regions derived by the automated labeling procedure developed by Fischl et al. (2002). Participant sex was included as a covariate in the model, which is in accordance with prior research that has demonstrated sex differences in GMV (Kaczkurkin, Raznahan, et al., 2019). Participant age and race/ethnicity were also included as covariates. Finally, MRI scanner model was included as a covariate to account for potential differences across scanners. Associations between volume and psychopathology were investigated using the following formula: regional GMV = β*age + β*sex + β*race/ethnicity + β*MRI scanner model + β*general psychopathology + β*internalizing + β*ADHD + β*conduct problems. In order to correct for multiple testing across regions, the false discovery rate ($q<.05$) was controlled using the stats package in R version 3.6.1 (http://www.r-project.org/). The four factors can be included in the same model without problems of multicollinearity due to their orthogonality. Post-stratification weights were used in these analyses to account for the stratification in data collection sites (Heeringa & Berglund, 2020). Additionally, analyses accounted for clustering within families, as the ABCD dataset includes some siblings and twins. Families were modeled with a random intercept.

2.5.2 Study 2: Partial Least Squares Analysis

Using again the latent factors of psychopathology identified by Moore et al. (2020), we examined associations between psychopathology and GMV using a PLS approach. These analyses were performed using the RGCCA (Tenenhaus et al., 2017) and mixOmics (Rohart et al., 2017) packages in R version 3.6.1. The particular PLS approach used in the current study maximizes covariance across variable sets (in this case, psychopathology dimensions

and regional GMVs), as compared to some other multivariate approaches, such as CCA, which standardize the variance and maximize correlations across variable sets (McIntosh & Mišić, 2013; Tenenhaus & Tenenhaus, 2011). CCA assumes that variance is noise; however, brain areas that have more variability across subjects may not reflect measurement error, but actual signal that is important to account for with PLS methods. A PLS approach was chosen for the current study in order to maximize the meaningful covariance signal in these data, rather than discarding it. PLS accomplishes this by fitting a regression model by projecting the predicted and observed variables into a new space. Specifically, PLS aims to maximize variance in one space (X), maximize variance in a second space (Y), and then maximize the correlation between X and Y. PLS is appropriate when there are multiple predictor variables (e.g., psychopathology factors), there are multiple observed variables measured on the same scale (e.g., brain regions), and it is presumed that variability in the observed variables is signal, not noise. In the PLS analysis conducted for the current study, the 68 cortical and 19 subcortical brain regions make up one variable set, while the 4 psychopathology dimensions make up a second variable set. Similar to the structural equation modeling, age, sex, and race/ethnicity were included as covariates. MRI serial number was also included as a covariate, in order to account for both MRI manufacturer and study site. Additionally, one family member from twin or sibling pairs was randomly chosen and excluded from the data prior to conducting the PLS analysis, so that only one participant from each family was included in the analyses.

2.6 Sensitivity Analyses

Multiple iterations of sensitivity analyses were conducted in both Study 1 and Study 2 to test the robustness of findings. In both studies, analyses were repeated with income and

parent's highest level of education included as additional covariates in accordance with prior literature demonstrating associations between those variables and brain structure in youth (Noble et al., 2015). Additionally, in both studies, analyses including medication status (whether or not participants reported current medications at the time of scanning) included as an additional covariate were completed to determine whether associations shift when controlling for medication use. Finally, in both studies, analyses were repeated including intracranial volume (ICV) and then including total GMV to determine whether associations between regional GMVs and psychopathology remained when controlling for cranial size or total GMV.

2.7 Data Availability

The ABCD Study data is available through the National Institute of Mental Health Data Archive (https://nda.nih.gov/abcd).

3. Results

3.1 Study 1 Results

3.1.1 Study 1 Primary Results

Following FDR correction for multiple comparisons, the factors for general psychopathology, conduct problems, and ADHD were each inversely associated with GMV across multiple regions (p_{fdr}-values ≤ .048). Additionally, for the general psychopathology

and conduct problems factors, the associations were relatively global. Of the 68 cortical and 19 subcortical regions that were included in analyses, the general factor was inversely associated with GMV in 54 cortical regions (Supplementary Table 1 and Figure 2), as well as all 19 subcortical regions (Supplementary Table 2). The conduct problems factor was inversely associated with GMV in 52 cortical regions (Supplementary Table 1 and Figure 3), as well as 15 subcortical regions (Supplementary Table 2). The ADHD symptoms factor was inversely associated with 25 cortical regions (Supplementary Table 1 and Figure 4), as well as 8 subcortical regions (Supplementary Table 2). There were no significant associations between the internalizing symptoms factor and regional GMV (p_{fdr}-values ≥ .068; Supplementary Tables 1 and 2). Effect sizes were expressed as standardized beta estimates, and the effect size range for each psychopathology factor was as follows: general psychopathology (-0.03 to -0.08), conduct problems (-0.04 to -0.09), and ADHD symptoms (-0.04 to -0.08) (Supplementary Tables 1 and 2).

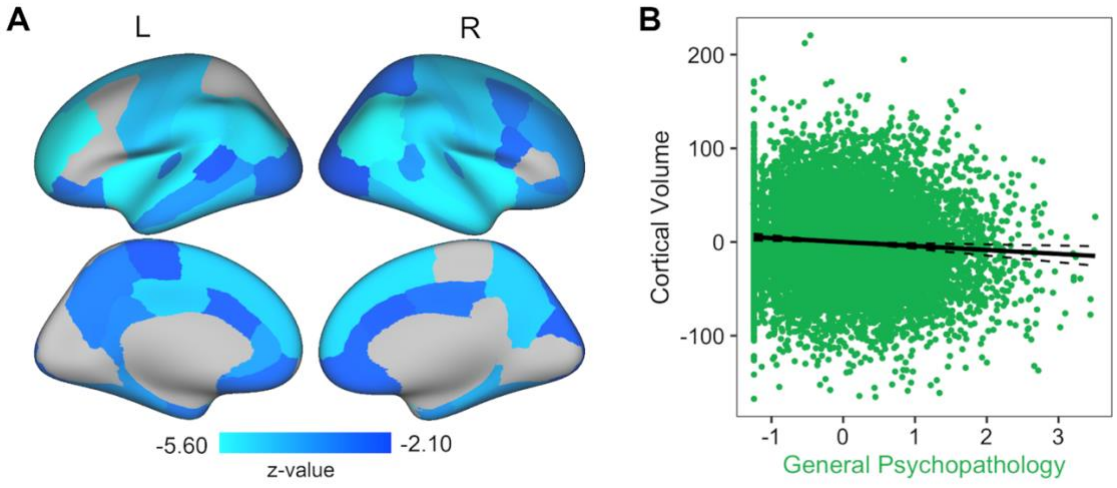

Figure 2. General psychopathology shows smaller brain volumes nearly globally. A) Greater general psychopathology scores were associated with smaller cortical GMV in 54 out of 68 regions (FDR corrected). B) As general psychopathology scores increase, cortical GMV decreases. Each dot in the plot symbolizes a participant. The full model R^2 = .31.

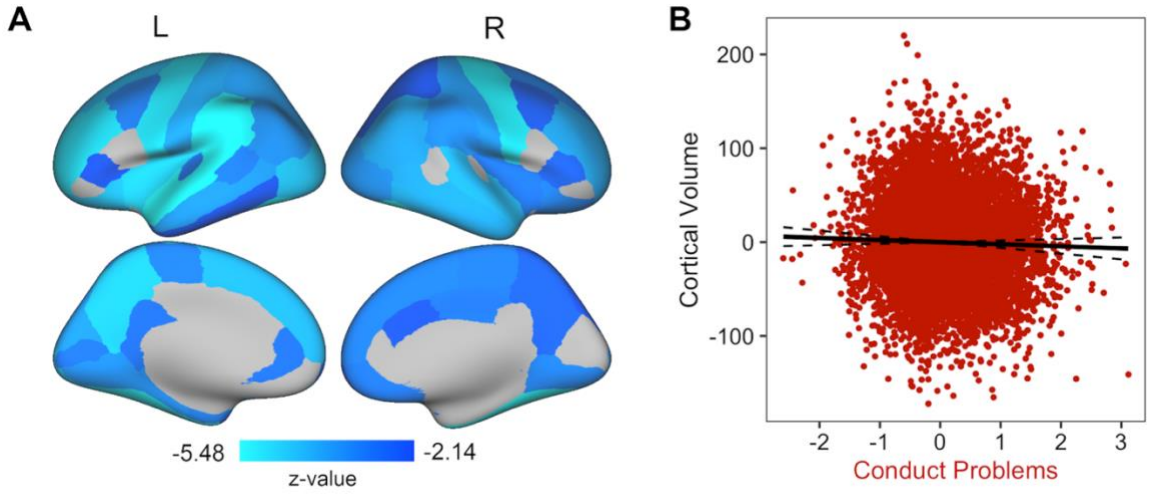

Figure 3. Conduct problems show smaller global brain volumes. A) The specific conduct problems factor was associated with smaller cortical GMV in 52 out of 68 regions (FDR corrected). B) An inverse relationship was apparent, with cortical GMV decreasing as conduct problems increase. Each dot in the plot symbolizes a participant. The full model R^2 = .31.

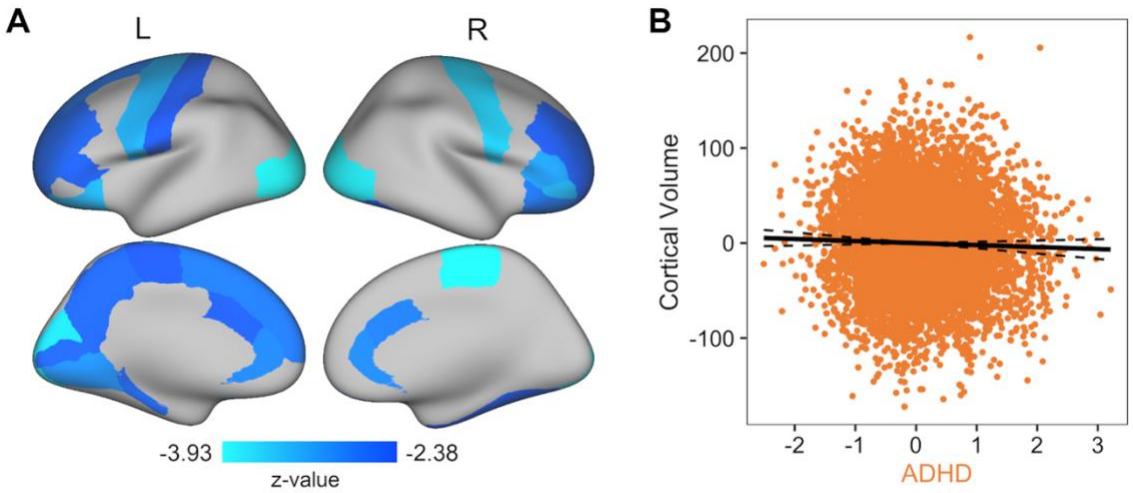

Figure 4. ADHD symptoms are associated with smaller volumes in a number of regions. A) The specific ADHD factor was associated with smaller cortical GMV in 25 out of 68 regions (FDR corrected). B) Greater ADHD scores were related to smaller cortical GMV. Each dot in the plot symbolizes a participant. The full model R^2 = .31.

3.1.2 Study 1 Sensitivity Results

Several iterations of sensitivity analyses were conducted in Study 1 to ensure that the primary results of the structural equation modeling were robust to possible confounds. Sensitivity results accounting for parent education and family income were largely convergent with the primary results (see Supplementary Tables 3 and 4 for cortical and subcortical results, respectively). Psychopathology was inversely associated with GMV in many regions for the general factor (37 cortical, 18 subcortical) and the conduct problems factor (29 cortical, 3 subcortical), with a weaker inverse association for the ADHD symptoms factor (14 cortical, 0 subcortical) (p_{fdr}-values ≤ .049). No significant associations were found between the internalizing symptoms factor and regional GMV (p_{fdr}-values ≥ .133). Sensitivity results accounting for medication use were also convergent with the primary results (see Supplementary Tables 5 and 6 for cortical and subcortical results, respectively). Psychopathology was inversely associated with GMV in many regions for the general factor (51 cortical, 19 subcortical) and conduct problems factor (50 cortical, 16 subcortical), with a weaker inverse association demonstrated for the ADHD symptoms factor (23 cortical, 8 subcortical) (p_{fdr}-values ≤ .049). No significant associations were found between the internalizing symptoms factor and regional GMV (p_{fdr}-values ≥ .068). Sensitivity results accounting for ICV or total cortical/subcortical GMV demonstrated that most region-specific significant results became not significant. This further supports the global nature of the relationship between smaller GMV and psychopathology. When accounting for ICV, the only significant association was an inverse association between general psychopathology and bilateral hippocampus GMV (left hippocampus: β = -0.04, p_{fdr}-value = .019; right hippocampus: β = -0.03, p_{fdr}-value = .019) (Supplementary Table 7). When accounting for total subcortical GMV, significant inverse associations remained between general

psychopathology and GMV of the bilateral hippocampus (left: β = -0.04, p_{fdr}-value = .010; right: β = -0.04, p_{fdr}-value = .010), bilateral accumbens area (left: β = -0.03, p_{fdr}-value = .041; right: β = -0.03, p_{fdr}-value = .038), and left amygdala (β = -0.03, p_{fdr}-value = .038), in addition to a positive association between general psychopathology and right cerebellum cortex GMV (β = 0.01, p_{fdr}-value = .038) (Supplementary Table 8). No other significant associations were identified (p_{fdr}-values ≥ .054).

3.2 Study 2 Results

3.2.1 Study 2 Primary Results

PLS analysis in the training sample (N = 4,138) yielded one stable latent variable that explains 97% of the covariance between the set of 4 psychopathology dimensions and the set of 87 regional brain volumes. This latent variable demonstrates that those with primarily general psychopathology symptoms, but also with a notable degree of ADHD symptoms and conduct problems, show smaller volumes globally across the brain (Figure 5). These results are consistent with the structural equation modeling results from Study 1. The loadings of each psychopathology dimension and brain region on the latent variable yielded from the PLS analysis in the training sample can be found in Supplementary Tables 9 and 10. Results of bootstrapping analysis with 10,000 iterations indicated that loadings for the general psychopathology, conduct problems, and ADHD symptoms factors are reliable, while the internalizing factor does not have a reliable loading (Figure 6). Thus, the internalizing factor was not interpreted. These results were replicated in the replication sample (N = 4,080), and the PLS analysis again yielded one stable latent variable that showed convergent patterns

across the psychopathology dimensions and brain volumes (Supplementary Figures 2 and 3; Supplementary Tables 11 and 12).

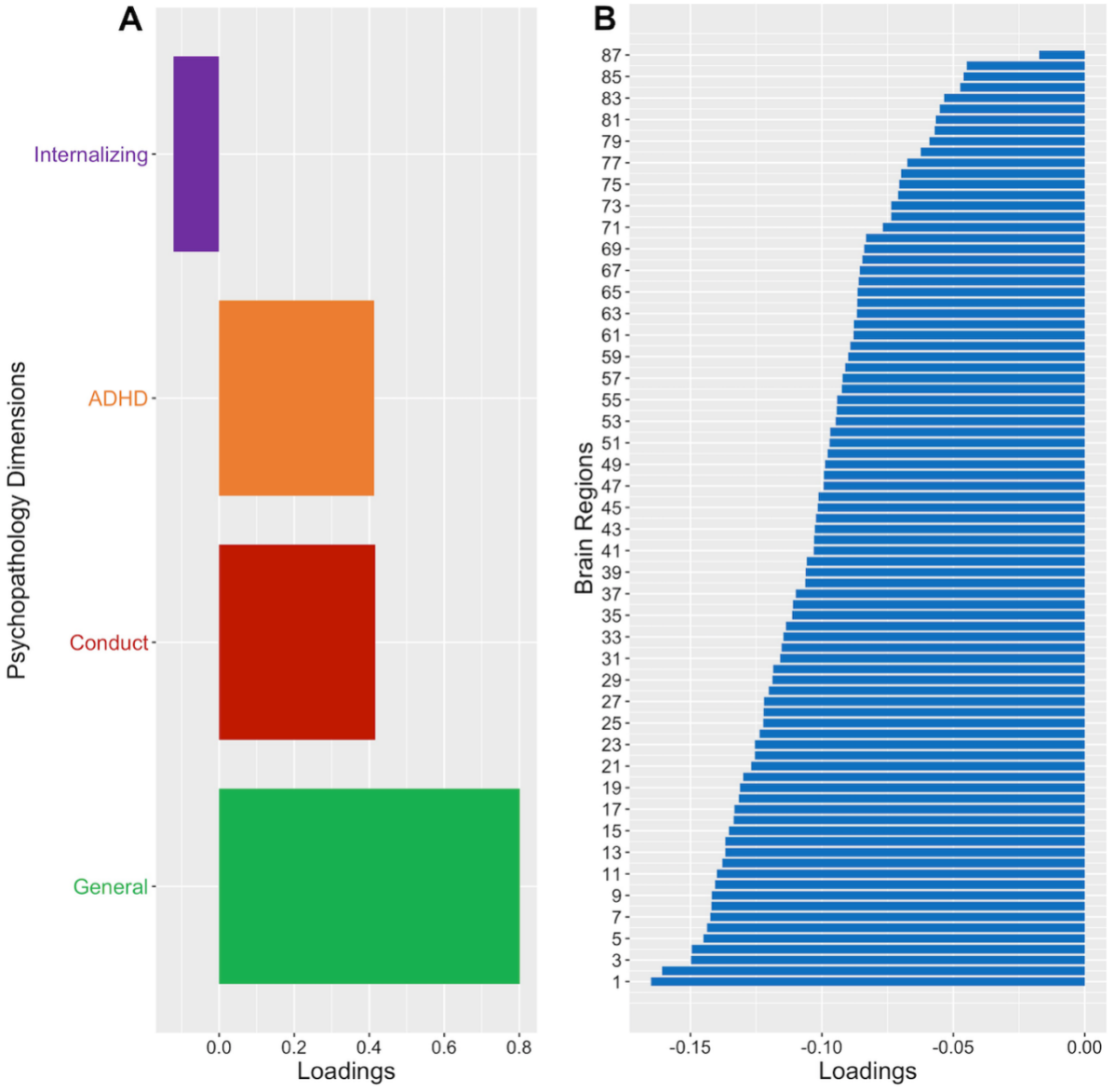

Figure 5. PLS analysis in the training group demonstrates that greater levels of general psychopathology, conduct problems, and ADHD symptoms are associated with smaller volumes across all brain regions. A) Positive loadings for general psychopathology, conduct problems, and ADHD symptoms. B) Negative loadings for all brain regions (see Supplementary Tables 9 and 10 for list of numerical loadings in descending order, based on absolute value, with the key for brain regions 1 (strongest loading) through 87 (weakest loading)).

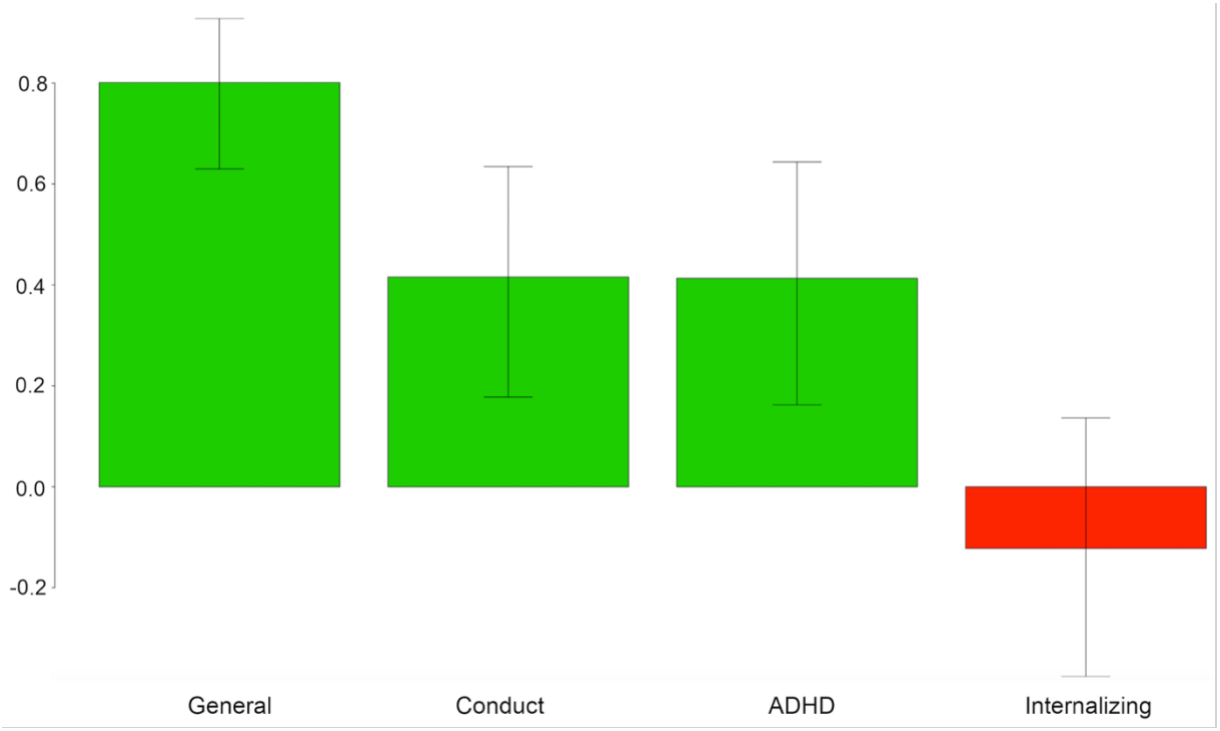

Figure 6. Bootstrapping analysis in the training group demonstrates reliable loadings for the general, conduct, and ADHD psychopathology dimensions. Reliable dimensions are shown in green and unreliable dimensions are shown in red. Results are based on bootstrapping analyses with 10,000 iterations.

3.2.2 Study 2 Sensitivity Results

Several versions of sensitivity analyses were conducted with the training sample to ensure that the primary PLS analysis results were robust to possible confounds. Results of sensitivity analyses controlling for 1. family income and parent education, 2. medication status, 3. ICV, and 4. total GMV as additional covariates were all largely convergent with the primary PLS results. Specifically, these sensitivity results suggested that those with primarily general psychopathology symptoms, but also with a notable degree of ADHD symptoms and conduct problems, show smaller volumes globally across the brain.

4. Discussion

The current project capitalized on a large sample (N = 9,607) of children with a narrowly defined age range (9 to 10-year-old) to investigate associations between dimensional psychopathology and neurostructural variation during development. These investigations were conducted through two different powerful statistical techniques, SEM analysis (Study 1) and PLS analysis (Study 2), in order to comprehensively assess the relationships between psychopathology and regional brain volume in a sample of children. Together, these methodological approaches address significant limitations of the prior literature surrounding the neural mechanisms of psychopathology. In particular, psychopathology was conceptualized from a dimensional perspective, both univariate and multivariate analyses were compared, and a developmental focus was employed.

In Study 1, we found that GMVs in many regions had significant associations with dimensions of general psychopathology, conduct problems, and ADHD symptoms. Analyses controlled for age, sex, race/ethnicity, and MRI manufacturer, and correction for multiple comparisons was conducted. The strongest association was observed for the general psychopathology factor, as smaller GMV was associated with greater general psychopathology for the vast majority of brain regions. The global nature of this association was further demonstrated when controlling for total cortical/subcortical GMV or ICV, as most regional associations were lost. Notably, a few regional associations did remain after controlling for ICV or total subcortical GMV. Specifically, a significant inverse association between bilateral hippocampus GMV and general psychopathology remained when controlling for ICV or total subcortical GMV. Additionally, when controlling for total subcortical GMV, inverse associations also remained between general psychopathology and GMVs of the bilateral accumbens area and left amygdala, and there was a significant positive

association between general psychopathology and right cerebellum cortex GMV. Sensitivity analyses suggest that the primary results of Study 1 are robust even after controlling for income, parental education, and medication use.

Study 2 yielded results that were largely consistent with Study 1, as PLS analysis demonstrated that those with primarily general psychopathology, but also with notable amounts of conduct problems and ADHD symptoms show smaller regional GMV across the brain. These results were consistent across both a training sample and a replication sample, which had similar demographic breakdowns. All Study 2 analyses controlled for age, sex, race/ethnicity, and MRI manufacturer/scan site. Sensitivity analyses suggest that the primary results of Study 2 are robust even after controlling for income, parental education, medication use, and ICV. Taken together, results from Study 1 and Study 2 suggest that globally smaller GMV in childhood may be a nonspecific risk factor for psychopathology across many mental disorders. Additionally, these results provide further support for the dimensional and transdiagnostic nature of psychopathology, which reinforces the importance of studying psychopathology from a dimensional perspective, rather than with a focus on discrete, arbitrarily defined categories.

These results are consistent with prior evidence that smaller GMV is associated with general psychopathology across multiple brain regions in children, adolescents, and/or young adults (Kaczkurkin, Park, et al., 2019; Moore et al., 2019; Romer et al., 2017; Snyder et al., 2017). The present results are also consistent with meta-analyses showing common GMV variations across multiple disorders (Goodkind et al., 2015) and functional activity (Sprooten et al., 2017). Moreover, the present study expands upon this work in several important ways. First, the broad age ranges used in prior studies make it difficult to disentangle the impact of development on these associations, while the current study focused on a large sample of children with a narrowly defined age range. Thus, our findings of inverse relationships

between general psychopathology and GMV suggest that the relationship between smaller brain volume and psychopathology is evident at this early developmental timepoint of age 9 to 10.

Additionally, most of the relevant prior work uses a univariate approach, in which each brain region or psychopathology measure is tested separately. While univariate approaches are widespread and useful, they do not allow for the simultaneous investigation of multiple interrelated sets of variables (i.e. neural measures and psychopathology symptoms). Further, in this particular context, univariate approaches cannot provide information about which brain regions cluster together with which psychopathology symptoms. Thus, it is helpful to complement univariate analyses with multivariate approaches, whenever possible. The current project does so, as it investigates the relationship between regional GMVs and dimensions of psychopathology using both a univariate approach (Study 1) and a multivariate approach (Study 2). Results from these two approaches are largely convergent in the current sample, which suggests that the global relationship between smaller GMV and factors of general psychopathology, conduct problems, and ADHD symptoms exists both when brain regions are tested independently and when brain regions and psychopathology dimensions are examined simultaneously.

Importantly, the univariate analyses in Study 1 suggest that above and beyond the relationship between general psychopathology and smaller brain volumes, there may also be specific or unique associations between ADHD or conduct problems and brain volumes. However, the multivariate approach in Study 2 was able to directly test this and did not find that ADHD or conduct problems shared a unique relationship with brain volume. Instead, it is the combined effect of general psychopathology, ADHD, and conduct problems (with general psychopathology contributing the most) that is associated with globally smaller brain volumes. Thus, the specificity of the relationships between GMV and the factors for conduct

problems and ADHD symptoms found in Study 1 does not remain in Study 2, which further demonstrates the merits of taking a multivariate approach to the delineation of brain-behavior relationships.

Of note, we found no significant associations between regional GMV and the specific internalizing factor in either Study 1 or Study 2. There are several potential explanations for this finding. First, the general psychopathology factor may account for the majority of the variance explained by internalizing-type symptoms and leave little for the residual internalizing factor to explain. Second, this finding may be related to the particular age of this sample, as the incidence of serious anxiety and mood disorders is greatest in adolescence, rather than childhood (Navarro-Pardo et al., 2012; Roza et al., 2003). Third, the internalizing factor in this sample may not be reliable, as suggested by the results of bootstrapping analyses in Study 2. Thus, an important future direction will be to use future waves of the longitudinal ABCD Study data to further parse the heterogeneous trajectories of brain development associated with internalizing psychopathology (Becht & Mills, 2020). Given that the ABCD Study captures neural development prior to the onset of puberty and that some participants will experience increases in internalizing symptoms over time, the ABCD Study provides a unique opportunity to prospectively evaluate changes in developmental trajectories related to internalizing psychopathology.

Relatedly, additional, broader future directions include examinations of whether distinctive neural variation patterns manifest as children mature and develop divergent patterns of psychopathology. Our current results suggest that GMV variations are quite global and non-specific, as they appear to span across many brain regions and many forms of psychopathology. However, while these associations appear broad and non-specific in the current analyses with the ABCD Study sample at Wave 1, it is possible that neurostructural deficits diverge into more specified patterns over the course of development. Therefore,

future data collection waves of this longitudinal ABCD Study could be pivotal to the delineation of these developmental processes and to our understanding of related risk factors and clinical outcomes.

There are several additional considerations and limitations related to the current project that are important to note. First, the effect sizes yielded from our analyses in Study 1 and the brain region loadings on the latent variable found in Study 2 were all relatively small. However, prior studies with large samples have consistently found small, but reliable, brain-behavior associations (Paulus & Thompson, 2019). Second, the derived psychopathology factors are based on parent-report symptom-level data. As such, the factors reflect parent impressions of children's symptoms and difficulties, rather than reflecting child self-report or formal diagnoses. Third, the non-randomness of the excluded data likely decreases the generalizability of findings and underestimates the effects for psychopathology.

In summary, findings from the current set of studies demonstrate that dimensions of general psychopathology, conduct problems, and ADHD symptoms are inversely associated with GMV in a global manner. These findings are consistent with the emerging notion that general psychopathology may be associated with non-specific structural variations in the brain, and may suggest that environmental and genetic factors that impact brain size are risk factors for general psychopathology. Additionally, several focal relationships were identified when this global association was accounted for by including ICV (bilateral hippocampus) or total subcortical GMV (bilateral hippocampus, left amygdala, bilateral accumbens area, right cerebellum cortex) as covariates. Together, these results support and expand upon prior work on the relationship between neurostructural variations and psychopathology in childhood, and further illuminate the dimensional, overlapping nature of psychopathology.

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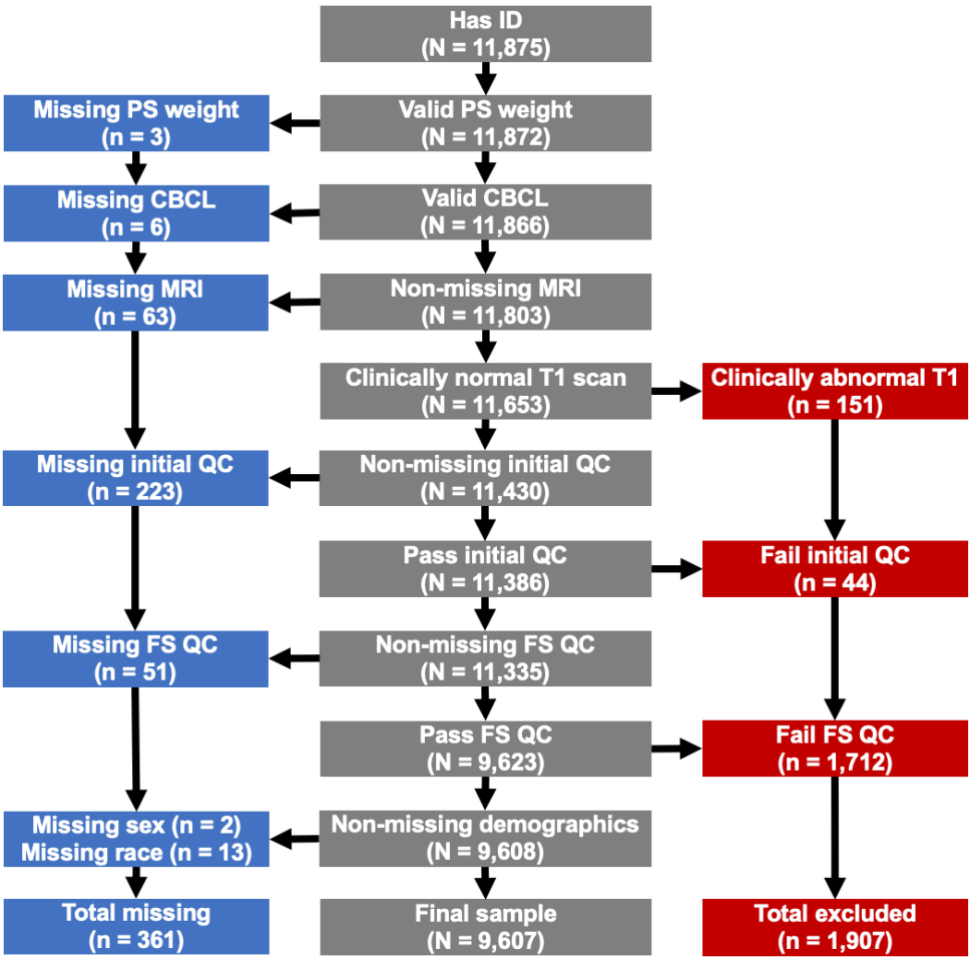
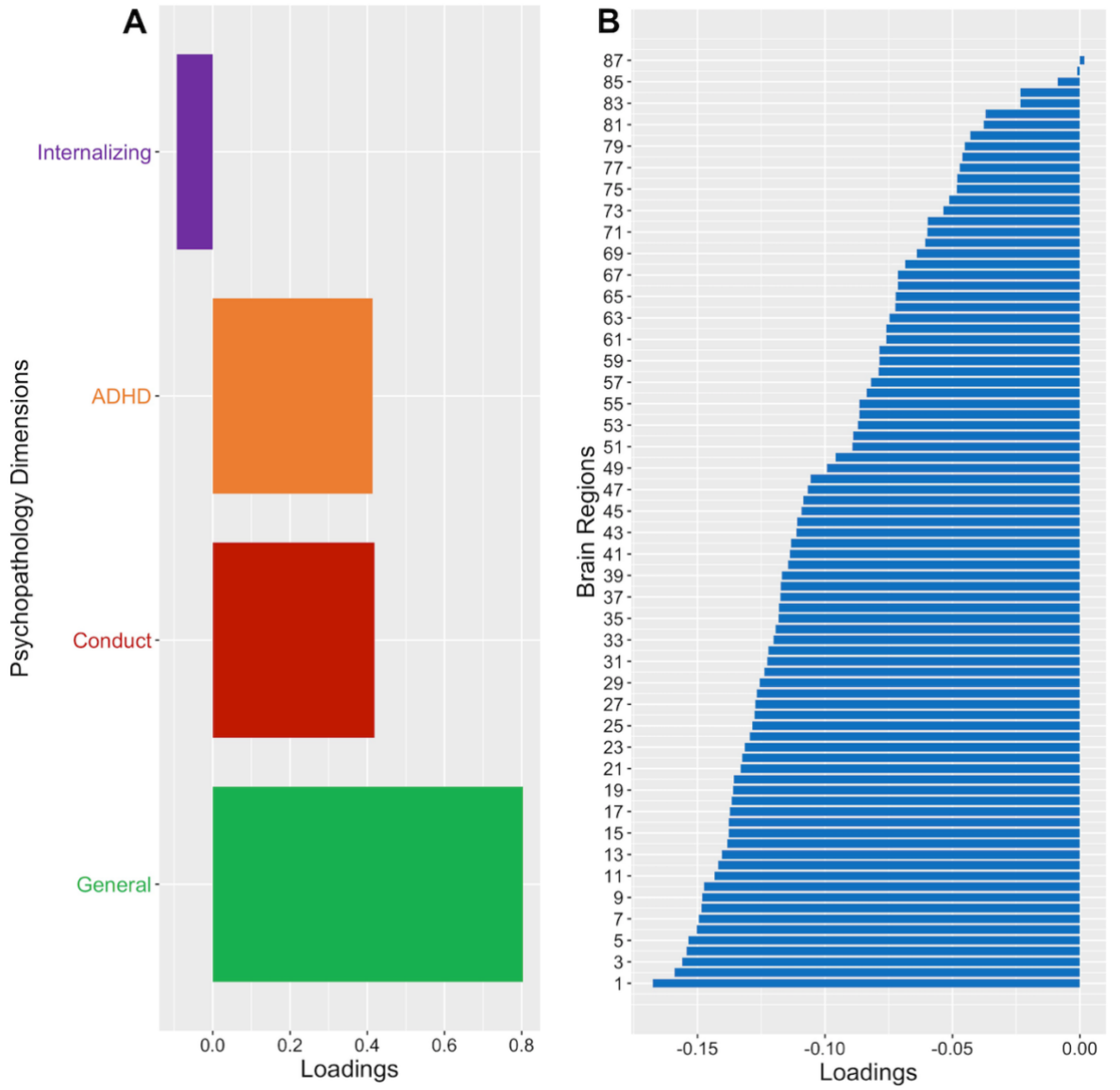
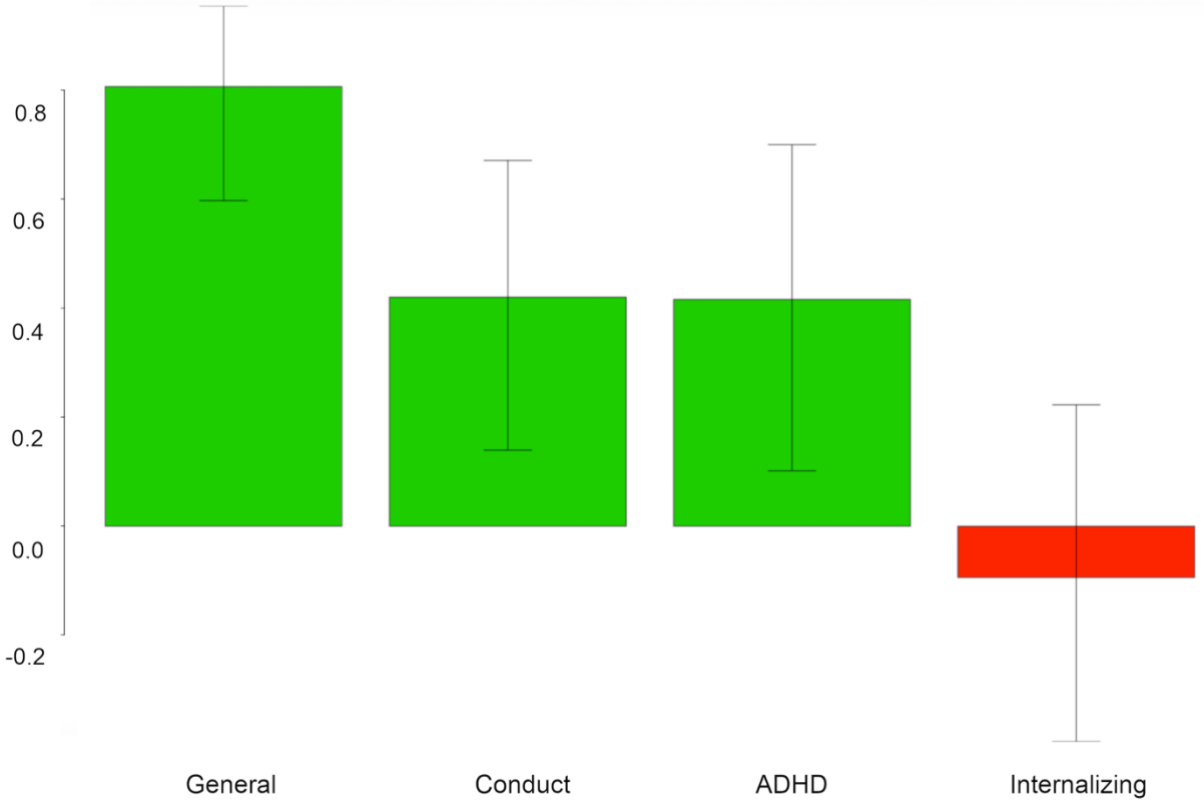
Appendix



Supplementary Figure 1. Flowchart indicating exclusions for missing data and quality control failure. Missing: There were 3 participants excluded for missing propensity weight data (PS weight), 6 for missing Child Behavior Checklist data (CBCL), 63 for missing a variable indicating the normality/abnormality of the structural MRI images ("mrif_score"), 223 for missing data on an initial quality assurance variable ("iqc_t1_ok_ser"), 51 for missing data on an additional quality assurance variable ("fsqc_qc"), 2 for missing sex data, 13 for missing race-ethnicity data. Exclusion: There were 151 participants excluded for abnormal structural images, as indicated by an "mrif_score" value of 0 ("Image artifacts prevent radiology read") or 4 ("Consider immediate clinical referral"). There were 44 excluded for failing to pass initial quality control (QC) measures, as indicated by an "iqc_t1_ok_ser" value of 0. There were 1,712 excluded for failing to pass quality assurance variables based on FreeSurfer quality control (FS QC) measures. Specifically, for QC score ("fsqc_qc"), responses of 0 ("reject") were excluded. The FS QC takes into account four different metrics: motion, pial overestimation, white matter underestimation, and inhomogeneity. For the motion score ("fsqc_qu_motion"), pial overestimation score ("fsqc_qu_pialover"), white matter underestimation score ("fsqc_qu_wmunder"), and inhomogeneity score ("fsqc_qu_homogeneity"), responses of >1 ("moderate" to "severe") were excluded and only responses of 0 ("absent") and 1 ("mild") were included.



Supplementary Figure 2. PLS analysis in the replication sample demonstrates that greater levels of general psychopathology, conduct problems, and ADHD symptoms are associated with smaller volumes across many brain regions. A) Positive loadings for general psychopathology, conduct problems, and ADHD symptoms. B) Negative loadings for vast majority of brain regions (see Supplementary Tables 11 and 12 for list of numerical loadings in descending order, based on absolute value, with the key for brain regions 1 (strongest loading) through 87 (weakest loading)).



Supplementary Figure 3. Bootstrapping analysis in the replication sample demonstrates reliable loadings for the general, conduct, and ADHD psychopathology dimensions. Reliable dimensions are shown in green and unreliable dimensions are shown in red. Results are based on bootstrapping analyses with 10,000 iterations.

Supplementary Table 1. *Results examining the relationship between cortical regional GMV and psychopathology dimensions*

Brain region	General		Specific Conduct		Specific Internalizing		Specific ADHD		
	β	p_{fdr}	β	p_{fdr}	β	p_{fdr}	β	p_{fdr}	R^2
Left banks of superior temporal sulcus	**-0.03**	**.027**	**-0.06**	**.005**	0.02	.293	-0.02	.319	.07
Left caudal anterior cingulate	**-0.04**	**.014**	-0.04	.082	0.03	.200	**-0.05**	**.044**	.04
Left caudal middle frontal	-0.02	.258	**-0.05**	**.005**	0.02	.396	-0.03	.145	.11
Left cuneus	-0.02	.296	**-0.06**	**.000**	0.03	.160	**-0.06**	**.011**	.16
Left entorhinal	**-0.04**	**.002**	**-0.05**	**.005**	0.00	.902	-0.01	.485	.18
Left fusiform	**-0.05**	**.000**	**-0.09**	**.000**	0.04	.147	-0.04	.055	.18
Left inferior parietal	**-0.07**	**.000**	**-0.06**	**.002**	0.02	.396	-0.03	.145	.14
Left inferior temporal	**-0.06**	**.000**	**-0.04**	**.040**	0.04	.147	-0.02	.457	.19
Left isthmus cingulate	**-0.05**	**.002**	**-0.05**	**.010**	0.03	.160	-0.02	.319	.15
Left lateral occipital	**-0.04**	**.005**	**-0.07**	**.000**	0.02	.354	**-0.06**	**.000**	.24
Left lateral orbitofrontal	**-0.04**	**.002**	**-0.07**	**.000**	0.02	.194	**-0.05**	**.015**	.20
Left lingual	-0.02	.164	**-0.06**	**.002**	0.03	.174	**-0.05**	**.025**	.15
Left medial orbitofrontal	**-0.04**	**.006**	-0.02	.213	0.00	.902	-0.02	.314	.23
Left middle temporal	**-0.05**	**.000**	**-0.07**	**.002**	0.03	.160	-0.01	.616	.19
Left parahippocampal	**-0.05**	**.000**	**-0.06**	**.002**	0.01	.448	**-0.05**	**.043**	.08
Left paracentral	**-0.03**	**.023**	**-0.06**	**.005**	0.01	.790	**-0.05**	**.046**	.08
Left pars opercularis	-0.03	.056	-0.02	.315	0.02	.413	0.00	.968	.08
Left pars orbitalis	**-0.04**	**.005**	-0.02	.418	0.02	.229	-0.02	.457	.13
Left pars triangularis	-0.03	.094	**-0.04**	**.040**	0.01	.482	**-0.05**	**.044**	.06
Left pericalcarine	-0.01	.363	**-0.06**	**.007**	0.03	.174	**-0.05**	**.043**	.09
Left postcentral	**-0.06**	**.000**	**-0.07**	**.000**	0.01	.749	**-0.04**	**.045**	.16
Left posterior cingulate	**-0.06**	**.000**	-0.04	.055	0.03	.200	-0.03	.259	.12
Left precentral	**-0.06**	**.000**	**-0.08**	**.000**	0.03	.160	**-0.06**	**.015**	.20
Left precuneus	**-0.04**	**.002**	**-0.08**	**.000**	0.02	.362	**-0.05**	**.043**	.20
Left rostral anterior cingulate	**-0.05**	**.000**	**-0.05**	**.010**	0.03	.160	**-0.05**	**.029**	.10
Left rostral middle frontal	**-0.07**	**.000**	**-0.08**	**.000**	0.04	.147	**-0.04**	**.043**	.20
Left superior frontal	**-0.06**	**.000**	**-0.07**	**.000**	0.03	.174	**-0.05**	**.032**	.20
Left superior parietal	-0.02	.242	**-0.07**	**.002**	0.02	.396	-0.03	.145	.18
Left superior temporal	**-0.07**	**.000**	**-0.08**	**.000**	0.03	.160	-0.02	.384	.16
Left supramarginal	**-0.06**	**.000**	**-0.08**	**.000**	0.02	.343	-0.02	.319	.19
Left frontal pole	0.01	.682	**-0.05**	**.018**	-0.02	.285	-0.03	.170	.11
Left temporal pole	**-0.04**	**.006**	**-0.05**	**.016**	0.02	.405	-0.01	.795	.07
Left transverse temporal	**-0.05**	**.002**	**-0.05**	**.009**	0.01	.589	-0.02	.457	.08
Left insula	**-0.07**	**.000**	**-0.07**	**.000**	0.03	.160	-0.03	.121	.21
Right banks of superior temporal sulcus	**-0.05**	**.000**	-0.02	.260	0.03	.168	-0.01	.783	.09
Right caudal anterior cingulate	**-0.03**	**.035**	**-0.04**	**.040**	0.01	.663	**-0.06**	**.028**	.04
Right caudal middle frontal	**-0.04**	**.005**	**-0.04**	**.027**	0.02	.230	-0.02	.457	.10
Right cuneus	**-0.03**	**.037**	-0.03	.160	0.02	.405	-0.03	.168	.14
Right entorhinal	**-0.05**	**.000**	0.00	.935	0.01	.706	0.02	.455	.11
Right fusiform	**-0.06**	**.000**	**-0.10**	**.000**	0.03	.174	**-0.04**	**.044**	.20
Right inferior parietal	**-0.08**	**.000**	**-0.07**	**.000**	0.04	.136	-0.01	.485	.19
Right inferior temporal	**-0.06**	**.000**	**-0.07**	**.000**	0.02	.293	-0.03	.128	.19
Right isthmus cingulate	-0.02	.164	-0.03	.106	0.03	.160	-0.01	.553	.11
Right lateral occipital	**-0.03**	**.045**	**-0.06**	**.000**	0.04	.147	**-0.06**	**.000**	.26
Right lateral orbitofrontal	**-0.05**	**.000**	**-0.05**	**.002**	0.03	.147	**-0.05**	**.029**	.23
Right lingual	-0.02	.132	**-0.06**	**.002**	0.03	.197	-0.04	.070	.14

Right medial orbitofrontal	**-0.03**	**.025**	**-0.05**	**.004**	0.02	.343	-0.03	.128	.14
Right middle temporal	**-0.07**	**.000**	**-0.07**	**.000**	0.02	.229	-0.03	.170	.22
Right parahippocampal	**-0.06**	**.000**	-0.02	.214	0.03	.174	-0.01	.553	.10
Right paracentral	-0.03	.075	**-0.06**	**.004**	-0.02	.405	**-0.08**	**.000**	.08
Right pars opercularis	**-0.04**	**.018**	-0.02	.304	0.03	.174	-0.02	.457	.08
Right pars orbitalis	**-0.05**	**.002**	-0.03	.089	0.02	.376	**-0.06**	**.011**	.12
Right pars triangularis	0.00	.934	**-0.05**	**.018**	0.00	.984	**-0.06**	**.015**	.07
Right pericalcarine	-0.01	.363	-0.04	.059	0.03	.174	-0.04	.073	.09
Right postcentral	**-0.07**	**.000**	**-0.07**	**.000**	0.02	.405	-0.02	.317	.13
Right posterior cingulate	**-0.04**	**.009**	**-0.06**	**.004**	-0.01	.754	-0.04	.070	.11
Right precentral	**-0.06**	**.000**	**-0.09**	**.000**	0.02	.321	**-0.06**	**.000**	.19
Right precuneus	**-0.06**	**.000**	**-0.05**	**.018**	0.03	.168	-0.02	.455	.21
Right rostral anterior cingulate	**-0.03**	**.023**	-0.03	.177	0.02	.285	**-0.06**	**.020**	.08
Right rostral middle frontal	**-0.05**	**.000**	**-0.07**	**.000**	0.03	.160	**-0.05**	**.044**	.18
Right superior frontal	**-0.07**	**.000**	**-0.06**	**.002**	0.03	.160	-0.04	.083	.19
Right superior parietal	**-0.04**	**.019**	**-0.04**	**.042**	0.01	.448	-0.03	.210	.19
Right superior temporal	**-0.07**	**.000**	**-0.08**	**.000**	0.03	.160	-0.02	.455	.13
Right supramarginal	**-0.07**	**.000**	**-0.07**	**.002**	0.03	.174	-0.02	.384	.14
Right frontal pole	**-0.03**	**.038**	**-0.04**	**.040**	0.00	.968	-0.03	.210	.13
Right temporal pole	-0.01	.649	-0.03	.130	0.02	.396	-0.01	.553	.04
Right transverse temporal	**-0.05**	**.000**	-0.02	.429	0.01	.490	0.00	.926	.10
Right insula	**-0.07**	**.000**	**-0.05**	**.004**	0.02	.247	-0.04	.073	.23

Note. N = 9,607. Coefficients in bold are significant after FDR correction (adopting a 5% false discovery rate) for 68 tests.

Supplementary Table 2. *Results examining the relationship between subcortical regional GMV and psychopathology dimensions*

Brain region	General		Specific Conduct		Specific Internalizing		Specific ADHD		
	β	p_{fdr}	β	p_{fdr}	β	p_{fdr}	β	p_{fdr}	R^2
Left cerebellum cortex	**-0.05**	**.000**	**-0.06**	**.003**	0.02	.199	**-0.05**	**.024**	.26
Left thalamus proper	**-0.06**	**.000**	**-0.08**	**.000**	0.03	.068	-0.04	.061	.24
Left caudate	**-0.06**	**.000**	**-0.07**	**.000**	0.03	.103	**-0.05**	**.048**	.09
Left putamen	**-0.05**	**.001**	-0.03	.066	0.03	.081	**-0.05**	**.032**	.17
Left pallidum	**-0.06**	**.000**	-0.02	.229	0.03	.103	-0.02	.418	.13
Left hippocampus	**-0.07**	**.000**	**-0.05**	**.013**	0.04	.068	-0.02	.457	.19
Left amygdala	**-0.06**	**.000**	**-0.04**	**.038**	0.02	.168	-0.01	.715	.28
Left accumbens area	**-0.06**	**.000**	**-0.05**	**.008**	0.02	.178	-0.03	.143	.25
Left ventral diencephalon	**-0.06**	**.000**	**-0.05**	**.005**	0.03	.115	**-0.05**	**.032**	.20
Right cerebellum cortex	**-0.05**	**.000**	**-0.05**	**.009**	0.03	.103	-0.04	.059	.27
Right thalamus proper	**-0.06**	**.000**	**-0.06**	**.003**	0.04	.068	-0.02	.418	.21
Right caudate	**-0.05**	**.000**	**-0.07**	**.000**	0.04	.068	**-0.05**	**.035**	.09
Right putamen	**-0.05**	**.001**	**-0.04**	**.026**	0.02	.168	**-0.06**	**.019**	.18
Right pallidum	**-0.05**	**.000**	-0.04	.051	0.03	.084	-0.03	.244	.19
Right hippocampus	**-0.07**	**.000**	**-0.06**	**.003**	0.04	.068	-0.01	.629	.20
Right amygdala	**-0.06**	**.000**	-0.03	.051	0.01	.321	0.00	.798	.26
Right accumbens area	**-0.06**	**.000**	**-0.04**	**.039**	0.02	.322	-0.02	.418	.17
Right ventral diencephalon	**-0.04**	**.001**	**-0.06**	**.003**	0.03	.081	**-0.06**	**.024**	.17
Brain stem	**-0.05**	**.000**	**-0.05**	**.006**	0.03	.081	**-0.05**	**.024**	.20

Note. N = 9,607. Coefficients in bold are significant after FDR correction (adopting a 5% false discovery rate) for 19 tests.

Supplementary Table 3. *Results examining the relationship between cortical regional GMV and psychopathology dimensions with income and parental education as additional covariates*

Brain region	General		Specific Conduct		Specific Internalizing		Specific ADHD		
	β	p_{fdr}	β	p_{fdr}	β	p_{fdr}	β	p_{fdr}	R^2
Left banks of superior temporal sulcus	-0.03	.068	-0.03	.122	0.02	.383	-0.02	.448	.07
Left caudal anterior cingulate	-0.03	.101	-0.03	.153	0.02	.473	-0.05	.063	.05
Left caudal middle frontal	0.00	.928	-0.04	.063	0.02	.362	-0.03	.309	.12
Left cuneus	-0.01	.702	**-0.04**	**.040**	0.03	.219	**-0.05**	**.039**	.16
Left entorhinal	**-0.04**	**.016**	-0.04	.051	-0.01	.755	-0.01	.699	.18
Left fusiform	**-0.04**	**.029**	**-0.06**	**.007**	0.03	.253	-0.03	.138	.19
Left inferior parietal	**-0.05**	**.000**	-0.04	.051	0.02	.422	-0.02	.366	.14
Left inferior temporal	**-0.05**	**.004**	-0.02	.312	0.03	.219	-0.01	.647	.19
Left isthmus cingulate	**-0.05**	**.004**	**-0.04**	**.049**	0.03	.219	-0.02	.457	.15
Left lateral occipital	-0.03	.094	**-0.05**	**.018**	0.02	.422	**-0.06**	**.017**	.25
Left lateral orbitofrontal	-0.03	.055	**-0.05**	**.011**	0.02	.290	**-0.05**	**.030**	.21
Left lingual	-0.01	.458	**-0.05**	**.040**	0.03	.253	-0.05	.068	.16
Left medial orbitofrontal	**-0.03**	**.028**	-0.02	.375	-0.01	.654	-0.03	.173	.22
Left middle temporal	**-0.04**	**.014**	-0.04	.055	0.03	.269	0.00	.906	.20
Left parahippocampal	**-0.04**	**.028**	-0.04	.056	0.01	.554	-0.04	.127	.09
Left paracentral	-0.02	.249	-0.04	.082	0.00	.991	-0.05	.083	.08
Left pars opercularis	-0.02	.377	0.00	.869	0.01	.519	0.00	.908	.08
Left pars orbitalis	**-0.04**	**.034**	0.01	.812	0.02	.290	0.00	.908	.13
Left pars triangularis	-0.02	.180	-0.03	.157	0.01	.519	-0.05	.081	.07
Left pericalcarine	0.00	.863	**-0.05**	**.049**	0.03	.290	-0.05	.081	.09
Left postcentral	**-0.04**	**.009**	-0.04	.053	0.00	.991	-0.04	.095	.17
Left posterior cingulate	**-0.04**	**.009**	-0.02	.267	0.02	.301	-0.02	.366	.13
Left precentral	**-0.05**	**.004**	**-0.06**	**.007**	0.04	.219	**-0.05**	**.030**	.21
Left precuneus	-0.03	.058	**-0.06**	**.007**	0.02	.441	-0.04	.081	.20
Left rostral anterior cingulate	**-0.04**	**.019**	-0.04	.100	0.03	.253	**-0.05**	**.037**	.11
Left rostral middle frontal	**-0.06**	**.000**	**-0.06**	**.000**	0.03	.219	-0.04	.081	.21
Left superior frontal	**-0.05**	**.000**	**-0.05**	**.023**	0.02	.413	**-0.05**	**.037**	.21
Left superior parietal	-0.01	.780	**-0.05**	**.020**	0.02	.422	-0.03	.204	.18
Left superior temporal	**-0.06**	**.000**	**-0.06**	**.000**	0.02	.290	-0.02	.372	.18
Left supramarginal	**-0.05**	**.000**	**-0.06**	**.007**	0.02	.441	-0.02	.548	.19
Left frontal pole	0.02	.282	-0.04	.056	-0.03	.290	-0.04	.103	.11
Left temporal pole	**-0.04**	**.039**	-0.04	.078	0.01	.775	0.01	.832	.08
Left transverse temporal	**-0.04**	**.028**	-0.04	.051	0.01	.597	-0.01	.832	.08
Left insula	**-0.06**	**.000**	**-0.06**	**.000**	0.02	.360	-0.03	.127	.21
Right banks of superior temporal sulcus	-0.03	.062	0.00	.983	0.03	.262	0.00	.896	.09
Right caudal anterior cingulate	-0.02	.226	-0.03	.137	0.01	.519	**-0.06**	**.037**	.05
Right caudal middle frontal	-0.03	.060	-0.03	.142	0.03	.253	-0.02	.366	.11
Right cuneus	-0.03	.133	-0.01	.555	0.01	.479	-0.02	.378	.15
Right entorhinal	**-0.04**	**.009**	0.00	.852	0.01	.611	0.02	.409	.11
Right fusiform	**-0.04**	**.022**	**-0.08**	**.000**	0.02	.383	-0.04	.103	.20
Right inferior parietal	**-0.06**	**.000**	**-0.05**	**.018**	0.04	.219	-0.01	.771	.20
Right inferior temporal	**-0.05**	**.000**	**-0.06**	**.007**	0.02	.410	-0.03	.200	.19
Right isthmus cingulate	-0.02	.304	-0.03	.214	0.04	.219	-0.01	.717	.11
Right lateral occipital	-0.02	.304	**-0.04**	**.043**	0.03	.219	**-0.06**	**.017**	.26
Right lateral orbitofrontal	**-0.04**	**.014**	**-0.04**	**.037**	0.03	.219	**-0.05**	**.037**	.23

Right lingual	-0.01	.666	-0.04	.051	0.03	.253	-0.04	.088	.15
Right medial orbitofrontal	-0.02	.183	**-0.04**	**.032**	0.00	.938	-0.03	.194	.14
Right middle temporal	**-0.05**	**.000**	**-0.05**	**.020**	0.02	.356	-0.02	.366	.23
Right parahippocampal	**-0.04**	**.007**	0.01	.582	0.03	.253	0.00	.896	.11
Right paracentral	-0.02	.320	**-0.05**	**.034**	-0.02	.413	**-0.07**	**.000**	.08
Right pars opercularis	-0.03	.101	-0.01	.645	0.03	.253	-0.01	.640	.08
Right pars orbitalis	**-0.04**	**.018**	-0.01	.553	0.02	.413	**-0.06**	**.030**	.13
Right pars triangularis	0.01	.716	-0.04	.051	0.00	.837	**-0.06**	**.027**	.07
Right pericalcarine	0.00	.838	-0.03	.200	0.03	.262	-0.04	.127	.09
Right postcentral	**-0.06**	**.000**	**-0.05**	**.043**	0.02	.413	-0.02	.448	.13
Right posterior cingulate	-0.02	.146	-0.04	.050	0.00	.837	-0.03	.204	.11
Right precentral	**-0.06**	**.000**	**-0.07**	**.000**	0.02	.363	**-0.06**	**.017**	.19
Right precuneus	**-0.05**	**.000**	-0.03	.214	0.03	.253	-0.01	.662	.21
Right rostral anterior cingulate	-0.03	.068	-0.02	.375	0.02	.441	**-0.06**	**.030**	.08
Right rostral middle frontal	**-0.04**	**.019**	**-0.06**	**.011**	0.03	.253	-0.05	.068	.19
Right superior frontal	**-0.06**	**.000**	-0.04	.056	0.02	.375	-0.04	.119	.20
Right superior parietal	-0.02	.249	-0.03	.200	0.01	.734	-0.03	.194	.19
Right superior temporal	**-0.05**	**.000**	**-0.06**	**.018**	0.02	.290	-0.02	.517	.14
Right supramarginal	**-0.05**	**.000**	**-0.05**	**.043**	0.02	.413	-0.01	.630	.14
Right frontal pole	-0.03	.062	-0.02	.249	0.00	.876	-0.02	.366	.13
Right temporal pole	0.00	.928	-0.02	.492	0.01	.639	-0.01	.662	.04
Right transverse temporal	**-0.04**	**.020**	0.00	.964	0.00	.837	0.01	.832	.10
Right insula	**-0.06**	**.000**	**-0.04**	**.036**	0.01	.611	-0.04	.086	.24

Note. N = 8,801. Coefficients in bold are significant after FDR correction (adopting a 5% false discovery rate) for 68 tests.

Supplementary Table 4. *Results examining the relationship between subcortical regional GMV and psychopathology dimensions with income and parental education as additional covariates*

Brain region	General		Specific Conduct		Specific Internalizing		Specific ADHD		
	β	p_{fdr}	β	p_{fdr}	β	p_{fdr}	β	p_{fdr}	R^2
Left cerebellum cortex	**-0.03**	**.018**	-0.04	.117	0.02	.384	-0.03	.217	.27
Left thalamus proper	**-0.04**	**.004**	**-0.06**	**.019**	0.03	.133	-0.03	.217	.25
Left caudate	**-0.04**	**.014**	**-0.05**	**.038**	0.03	.159	-0.04	.187	.10
Left putamen	**-0.03**	**.030**	-0.02	.281	0.02	.231	-0.05	.070	.18
Left pallidum	**-0.05**	**.004**	0.00	.815	0.03	.159	-0.02	.516	.13
Left hippocampus	**-0.03**	**.023**	-0.03	.147	0.03	.159	-0.05	.076	.21
Left amygdala	**-0.05**	**.000**	-0.02	.281	0.03	.159	-0.02	.516	.20
Left accumbens area	**-0.04**	**.003**	-0.02	.404	0.01	.437	-0.01	.656	.29
Left ventral diencephalon	**-0.05**	**.000**	-0.04	.117	0.01	.437	-0.03	.234	.24
Right cerebellum cortex	**-0.04**	**.004**	-0.03	.158	0.03	.159	-0.04	.080	.21
Right thalamus proper	**-0.03**	**.027**	-0.03	.176	0.02	.218	-0.02	.447	.28
Right caudate	**-0.05**	**.003**	-0.04	.117	0.04	.133	-0.01	.656	.22
Right putamen	**-0.04**	**.014**	**-0.05**	**.038**	0.03	.159	-0.04	.101	.10
Right pallidum	**-0.03**	**.034**	-0.03	.187	0.01	.437	-0.06	.057	.19
Right hippocampus	**-0.04**	**.022**	-0.02	.281	0.03	.159	-0.02	.447	.19
Right amygdala	**-0.05**	**.000**	-0.03	.158	0.03	.159	-0.01	.656	.21
Right accumbens area	**-0.04**	**.010**	-0.02	.281	0.00	.902	-0.01	.656	.26
Right ventral diencephalon	**-0.06**	**.000**	-0.03	.187	0.00	.945	-0.02	.447	.18
Brain stem	-0.03	.051	-0.04	.117	0.03	.159	-0.05	.066	.18

Note. N = 8,801. Coefficients in bold are significant after FDR correction (adopting a 5% false discovery rate) for 19 tests.

Supplementary Table 5. *Results examining the relationship between cortical regional GMV and psychopathology dimensions with medication added as an additional covariate*

Brain region	General		Specific Conduct		Specific Internalizing		Specific ADHD		
	β	p_{fdr}	β	p_{fdr}	β	p_{fdr}	β	p_{fdr}	R^2
Left banks of superior temporal sulcus	**-0.03**	**.025**	**-0.06**	**.007**	0.02	.310	-0.02	.305	.07
Left caudal anterior cingulate	**-0.04**	**.016**	-0.03	.104	0.03	.182	**-0.05**	**.047**	.04
Left caudal middle frontal	-0.02	.299	**-0.05**	**.009**	0.02	.362	-0.03	.167	.11
Left cuneus	-0.02	.303	**-0.06**	**.003**	0.03	.144	**-0.06**	**.011**	.16
Left entorhinal	**-0.04**	**.003**	**-0.05**	**.006**	0.00	.887	-0.01	.499	.18
Left fusiform	**-0.06**	**.000**	**-0.08**	**.000**	0.04	.136	-0.04	.055	.18
Left inferior parietal	**-0.07**	**.000**	**-0.06**	**.005**	0.02	.323	-0.03	.179	.14
Left inferior temporal	**-0.06**	**.000**	**-0.04**	**.043**	0.04	.102	-0.01	.499	.19
Left isthmus cingulate	**-0.04**	**.002**	**-0.05**	**.013**	0.03	.146	-0.02	.391	.15
Left lateral occipital	**-0.04**	**.003**	**-0.07**	**.000**	0.02	.317	**-0.06**	**.000**	.24
Left lateral orbitofrontal	**-0.05**	**.002**	**-0.06**	**.000**	0.02	.178	**-0.05**	**.015**	.20
Left lingual	-0.02	.137	**-0.06**	**.005**	0.03	.155	**-0.05**	**.025**	.15
Left medial orbitofrontal	**-0.04**	**.005**	-0.02	.222	0.00	.887	-0.02	.331	.23
Left middle temporal	**-0.05**	**.000**	**-0.06**	**.000**	0.03	.146	-0.01	.664	.19
Left parahippocampal	**-0.06**	**.000**	**-0.06**	**.005**	0.01	.442	**-0.05**	**.047**	.08
Left paracentral	**-0.03**	**.033**	**-0.05**	**.007**	0.01	.754	-0.05	.055	.08
Left pars opercularis	-0.03	.075	-0.02	.336	0.02	.362	0.00	.918	.08
Left pars orbitalis	**-0.04**	**.003**	-0.01	.471	0.02	.212	-0.02	.471	.13
Left pars triangularis	-0.02	.130	**-0.04**	**.049**	0.01	.424	**-0.05**	**.047**	.06
Left pericalcarine	-0.01	.378	**-0.05**	**.010**	0.03	.150	**-0.05**	**.047**	.09
Left postcentral	**-0.06**	**.000**	**-0.06**	**.003**	0.01	.741	-0.04	.055	.16
Left posterior cingulate	**-0.06**	**.000**	-0.03	.089	0.03	.179	-0.02	.314	.12
Left precentral	**-0.06**	**.000**	**-0.07**	**.000**	0.03	.146	**-0.05**	**.015**	.20
Left precuneus	**-0.04**	**.003**	**-0.07**	**.000**	0.02	.310	**-0.04**	**.047**	.20
Left rostral anterior cingulate	**-0.05**	**.000**	**-0.05**	**.017**	0.03	.146	**-0.05**	**.034**	.10
Left rostral middle frontal	**-0.07**	**.000**	**-0.07**	**.000**	0.04	.102	**-0.04**	**.047**	.20
Left superior frontal	**-0.06**	**.000**	**-0.07**	**.000**	0.03	.150	**-0.05**	**.047**	.20
Left superior parietal	-0.01	.350	**-0.06**	**.003**	0.02	.317	-0.03	.204	.18
Left superior temporal	**-0.07**	**.000**	**-0.08**	**.000**	0.03	.146	-0.02	.371	.16
Left supramarginal	**-0.06**	**.000**	**-0.08**	**.000**	0.02	.310	-0.02	.328	.19
Left frontal pole	0.01	.531	**-0.05**	**.017**	-0.02	.317	-0.03	.211	.11
Left temporal pole	**-0.04**	**.005**	**-0.05**	**.016**	0.01	.424	-0.01	.750	.07
Left transverse temporal	**-0.05**	**.002**	**-0.05**	**.009**	0.01	.615	-0.02	.470	.08
Left insula	**-0.07**	**.000**	**-0.07**	**.000**	0.03	.136	-0.03	.150	.21
Right banks of superior temporal sulcus	**-0.05**	**.000**	-0.02	.271	0.03	.150	-0.01	.730	.09
Right caudal anterior cingulate	-0.03	.050	**-0.04**	**.041**	0.01	.600	**-0.06**	**.028**	.04
Right caudal middle frontal	**-0.04**	**.011**	**-0.04**	**.047**	0.03	.174	-0.01	.528	.10
Right cuneus	-0.03	.053	-0.03	.206	0.02	.354	-0.03	.204	.14
Right entorhinal	**-0.05**	**.000**	0.00	.966	0.01	.727	0.02	.443	.11
Right fusiform	**-0.06**	**.000**	**-0.10**	**.000**	0.03	.170	**-0.04**	**.047**	.20
Right inferior parietal	**-0.07**	**.000**	**-0.07**	**.000**	0.04	.102	-0.01	.513	.19
Right inferior temporal	**-0.06**	**.000**	**-0.07**	**.000**	0.02	.292	-0.03	.132	.19
Right isthmus cingulate	-0.02	.155	-0.03	.159	0.03	.146	-0.01	.629	.11
Right lateral occipital	-0.03	.051	**-0.06**	**.003**	0.04	.102	**-0.06**	**.000**	.26
Right lateral orbitofrontal	**-0.05**	**.000**	**-0.05**	**.005**	0.04	.136	**-0.05**	**.031**	.23
Right lingual	-0.02	.099	**-0.06**	**.006**	0.03	.178	-0.04	.073	.14

Right medial orbitofrontal	**-0.04**	**.016**	**-0.05**	**.006**	0.02	.317	-0.03	.132	.14
Right middle temporal	**-0.07**	**.000**	**-0.07**	**.000**	0.02	.204	-0.03	.187	.22
Right parahippocampal	**-0.06**	**.000**	-0.02	.206	0.03	.196	-0.01	.499	.10
Right paracentral	-0.03	.079	**-0.06**	**.006**	-0.01	.424	**-0.07**	**.000**	.07
Right pars opercularis	**-0.04**	**.016**	-0.02	.334	0.03	.146	-0.02	.499	.08
Right pars orbitalis	**-0.05**	**.002**	-0.03	.087	0.02	.323	**-0.06**	**.011**	.12
Right pars triangularis	0.00	.936	**-0.05**	**.024**	0.00	.963	**-0.06**	**.015**	.07
Right pericalcarine	-0.01	.404	-0.04	.085	0.03	.150	-0.04	.083	.09
Right postcentral	**-0.07**	**.000**	**-0.07**	**.000**	0.01	.424	-0.02	.328	.13
Right posterior cingulate	**-0.04**	**.014**	**-0.05**	**.007**	0.00	.852	-0.04	.100	.11
Right precentral	**-0.06**	**.000**	**-0.09**	**.000**	0.02	.302	**-0.06**	**.000**	.19
Right precuneus	**-0.06**	**.000**	**-0.05**	**.020**	0.03	.146	-0.02	.471	.21
Right rostral anterior cingulate	**-0.03**	**.034**	-0.03	.160	0.02	.247	**-0.06**	**.025**	.08
Right rostral middle frontal	**-0.05**	**.000**	**-0.07**	**.000**	0.04	.136	**-0.04**	**.047**	.18
Right superior frontal	**-0.07**	**.000**	**-0.05**	**.006**	0.03	.146	-0.04	.107	.19
Right superior parietal	**-0.03**	**.020**	-0.04	.078	0.01	.424	-0.03	.243	.19
Right superior temporal	**-0.07**	**.000**	**-0.08**	**.000**	0.03	.146	-0.02	.470	.13
Right supramarginal	**-0.07**	**.000**	**-0.06**	**.003**	0.03	.146	-0.02	.439	.14
Right frontal pole	**-0.03**	**.037**	-0.04	.056	0.00	.963	-0.03	.232	.13
Right temporal pole	-0.01	.545	-0.03	.160	0.02	.372	-0.01	.588	.04
Right transverse temporal	**-0.05**	**.002**	-0.01	.471	0.01	.428	0.00	.894	.10
Right insula	**-0.07**	**.000**	**-0.05**	**.007**	0.02	.212	-0.04	.094	.23

Note. N = 9,597. Coefficients in bold are significant after FDR correction (adopting a 5% false discovery rate) for 68 tests.

Supplementary Table 6. *Results examining the relationship between subcortical regional GMV and psychopathology dimensions with medication added as an additional covariate*

Brain region	General		Specific Conduct		Specific Internalizing		Specific ADHD		
	β	p_{fdr}	β	p_{fdr}	β	p_{fdr}	β	p_{fdr}	R^2
Left cerebellum cortex	**-0.05**	**.000**	**-0.06**	**.003**	0.02	.210	**-0.05**	**.024**	.26
Left thalamus proper	**-0.06**	**.000**	**-0.08**	**.000**	0.03	.068	-0.04	.057	.24
Left caudate	**-0.05**	**.000**	**-0.07**	**.000**	0.03	.103	**-0.05**	**.048**	.09
Left putamen	**-0.05**	**.001**	-0.03	.076	0.03	.093	**-0.05**	**.030**	.17
Left pallidum	**-0.06**	**.000**	-0.02	.235	0.03	.124	-0.02	.404	.13
Left hippocampus	**-0.05**	**.000**	**-0.05**	**.006**	0.03	.079	**-0.05**	**.024**	.20
Left amygdala	**-0.07**	**.000**	**-0.05**	**.013**	0.04	.068	-0.02	.404	.19
Left accumbens area	**-0.06**	**.000**	**-0.04**	**.030**	0.02	.165	-0.01	.728	.28
Left ventral diencephalon	**-0.06**	**.000**	**-0.05**	**.007**	0.02	.165	-0.03	.159	.25
Right cerebellum cortex	**-0.06**	**.000**	**-0.06**	**.005**	0.02	.129	**-0.05**	**.032**	.20
Right thalamus proper	**-0.05**	**.000**	**-0.05**	**.007**	0.03	.107	-0.04	.057	.27
Right caudate	**-0.06**	**.000**	**-0.06**	**.003**	0.04	.068	-0.02	.404	.21
Right putamen	**-0.05**	**.000**	**-0.07**	**.000**	0.04	.068	**-0.05**	**.035**	.09
Right pallidum	**-0.05**	**.001**	**-0.04**	**.030**	0.02	.165	**-0.06**	**.019**	.18
Right hippocampus	**-0.05**	**.001**	-0.03	.057	0.03	.093	-0.03	.239	.19
Right amygdala	**-0.07**	**.000**	**-0.06**	**.003**	0.04	.068	-0.01	.645	.20
Right accumbens area	**-0.05**	**.000**	**-0.04**	**.038**	0.02	.282	0.00	.815	.26
Right ventral diencephalon	**-0.06**	**.000**	**-0.04**	**.030**	0.02	.282	-0.02	.395	.17
Brain stem	**-0.05**	**.001**	**-0.06**	**.003**	0.03	.093	**-0.06**	**.019**	.17

Note. N = 9,597. Coefficients in bold are significant after FDR correction (adopting a 5% false discovery rate) for 19 tests.

Supplementary Table 7. *Results examining the relationship between subcortical regional GMV and psychopathology dimensions with ICV added as an additional covariate*

Brain region	General		Specific Conduct		Specific Internalizing		Specific ADHD		
	β	p_{fdr}	β	p_{fdr}	β	p_{fdr}	β	p_{fdr}	R^2
Left cerebellum cortex	-0.01	.393	-0.02	.694	0.00	.882	-0.02	.494	.48
Left thalamus proper	-0.01	.393	-0.03	.285	0.01	.551	0.00	.946	.63
Left caudate	-0.01	.393	-0.03	.583	0.01	.582	-0.02	.532	.34
Left putamen	-0.02	.393	0.00	.994	0.02	.551	-0.03	.494	.34
Left pallidum	-0.03	.133	0.01	.866	0.02	.553	0.00	.946	.26
Left hippocampus	**-0.04**	**.019**	-0.01	.840	0.02	.551	0.01	.653	.40
Left amygdala	-0.03	.120	-0.01	.840	0.01	.704	0.02	.532	.43
Left accumbens area	-0.02	.133	-0.02	.694	0.01	.749	-0.01	.764	.40
Left ventral diencephalon	-0.01	.393	-0.01	.840	0.01	.749	-0.01	.532	.57
Right cerebellum cortex	-0.01	.393	-0.01	.762	0.01	.592	-0.01	.617	.47
Right thalamus proper	-0.01	.393	-0.01	.840	0.02	.551	0.02	.494	.56
Right caudate	-0.01	.393	-0.03	.583	0.02	.551	-0.02	.515	.35
Right putamen	-0.01	.473	-0.01	.882	0.01	.704	-0.03	.494	.38
Right pallidum	-0.01	.393	0.00	.983	0.02	.553	0.00	.959	.38
Right hippocampus	**-0.03**	**.019**	-0.02	.694	0.02	.551	0.02	.494	.44
Right amygdala	-0.02	.176	0.00	.929	0.00	.987	0.02	.494	.43
Right accumbens area	-0.03	.128	-0.01	.840	0.00	.987	0.00	.946	.34
Right ventral diencephalon	0.01	.609	-0.01	.738	0.01	.582	-0.02	.494	.53
Brain stem	-0.01	.544	-0.01	.840	0.01	.553	-0.02	.494	.52

Note. N = 9,607. Coefficients in bold are significant after FDR correction (adopting a 5% false discovery rate) for 19 tests.

Supplementary Table 8. *Results examining the relationship between subcortical regional GMV and psychopathology dimensions with total subcortical GMV added as an additional covariate*

Brain region	General		Specific Conduct		Specific Internalizing		Specific ADHD		
	β	p_{fdr}	β	p_{fdr}	β	p_{fdr}	β	p_{fdr}	R^2
Left cerebellum cortex	0.01	.057	0.00	.851	-0.01	.361	0.00	.969	.90
Left thalamus proper	-0.02	.165	-0.03	.399	0.01	.676	0.00	.969	.57
Left caudate	-0.02	.231	-0.03	.418	0.01	.676	-0.01	.662	.33
Left putamen	-0.02	.261	0.00	.953	0.02	.676	-0.02	.573	.35
Left pallidum	-0.03	.057	0.01	.883	0.01	.676	0.01	.969	.26
Left hippocampus	**-0.04**	**.010**	-0.01	.851	0.02	.676	0.01	.696	.39
Left amygdala	**-0.03**	**.038**	-0.01	.851	0.01	.748	0.01	.635	.41
Left accumbens area	**-0.03**	**.041**	-0.02	.627	0.01	.775	-0.01	.761	.36
Left ventral diencephalon	-0.02	.215	-0.01	.851	0.00	.918	-0.01	.662	.57
Right cerebellum cortex	**0.01**	**.038**	0.01	.418	-0.01	.676	0.01	.573	.90
Right thalamus proper	-0.02	.188	-0.01	.851	0.01	.676	0.02	.573	.54
Right caudate	-0.02	.231	-0.03	.418	0.02	.676	-0.02	.635	.32
Right putamen	-0.01	.374	-0.01	.898	0.01	.775	-0.03	.573	.39
Right pallidum	-0.01	.367	0.00	.953	0.01	.676	0.00	.969	.40
Right hippocampus	**-0.04**	**.010**	-0.02	.627	0.02	.676	0.02	.573	.42
Right amygdala	-0.03	.054	-0.01	.883	0.00	.993	0.02	.635	.39
Right accumbens area	**-0.03**	**.038**	-0.01	.851	0.00	.993	0.00	.969	.31
Right ventral diencephalon	0.00	.967	-0.01	.738	0.01	.676	-0.02	.573	.52
Brain stem	0.00	.967	0.00	.953	0.01	.738	-0.01	.635	.68

Note. N = 9,607. Coefficients in bold are significant after FDR correction (adopting a 5% false discovery rate) for 19 tests.

Supplementary Table 9. *Psychopathology loadings yielded from PLS analysis in the training sample examining the relationship between regional GMV and psychopathology dimensions*

Psychopathology Dimension	Loading
General Psychopathology	0.801
Conduct Problems	0.416
ADHD Symptoms	0.413
Internalizing Symptoms	-0.122

Note. N = 4,138. Loadings are listed in descending order of absolute value.

Supplementary Table 10. *Brain volume loadings yielded from PLS analysis in the training sample examining the relationship between regional GMV and psychopathology dimensions*

Brain Region Number	Brain Region Name	Loading
1	Left superior frontal	-0.165
2	Left rostral middle frontal	-0.161
3	Right inferior parietal	-0.150
4	Right fusiform	-0.150
5	Right inferior temporal	-0.145
6	Right superior frontal	-0.144
7	Left fusiform	-0.142
8	Right superior temporal	-0.142
9	Left insula	-0.142
10	Right precentral	-0.141
11	Right middle temporal	-0.140
12	Brain stem	-0.138
13	Left superior temporal	-0.137
14	Left postcentral	-0.137
15	Left precentral	-0.135
16	Right rostral middle frontal	-0.134
17	Left precuneus	-0.133
18	Left supramarginal	-0.132
19	Right hippocampus	-0.131
20	Left inferior parietal	-0.130
21	Left hippocampus	-0.127
22	Right lateral orbitofrontal	-0.126
23	Left ventral diencephalon	-0.125
24	Left rostral anterior cingulate	-0.124
25	Right precuneus	-0.122
26	Right insula	-0.122
27	Right posterior cingulate	-0.122
28	Left thalamus proper	-0.120
29	Right ventral diencephalon	-0.119
30	Left cerebellum cortex	-0.119
31	Left parahippocampal	-0.116
32	Left inferior temporal	-0.115
33	Right amygdala	-0.115
34	Left posterior cingulate	-0.114
35	Left banks of superior temporal sulcus	-0.111
36	Right supramarginal	-0.111
37	Right caudal anterior cingulate	-0.110
38	Right postcentral	-0.106

39	Left lateral orbitofrontal	-0.106
40	Left middle temporal	-0.106
41	Left lateral occipital	-0.103
42	Left caudate	-0.103
43	Right parahippocampal	-0.103
44	Left pars triangularis	-0.102
45	Right lateral occipital	-0.102
46	Left lingual	-0.101
47	Left paracentral	-0.099
48	Left amygdala	-0.099
49	Right thalamus proper	-0.099
50	Right frontal pole	-0.098
51	Left isthmus cingulate	-0.097
52	Right rostral anterior cingulate	-0.097
53	Right cerebellum cortex	-0.095
54	Left caudal anterior cingulate	-0.094
55	Right superior parietal	-0.094
56	Left accumbens area	-0.092
57	Right putamen	-0.092
58	Left entorhinal	-0.091
59	Right lingual	-0.090
60	Right caudate	-0.089
61	Right paracentral	-0.088
62	Left transverse temporal	-0.088
63	Left pericalcarine	-0.087
64	Left cuneus	-0.087
65	Right cuneus	-0.086
66	Left temporal pole	-0.086
67	Right pars trangularis	-0.086
68	Right transverse temporal	-0.085
69	Right accumbens area	-0.084
70	Right pars orbitalis	-0.083
71	Right medial orbitofrontal	-0.077
72	Left putamen	-0.074
73	Right isthmus cingulate	-0.074
74	Left pallidum	-0.071
75	Left superior parietal	-0.071
76	Left pars orbitalis	-0.070
77	Left caudal middle frontal	-0.068
78	Right pallidum	-0.062
79	Right banks of superior temporal sulcus	-0.059
80	Left pars opercularis	-0.057

81	Right pericalcarine	-0.057
82	Right pars opercularis	-0.055
83	Left frontal pole	-0.054
84	Right temporal pole	-0.047
85	Right entorhinal	-0.046
86	Left medial orbitofrontal	-0.045
87	Right caudal middle frontal	-0.017

Note. N = 4,138. Loadings are listed in descending order of absolute value and labeled as 1 through 87, accordingly.

Supplementary Table 11. *Psychopathology loadings yielded from PLS analysis in the replication sample examining the relationship between regional GMV and psychopathology dimensions*

Psychopathology Dimension	Loading
General Psychopathology	0.803
Conduct Problems	0.418
ADHD Symptoms	0.414
Internalizing Symptoms	-0.094

Note. N = 4,080. Loadings are listed in descending order of absolute value.

Supplementary Table 12. *Brain volume loadings yielded from PLS analysis in the replication sample examining the relationship between regional GMV and psychopathology dimensions*

Brain Region Number	Brain Region Name	Loading
1	Left thalamus proper	-0.167
2	Left insula	-0.159
3	Left precentral	-0.156
4	Left rostral middle frontal	-0.154
5	Right insula	-0.154
6	Right precentral	-0.150
7	Right caudate	-0.149
8	Right pars orbitalis	-0.148
9	Right lateral orbitofrontal	-0.148
10	Left postcentral	-0.147
11	Left inferior parietal	-0.143
12	Right accumbens area	-0.142
13	Right inferior temporal	-0.140
14	Left hippocampus	-0.138
15	Right cerebellum cortex	-0.138
16	Left accumbens area	-0.138
17	Left caudate	-0.137
18	Left rostral anterior cingulate	-0.137
19	Right paracentral	-0.136
20	Left cerebellum cortex	-0.136
21	Left ventral diencephalon	-0.133
22	Right postcentral	-0.132
23	Right supramarginal	-0.131
24	Right middle temporal	-0.129
25	Left middle temporal	-0.128
26	Left superior frontal	-0.128
27	Right lateral occipital	-0.127
28	Right rostral middle frontal	-0.127
29	Brain stem	-0.126
30	Left precuneus	-0.124
31	Left lateral occipital	-0.123
32	Right putamen	-0.122
33	Right fusiform	-0.120
34	Left putamen	-0.119
35	Right hippocampus	-0.118
36	Left inferior temporal	-0.118
37	Right caudal anterior cingulate	-0.117

38	Right thalamus proper	-0.117
39	Right superior frontal	-0.117
40	Right inferior parietal	-0.114
41	Right pallidum	-0.114
42	Left fusiform	-0.113
43	Right parahippocampal	-0.111
44	Left lateral orbitofrontal	-0.111
45	Right caudal middle frontal	-0.109
46	Left superior temporal	-0.108
47	Right superior temporal	-0.107
48	Right ventral diencephalon	-0.106
49	Right amygdala	-0.099
50	Left pars triangularis	-0.096
51	Right rostral anterior cingulate	-0.089
52	Left caudal anterior cingulate	-0.089
53	Left paracentral	-0.087
54	Left amygdala	-0.087
55	Left pallidum	-0.087
56	Left posterior cingulate	-0.084
57	Left parahippocampal	-0.082
58	Right superior parietal	-0.079
59	Right posterior cingulate	-0.079
60	Left entorhinal	-0.079
61	Right entorhinal	-0.076
62	Left supramarginal	-0.076
63	Left isthmus cingulate	-0.075
64	Right medial orbitofrontal	-0.072
65	Right precuneus	-0.072
66	Left banks of superior temporal sulcus	-0.071
67	Left caudal middle frontal	-0.071
68	Left superior parietal	-0.069
69	Right banks of superior temporal sulcus	-0.064
70	Right pars opercularis	-0.061
71	Right pericalcarine	-0.060
72	Left cuneus	-0.060
73	Left temporal pole	-0.054
74	Left lingual	-0.051
75	Left pericalcarine	-0.048
76	Right temporal pole	-0.048
77	Left media lorbitofrontal	-0.047
78	Left transverse temporal	-0.046
79	Left pars orbitalis	-0.045

80	Right cuneus	-0.043
81	Right lingual	-0.038
82	Right pars triangularis	-0.037
83	Left pars opercularis	-0.023
84	Right isthmus cingulate	-0.023
85	Left frontal pole	-0.009
86	Right transverse temporal	-0.001
87	Right frontal pole	0.002

Note. N = 4,080. Loadings are listed in descending order of absolute value and labeled as 1 through 87, accordingly.