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Distinct patterns of reduced prefrontal and limbic grey matter volume in childhood general and internalizing psychopathology

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Abstract

Reduced grey matter volume (GMV) is widely implicated in psychopathology, but studies have found mostly overlapping areas of GMV reduction across disorders rather than unique neural signatures, potentially due to pervasive comorbidity. GMV reductions may be associated with broader psychopathology dimensions rather than specific disorders. We used an empirically supported bifactor model consisting of common psychopathology and internalizing- and externalizing-specific factors to evaluate whether latent psychopathology dimensions yield a clearer, more parsimonious pattern of GMV reduction in prefrontal and limbic/paralimbic areas implicated in individual disorders. A community sample of children (n=254, ages 6–10) was used to to evaluate whether GMV reductions could constitute early neural risk factors. The common psychopathology factor was associated with reduced GMV in prefrontal areas (dorsal, orbitofrontal, ventrolateral). The internalizing-specific factor was related to reduced GMV in limbic/paralimbic areas (hippocampus, amygdala, insula). No significant associations were found between GMV and the externalizing-specific factor after accounting for common psychopathology.

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Author Contributions

HRS conducted the primary analyses and drafted the manuscript. BLH conceived of the paper, drafted the manuscript, and assisted with analyses. CS, KH, and EPD designed the original study, collected the data (including participants' mental health reports and MRI collection and analysis), assisted with analyses, and provided editorial feedback on the paper.

Keywords

p factor; internalizing; externalizing; middle childhood; grey matter volume

One of the most compelling, ubiquitous ideas in modern psychiatry is that particular brain areas affect risk to and expression of psychopathology. This predominant hypothesis has dominated the field for decades, and hundreds of studies have used brain imaging methods, including measurement of grey matter volume (GMV), to search for unique biomarkers that singularly characterize specific psychiatric disorders (e.g., First et al., 2012; Insel et al., 2010). At the same time, however, research in child and adult psychopathology has overwhelmingly demonstrated that comorbidity of psychiatric disorders, based on modern DSM nosologies, is a rampant fact (e.g., Kessler et al., 2012).

To understand underlying neural influences linked to psychopathology, scores of studies have adopted an approach to examine grey matter volume (GMV) in psychiatric disorders using case control designs that compare putatively discrete pure diagnostic groups to healthy controls. The core problem with this approach is the overlapping comorbidity of these psychopathologies and the ensuing possibility that the hypothesis of unique biomarkers and specific neural signatures associated with a singular psychiatric diagnosis may not be accurate (e.g., Kapur, Phillips, & Insel, 2012). Given this abundant comorbidity, the typical research strategy of using pure diagnostic groups compared to normal controls will likely yield an inaccurate and inconsistent corpus of research. Indeed, most previous research has not demonstrated a clear, one-to-one specificity between GMV in particular brain regions and specific psychiatric diagnoses (Goodkind et al., 2015). An alternative approach that emphasizes latent dimensional psychopathology classification may yield a clearer and more parsimonious pattern. This paper examines whether GMV in key neural substrates implicated across psychiatric diagnoses is associated with general and specific latent psychopathology dimensional liabilities, as organized via modern bifactor models of psychopathology (i.e., the general psychopathology [p factor], internalizing-specific and externalizing-specific dimensions; Caspi et al., 2014) in children.

A few joint neural areas may underlie multiple psychiatric disorders. Meta-analyses of studies comparing adult psychiatric patients to healthy controls generally show reduced GMV in common areas, including prefrontal cortex and limbic regions, across disorders including major depression (MDD), bipolar disorder (BD), schizophrenia, and anxiety disorders (Haijma et al., 2013; Shang et al., 2014; Wise et al., 2016). Prefrontal cortex, including dorsolateral, ventrolateral and orbitofrontal areas, are part of a cognitive control network subserving multiple executive function abilities (e.g., flexibility, working memory, inhibition; e.g., Niendam et al., 2012). Limbic and paralimbic areas are involved in affective processes, including detecting and responding to affectively salient information (amygdala), emotional memory (medial temporal lobe [MTL] structures), and visceral/autonomic functions (anterior insula). Critically, these networks interact, with affective processes influence cognition and cognitive control processes regulate affective responses, such that dysfunction in either system may result in psychopathology (e.g., Cole, Repovs, & Anticevic, 2014).

Most of these meta-analyses were conducted with the intent to review and summarize findings showing how GMV loss in particular brain areas are associated with specific psychiatric disorders. Yet, the fact that multiple disorders show overlapping patterns of reduced GMV suggests an alternative hypothesis that a few joint neural areas may underlie risk to and manifestation of multiple psychiatric disorders. This hypothesis is consistent with a recent meta-analysis showing that only a few common neural substrates, namely the dorsal anterior cingulate and the insula, were related to multiple, supposedly discrete, psychiatric disorders in adults, including schizophrenia, bipolar disorder, depression, anxiety disorders, and substance use disorders (Goodkind et al., 2015). In this meta-anlaysis, the pattern of common GMV reductions in these regions also was assoiated with poor executive functioning (EF) in healthy participants, and poor EF has been found to be a transdiagnostic predictor of multiple psychiatric diagnoses (e.g., for review see Snyder, Miyake, & Hankin, 2015). Taken together, the various meta-analyses showing GMV loss in common areas, including in prefrontal cortex and limbic regions, across multiple specific disorders along with the findings from the Goodkind et al. (2015) meta-analysis suggest an intriguing hypothesis. Specifically, they suggest that the search for one-to-one brain area to diagnosis mappings may not be successful, given both the pervasive comorbidity across psychiatric disorders and the well-established organization of the brain into interacting networks. Rather, there may be fewer and simpler brain-psychopathology associations that reflect links between wider brain networks and broader psychopathology dimensions.

The meta-analyses discussed above, which provide initial indirect support for this newer, alternative hypothesis that alterations in a common set of neural substrates underlie multiple psychiatric disorders, are primarily based on studies that investigated adult psychiatric patients compared to healthy controls using case control designs. As such, the findings from the individual studies included in the meta-analyses have particular limitations that the present study sought to overcome. First, such research in adults cannot determine whether reduced GMV is (i) evidence of an early developmental marker; (ii) a risk factor for psychiatric disorder; (iii) a consequence of often long-term psychopathology or (iv) a possible medication side effect. As such, the meta-analytic findings cannot determine whether GMV reductions are risk for psychopathology as opposed to a correlate or consequence of the psychiatric disorder.

Although less research has examined GMV in youth psychopathology, at least some of these GMV reductions are present during childhood and adolescence when these disorders are first emerging, suggesting they may reflect atypical neural development. Specifically, there is evidence for reduced prefrontal GMV in youths with MDD and BD (for review see Serafini et al., 2014), generalized anxiety disorder (Strawn et al., 2013), post-traumatic stress disorder (De Bellis et al., 2002), conduct disorder (CD; for meta-analysis see Rogers & De Brito, 2016) and attention deficit hyperactivity disorder (ADHD; for review see Nakao, Radua, Rubia, & Mataix-Cols, 2011). Reduced GMV in limbic/paralimbic structures, including the hippocampus, amygdala, anterior cingulate and insular cortices, have also been reported in youth with MDD and BD (for review see Serafini et al., 2014), anxiety disorders (Milham et al., 2005), and CD (for meta-analysis see Rogers & De Brito, 2016). However, areas of GMV reduction have not been consistent across studies within disorders, potentially due to small sample sizes and differing comorbidity across studies.

Critically, such past research with adults and youth have used case-control designs. Due to ubiquitous comorbidity, such designs do not allow the GMV differences related to common, general psychopathology to be differentiated from links specific to particular types of psychopathology. To accurately examine the hypothesis that there are shared neural substrates associated with broad latent psychopathology liability, we used a recent latent, dimensional bifactor model of psychopathology that has been supported in children, adolescents, and adults, across a variety of measures and methods, and predicts important outcomes, including in school, employment, social service usage, and criminal activity (e.g., Caspi et al., 2014; Laceulle, Vollebergh, & Ormel, 2015; Lahey, Applegate, et al., 2012a; Lahey et al., 2015; Murray, Eisner, & Ribeaud, 2016; Patalay et al., 2015; Snyder, Young, & Hankin, 2016).

Specifically, these studies all find a general latent factor that represents the liability to experience common, co-occuring symptoms (i.e., the p factor, Caspi et al., 2014) as well as internalizing-specific and externaling-specific dimensions that are independent of the general p factor. The p factor characterizes, in a single latent variable, the co-occurrence that is common across all measured psychopathology symptoms. After statistically accounting for common psychopathology variance via the p factor, the covariance that remains is captured and organized by independent internalizing- and externalizing-specific latent factors. Thus, using this latent psychopathology model, in this study we can directly examine the hypothesis that a few shared neural substrates are transdiagnostically associated with the p factor, which represents the general liability to experience broad, co-occurring emotional and behavioral problems, and other shared neural substrates may relate to the independent latent liabilities to internalizing and externalizing dimensions.

We examined whether GMV reductions could constitute early emerging neural risk factors or correlates of broad psychopathology dimensions. Specifically, we examined links between latent p factor, internalizing-specific and externalizing-specific factors and GMV in a community sample of children, focusing on prefrontal and limbic/paralimbic areas most frequently identified in GMV studies of individual disorders, and linked to executive function and affective processes hypothesized as transdiagnostic risks for development of psychopathology (e.g., Cole et al., 2014). Investigating links between latent psychopathology factors and GMV during middle childhood, when neurodevelopmental processes are rapidly unfolding and many forms of psychopathology have their origins (e.g., Copeland, Wolke, Shanahan, & Costello, 2015; Miettunen et al., 2014), represents a critically important step to understanding early neural risk for the development of psychopathology dimensions.

Methods

Participants

Participants were a diverse community sample of 254 children (average age 7.9 years, range 6.09–10.95 years, 46% female) and their mothers, recruited from hospital birth records in the Los Angeles metro area. See Table 1 for additional demographic information. Participants had normal neurologic findings based on review by a neuroradiologist. All children were typically developing and in the appropriate grade for their age. Levels of

psychopathology in the sample were generally consistent with population norms. Rates of clinically elevated symptoms on the Child Behavior Checklist (CBCL) DSM-oriented scales ranged from 4% for affective problems and ADHD to 9% for anxiety, in line with large scale epidemiological studies of youth (e.g., Polanczyk, Salum, Sugaya, Caye, & Rohde, 2015), and mean levels of symptoms were similar to pooled estimates across studies using the CBCL (e.g., Rescorla et al., 2007).

Procedure

Participating families competed a laboratory visit in which mothers completed questionnaire measures about their child. Imaging data was acquired at a second visit on average 2.5 months later (SD=4.8 months). Families were compensated for their participation and travel costs. The study was approved by the Institutional Review Board and parents provided informed consent.

Psychopathology Questionnaires

Child Behavior Checklist (CBCL, Achenbach & Rescorla, 2001)—Child psychopathology was measured using the parent report form (CBCL) from the Achenbach System of Empirically Based Assessment. The CBCL is a widely used measure of youth mental health and behavioral problems, and demonstrates good test-retest reliability, and discriminant, convergent and predictive validity with other measures of psychopathology (e.g., Achenbach & Rescorla, 2001). See Table 1 for descriptive statistics and internal consistencies in the current study sample.

The CBCL contains items representing a broad scope of behaviors. Responses were made by mothers on a 3- point Likert scale ranging from 0 (not true) to 2 (very true). The following empirically-based subscales were included: Aggressive Behavior (18 items, e.g., “Gets in many fights”, “Cruelty, bullying or meanness to others”), Anxious/Depressed (13 items, e.g., “Worries”, “Cries a lot”), Attention Problems (10 items, e.g., “Can’t concentrate, can’t pay attention for long”, “Can’t sit still, restless or hyperactive”), Rule-Breaking Behavior (17 items, e.g., “Breaks rules and home, school or elsewhere” “Doesn’t seem to feel guilty after misbehaving”), Thought Problems (15 items, e.g. “Can’t get his/her mind of certain thoughts/obsessions”, “Strange behaviors”), Somatic Complaints (11 items, e.g., “Stomaches”, “Headaches”), Social Problems (11 items, e.g., “Doesn’t get along with other kids”, “Complains of loneliness”), and Withdrawn/Depressed (8 items, e.g., “There is very little he/she enjoys”, “Unhappy, sad or depressed”).

In the CBCL scoring system, the Anxious/Depressed, Withdrawn/Depressed and Somatic Complaints subscales are classed as assessing an internalizing dimension, the Aggressive Behavior and Rule-Breaking Behavior as assessing an externalizing dimension, and the remaining subscales (Attention, Social and Thought problems) are not assigned to either the internalizing or externalizing scales but are included in the total problem measure.

Children’s Behavior Questionnaire (CBQ, Rothbart, Ahadi, Hershey, & Fisher, 2001)—To increase coverage of child psychopathology symptoms not fully covered in the CBCL and increase the number of indicators for latent variable modeling, two subscales

from CBQ were also included: Anger/Frustration (13 items, e.g., “Easily gets irritated when he/she has trouble with some task”, “Gets mad when provoked by other children”) and Fear (12 items, e.g., “Is afraid of the dark”, “Is afraid of loud noises”). The CBQ is widely used in research with children, and has good test-retest and inter-rater reliability and convergent validity (e.g., Rothbart et al., 2001). Responses were made by mothers on a 7-point Likert scale ranging from 1 (extremely untrue of your child) to 7 (extremely true of your child). See Table 1 for descriptive statistics and internal consistencies in the current study sample.

MRI Methods

MR Acquisition: MRI scans were acquired on a 3 T Philips Achieva system. A high resolution T1 weighted anatomical scan was acquired using a 3D MPRAGE pulse sequence that covered the whole brain. The images were acquired in the sagittal orientation with FOV = 240 × 240 mm2, 1 mm3 isotropic voxel dimensions, 150 slices, TR = 11 ms, TE=3.3 ms, inversion pulse delay=1100 ms and flip angle=18°. No signal averaging and no SENSE acceleration were used. The images were reviewed by the MR operator immediately after the scan was completed. If there were visible signs of motion artifacts the scan was repeated.

Image Processing: Cortical surface reconstruction and volumetric segmentation was performed with FreeSurfer (http://surfer.nmr.mgh.harvard.edu/). Intensity normalization was applied prior to segmentation to minimize errors in identifying the boundaries (Sled, Zijdenbos, & Evans, 1998), followed by removal of non-brain tissues (Ségonne et al., 2004). Images were transformed into the Talairach space and subcortical structures segmented (Fischl et al., 2002; 2004). Pial and white matter surfaces were located by finding the highest intensity gradient (Fischl & Dale, 2000). Surface inflation was applied to each individual brain (Fischl, Sereno, & Dale, 1999a) and the inflated brains registered to a spherical atlas using individual cortical folding patterns to achieve accurate registration of cortical geometry (Fischl, Sereno, Tootell, & Dale, 1999b). The cortical surface images were visually inspected for segmentation errors and corrected as needed.

Statistical Analyses

Structural equation modeling was conducted in Mplus (L. K. Muthén & Muthén, 2012) using full information maximum likelihood (FIML) estimation to handle missing data.

Latent Psychopathology Model—A confirmatory factor analysis (CFA) of the psychopathology measures was conducted based on previous p factor models in youth (e.g., Laceulle et al., 2015; Snyder et al., 2016) and the established structure of the CBCL (Achenbach & Rescorla, 2001). Specifically, we followed the standard scoring of the CBCL into internalizing (Anxious/Depressed, Withdrawn/Depressed and Somatic Complaints), externalizing (Rule Breaking Behavior, Aggressive Behavior) and other (Social Problems, Thought Problems, Attention Problems) subscales (Achenbach & Rescorla, 2001). The CBQ Fear and Anger/Frustration subscales were included as additional internalizing and externalizing measures respectively. All measures were loaded onto the p factor. Internalizing measures were additionally loaded onto an internalizing-specific factor and externalizing measures onto an externalizing-specific factor, capturing unique variance not accounted for by the p factor. Factors were constrained not to correlate because what is

shared between factors is already captured by the common factor (e.g., Chen, Hayes, Carver, Laurenceau, & Zhang, 2012). Modification indices were inspected and residual correlations added between the Thought Problems subscale and the Somatic Complaints, Anxious/Depressed and Social Problems subscales to improve model fit.

Regional ROI regression analyses—As a theory-based method of data reduction, we first examined larger anatomical region of interest. The GMV of FreeSurfer defined ROIs within each anatomical area were summed to calculate total GMV for the following larger anatomical regional ROIs: (1) dorsal PFC (DPFC: superior frontal [SFG], rostral and caudal middle frontal gyri [MFG]); (2) ventrolateral PFC (VLPFC: inferior frontal gyri [IFG] pars opercularis, triangularis, and orbitalis) (3) orbitofrontal (lateral and medial OFC); (4) anterior cingulate (rostral and caudal ACC); (5) insula (left and right); (6) amygdala (left and right); and (7) medial temporal lobe (MTL: hippocampi, parahippocampal gyri and entorhinal corteces). In addition, occipital areas (pericalcerine, cuneus, and lateral occipital cortices), were included as a discriminant validity region, to test the specificity of results to hypothesized prefrontal and limbic areas. Regression analyses were conducted predicting regional ROI GMV with the p factor, internalizing-specific factor and externalizing-specific factor, controlling for age and gender. Additional analyses checked for interactions between each psychopathology factor and age or gender in predicting each brain volume factor.

Follow-up Regression Analyses—To determine which specific anatomical areas within each regional brain volume were associated with the latent psychopathology factors, for regional ROIs predicted by each psychopathology factor, we ran follow-up regressions predicting each standard FreeSurfer anatomical ROI within that region, controlling for age and gender. False discovery rate (FDR) correction was used to correct for multiple comparisons across all the follow-up regressions.

Results

Confirmatory Factor Analyses

The p factor measurement model was first tested to ensure it fit the data well. The model achieved good fit (CFI = .99, TLI=.99, RMSEA=.044, SRMR=.026), and all indicators loaded significantly on their specified factors (Table 1, Supplemental Materials Table S2).

Regional ROI Regression Analyses (Table 2, Figure 1)

Regression analyses were conducted predicting the regional ROIs with the p factor, internalizing-specific factor and externalizing-specific factor, controlling for age and gender; handedness was not a significant predictor and did not affect results in any analysis, so was dropped from inclusion in the model. Higher levels of common psychopathology were associated with smaller volumes in dorsal PFC ($\beta = -0.16$), ventrolateral PFC ($\beta = -0.15$) and orbitofrontal cortex ($\beta = -0.19$). The p factor did not significantly predict any of the limbic/paralimbic factors, nor the occipital control factor. Higher levels of the internalizing-specific factor were significantly associated with smaller volumes for the medial temporal lobe ($\beta = -0.24$), amygdala ($\beta = -0.25$), and insula ($\beta = -0.35$). The internalizing-specific factor did not significantly predict prefrontal volumes or the occipital control region. The

externalizing-specific factor did not significantly predict any brain volume factor. None of the significant relations between psychopathology and regional ROIs was moderated either by age or gender (*p*s ≥ .2). Alternative analyses using regional brain volume factors rather than manifest regional ROIs, produced nearly identical results (Supplmental Materials Tables S3–S5).

Individual ROI Follow-up Regressions (Table 3)

Within the dorsal PFC, the p factor significantly predicted the volume of the left and right superior frontal gyri and rostral middle frontal gyri; all but the right superior frontal gyrus remained significant with FDR correction. Within the ventrolateral PFC, the p factor significantly predicted the volume of the right inferior frontal gyrus pars orbitalis (significant with FDR correction) and left inferior frontal gyrus pars triangularis (significant uncorrected). Within the orbitofrontal cortex, the p factor significantly predicted all ROIs–left and right lateral and medial orbitofrontal cortex–and these associations remained significant with FDR correction. The internalizing-specific factor significantly predicted the left and right amygdalas, hippocampi, and insulas; all but the left amygdala remained significant with FDR correction.

Exploratory Whole Brain Analysis (Supplmentary Materials, Tables S8–S9, Figure S1)

To explore whether areas not included in the ROI analysis might be associated with the latent psychopathology factors, whole brain analysis was conducted correlating volume across the cortex with p factor, internalizing-specific and externalizing-specific factor scores. See Supplementary Materials for methods and detailed results. Cortical volume was significantly negatively correlated with p factor scores in multiple prefrontal areas as well as the right posterior cingulate cortex, right parahippocampal gyrus, and bilateral entorhinal cortex and temporal pole (Table S8). Few areas were significantly correlated with the internalizing or externalizing-specific factor scores in the whole-brain analysis.

Alternative internalizing and externalizing factor model

A traditional two factor internalizing-externalizing model (with no p factor) was created followed the standard scoring of the CBCL into internalizing (Anxious/Depressed, Withdrawn/Depressed and Somatic Complaints) and externalizing (Rule Breaking Behavior, Aggressive Behavior). The CBQ Fear and Anger/Frustration subscales were included as additional internalizing and externalizing measures respectively. The CBCL subscales not scored as part of the internalizing or externalizing subscales were not included in this model. The model achieved good to adequate fit (CFI = .98, TLI=.97, RMSEA=.058, SRMR=.035), and all indicators loaded significantly on their specified factors (Table S6). The internalizing and externalizing factors were strongly positively correlated with one another (*r* = .69).

Controlling for age and gender, the internalizing factor was associated with lower GMV in DPFC, VLPFC, OFC, MTL, amygdala and insula, and all of these effects except OFC remained significant controlling for the externalizing factor (Table S7). Controlling for age and gender, the externalizing factor was associated with lower GMV in the DPFC, OFC and MTL (Table S7). However, controlling for the internalizing factor, the externalizing factor did not significantly predict GMV in any region.

Discussion

The current study used an empirically based latent bifactor structure that optimally organizes psychopathology in a sample of children to examine links between latent common psychopathology (p factor), internalizing-specific and externalizing-factors and GMV for the first time, during a critical developmental period for both brain development and risk for early emerging psychopathology. Hundreds of studies have found smaller GMV in various brain regions to be associated with many psychiatric disorders. Often the smaller GMV is observed in prefrontal areas important for executive function, and in limbic/paralimbic areas important for affective processes (Haijma et al., 2013; Rogers & De Brito, 2016; Serafini et al., 2014; Shang et al., 2014; Wise et al., 2016). However, rampant comorbidity among DSM-based disorders makes it nearly impossible to cleanly interpret and synthesize these past results.

This point is reinforced and illustrated by the analysis in the current study of internalizing and externalizing factors considered separately, without taking comorbidity between them into account. In these analyses, there appears to be a diffuse, non-specific pattern of associations with GMV, with lower volumes in DPFC, OFC and MTL associated with both dimensions of psychopathology. This is consistent with overlapping findings in previous research considering individual disorders or symptom dimensions. Because internalizing and externalizing dimensions are highly correlated (and frequently comorbid at the diagnostic category level), associations with each factor individually could be driven by what is specific to that factor, by comorbidity with the other factor, and/or by common psychopathology. The p factor model greatly clarifies these results, revealing a much simpler and conceptually clearer pattern of relations between GMV and vulneralibility to pscychopathology. Smaller GMV in prefrontal areas was associated with latent common psychopathology, and smaller GMV in limbic/paralimbic brain areas with internalizing-specific psychopathology. Importantly, there were no associations between the psychopathology factors and GMV in occipital cortex, which served as a discriminant validity region not hypothesized to be related to psychopathology. Thus, our results showed clear brain system specific relations with psychopathology.

First, what is common across multiple forms of psychopathology (the p factor) was associated with reduced prefrontal GMV, including areas of DPFC, VLPFC, and OFC, providing direct evidence linking the p factor to PFC areas critical for executive function, consistent with recent evidence linking the p factor to executive function task performance (Castellanos-Ryan et al., 2016; Martel et al., 2017). Importantly, these results also clarify earlier findings demonstrating smaller prefrontal GMV across many different psychiatric disorders, including depression, anxiety, ADHD, and psychosis, suggesting these associations may be driven by what is shared across disorders rather than disorder-specific factors. Moreover, these associations are present early in development in a typically-developing sample, suggesting that smaller GMV in these prefrontal areas may constitute an early risk factor for general liability to psychopathology.

Second, the internalizing-specific factor was associated with smaller GMV in limbic/paralimbic areas, including the insular cortices, amygdalas and hippocampi bilaterally.

These results confirm previous findings linking these regions to individual mood and anxiety disorders in youths (Serafini et al., 2014). Importantly, because the bifactor model organizes common variance shared across all symptom measures into the p factor, which is independent from specific internalizing symptom variance, we can be confident that these findings of smaller GMV in limbic areas are truly associated with specific internalizing symptoms that are not shared with general, comorbid psychopathology, clarifying these previous findings. The ACC was the only limbic/paralimbic area not significantly associated with the internalizing-specific factor (although there was a trend level association). Since previous evidence of reduced ACC volume associated with psychopathology has been largely from adult samples (e.g., Goodkind et al., 2015), it is possible that ACC volume reductions may occur as a result of psychpathology, rather than being a risk factor for psychopathology, and are thus not present earlier in development.

Third, an externalizing factor, considered alone, was associated with reduced GMV in DPFC, OFC and MTL, consistent with past research with conduct and antisocial behavior problems which found GMV reductions in some prefrontal and limbic areas (Aoki, Inokuchi, & Nakao, 2013; Rogers & De Brito, 2016). Critically however, once common psychopathology was accounted for via the p factor, what is specific to externalizing was not associated with reduced GMV in any tested brain region. Thus, these associatons are not specific to externalizing, but rather are driven by common psychopathology, as captured by the p factor (DPFC and OFC), or comorbidity with internalizing psychopathology (MTL). Externalizing problems are characterized predominantly by deficits in executive functioning, poor self control, and disinhibition (Beauchaine & McNulty, 2013), processes largely instantiated via prefrontal areas. One explanation is that poor executive functioning and low self control may be transdiagnostic factors that confer risk to multiple forms of psychopathology (Beauchaine & Thayer, 2015; Snyder et al., 2015), including externalizing problems. Thus, these findings do not contradict prior fincings linking externalizing problems to GMV in prefrontal regions. Rather, these data suggest that GMV reductions associated with individual externalizing problems may be accounted for by common psychopathology variance, because prefrontal areas are salient for general psychopathology (in this study) and DSM-based diagnoses of externalizing problems (in past studies of singular conduct and antisocial disorders).

Several aspects of this study provide novel insights on associations between brain anatomy and psychopathology. First, we directly tested links between brain anatomy and latent psychopathology dimensions, rather than individual DSM-based psychiatric disorders. Latent dimensional models help to account for comorbidity and capture underlying dimensions that better represent the structure of psychopathology (e.g., Eaton et al., 2013). Second, findings advance understanding of how brain structure and psychopathology are related early in development. Many prevalent forms of psychopathology begin in childhood and adolescence (e.g., Merikangas et al., 2010). During middle childhood, prefrontal and limbic regions undergo rapid development (e.g., Muftuler et al., 2011), and individual variability in brain systems predicts some subsequent psychopathology (e.g., Green, Goff, & Gee, 2016). Our findings suggests that GMV reductions may reflect atypical neural development, consistent with a neurodevelopmental risk model, rather than a consequence of long-term psychopathology. However, since there are no previous studies examining links

between latent psychopathology factors and GMV at any age (previous studies have all used diagnostic categories or individual manifest symptom measures), it is currently impossible to directly compare effect sizes across ages. The current study is cross-sectional, so future cross-age comparisons and longitudinal research is needed to determine if brain structural differences are differentially associated with psychopathology at different points in development, and if they precede, and thus may constitute a risk factor for, the development of psychopathology.

Future research is also needed to identify the specific neural mechanisms involved. Associations of psychopathology with reduced GMV during childhood could reflect any combination of reduced neurogenesis, reduced synaptic proliferation, accelerated synaptic pruning, and/or loss of cells (e.g., Sandman, Glynn, & Davis, 2016; Stiles & Jernigan, 2010). For example, during typical development in the age range of the current study (6–10 years), synaptic pruning causes grey matter decreases in many brain regions (e.g., Gogtay & Thompson, 2010; Muftuler et al., 2011), and childhood depression has recently been found to be associated with an accelerated reduction in grey matter during this period (Luby et al., 2016). Thus, it will be important to understand how early emerging latent psychopathology dimensions are potentially related to different trajectories of this developmental process. In addition, while the current study focused on prefrontal and limibic areas, other areas, including the striatum, are of potential interest and may be especially implicated in particular disorders (e.g., ADHD, OCD). These additional areas will be important to investigate further in youth (e.g., with studies optimized for high-resolution imaging of subcortical structures).

Finally, future research is needed to investigate how GMV-latent psychopathology links may be similar or different across populations. The current study used an unselected, general community sample of children to capture the full range of psychopathology symptom levels dimensionally. GMV reduction patterns might be different in selected high-risk or treatment-seeking samples. In addition, while age did not moderate the findings within the 6–10 year old age range of the current study, associations between GMV and psychopathology are likely to change over longer developmental periods, as the neural processes described above unfold and psychopathology also undergoes developmental change. Thus, research is needed to compare findings from different periods of childhood, adolescence and adulthood.

In summary our findings reveal an elegant organization of brain areas related to psychopathology. General psychopathology was associated with reduced GMV in prefrontal areas essential for executive function and internalizing-specific psychopathology was related to reduced GMV in limbic/paralimbic areas implicated in affective processes. Results suggest that using modern, latent dimensional models of psychopathology has the potential to clarify previous findings and shed new light on a few core neural substrates that may affect early emerging risk to psychopathology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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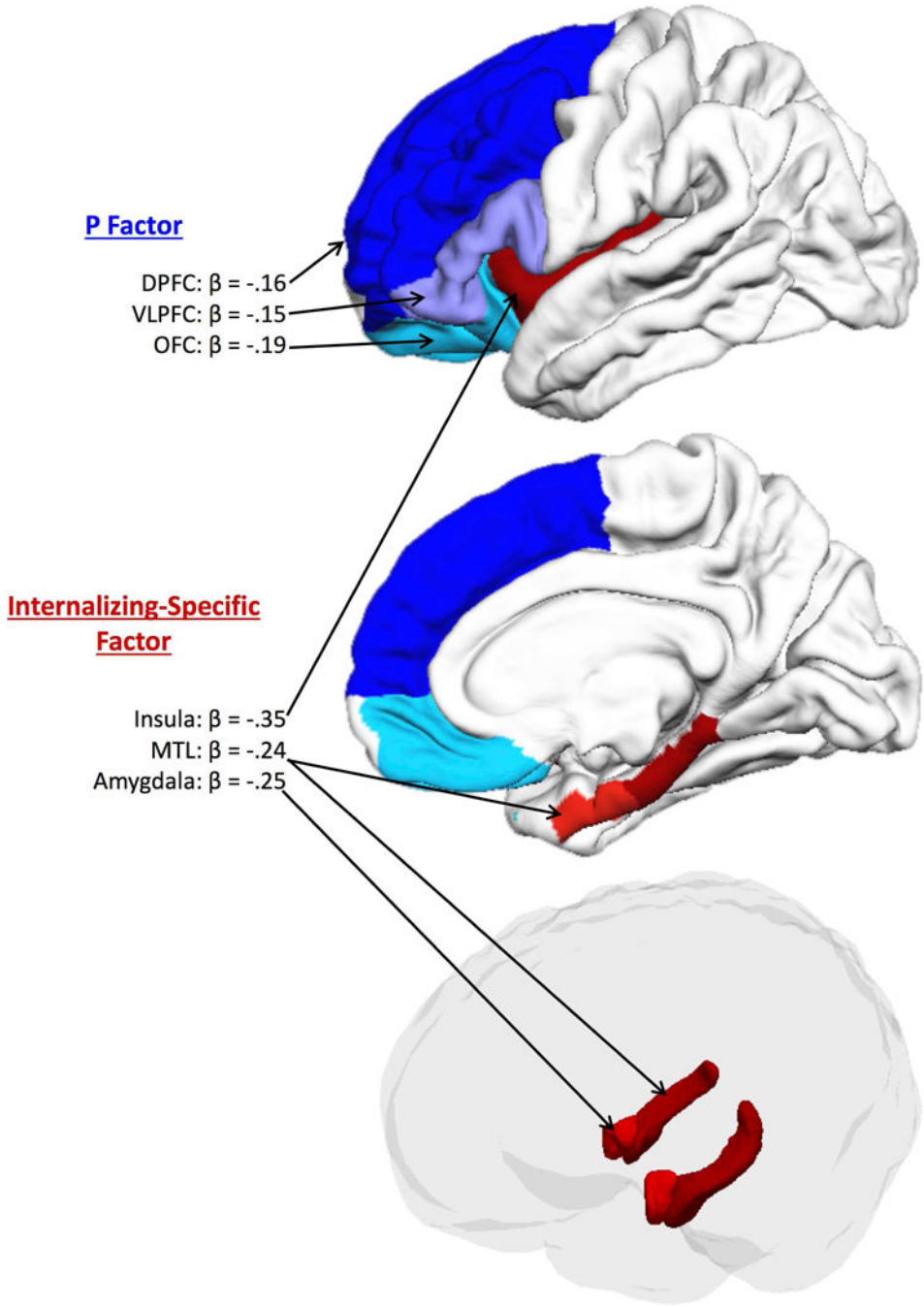

Figure 1.
Bilateral grey matter volume reductions (GMV) in DPFC, VLPC, and OFC were significantly associated with the latent p factor of psychopathology; bilateral GMV reduction in insula, medial temporal lobe, and amygdala were significantly associated with unique internalizing-specific variance that is independent of general psychopathology p factor variance.

Table 1

Demographics and Descriptive Statistics

Demographics					
Gender (% female)	46%				
Race/Ethnicity	39% Hispanic, 31% Non-Hispanic White, 23% more than one race, 4% African American, 3% Asian/Pacific Islander				
Median Family Income	$70,000–$80,000 range				
	Mean	SD			
Age	7.92	1.38			
WISC IQ	103.57	14.53			
Years parental education	14.15	2.60			
CBCL DSM Scales:	Raw Mean	Raw SD	T score Mean	T score SD	% Clinically Elevated (T > 66)
DSM Affective Problems	1.46	1.80	54.20	5.48	4.2%
DSM Anxiety	1.73	1.85	54.89	6.32	8.9%
DSM Somatic Problems	1.26	1.51	56.39	6.57	8.8%
DSM ADHD	3.57	2.89	54.44	5.70	4.2%
DSM Oppositional Defiant	2.39	2.13	54.89	6.04	5.1%
DSM Conduct Problems	1.63	2.48	53.96	9.59	5.1%

Descriptive Statistics and Factor Loadings						
Measure	Mean	SD	α	Standardized Factor Loadings		
				p factor	Internalizing-specific	Externalizing-specific
CBCL Anxious/Depressed	3.33	2.77	.68	.63	.46	–
CBCL Withdrawn/Depressed	1.38	1.70	.65	.63	.24	–
CBCL Somatic Complaints	1.89	2.08	.65	.53	.33	–
CBQ Fear	3.98	1.00	.75	.24	.25	–
CBCL Rule Breaking	1.69	1.92	.63	.66	–	.35
CBCL Aggressive Behavior	4.95	4.92	.87	.79	–	.61
CBQ Anger/Frustration	4.10	0.88	.85	.50	–	.18
CBCL Attention Problems	3.82	3.36	.79	.69	–	–
CBCL Social Problems	2.72	2.57	.64	.84	–	–
CBCL Thought Problems	2.24	2.46	.57	.74	–	–

Table 2

Regional ROI Regressions

Psychopathology Factor	Brain Region	β [95% CI1	SE	z	*p*
p factor		**−0.16 [−0.29, −0.03]**	**0.06**	**−2.49**	**.013** *
Internalizing-specific	DPFC	−0.16 [−0.45, 0.12]	0.15	−1.18	.264
Externalizing-specific		−0.01 [−0.15, 0.13]	0.07	−0.15	.882
p factor		**−0.15 [−0.28, −0.02]**	**0.07**	**−2.28**	**.023** *
Internalizing-specific	VLPFC	−0.06 [−0.30, 0.18]	0.12	−0.51	.608
Externalizing-specific		0.06 [−0.08, 0.21]	0.07	0.88	.378
p factor		**−0.19 [−0.32, −0.07]**	**0.06**	**−3.04**	**.002** *
Internalizing-specific	OFC	0.02 [−0.21, 0.25]	0.12	0.15	.883
Externalizing-specific		−0.01 [−0.15, 0.13]	0.07	−0.14	.892
p factor		−0.01 [−0.15, 0.13]	0.07	−0.13	.899
Internalizing-specific	ACC	−0.09 [−0.33, 0.16]	0.12	−0.70	.448
Externalizing-specific		0.02[−0.14, 0.14]	0.08	0.20	.845
p factor		−0.12 [−0.25, 0.01]	0.07	−1.84	.066
Internalizing-specific	MTL	**−0.24 [−0.46, −0.02]**	**0.11**	**−2.14**	**.032** *
Externalizing-specific		−0.07 [−0.21, 0.07]	0.07	−0.95	.341
p factor	Amygdala	−0.07 [−0.20, 0.05]	0.06	−1.17	.241
Internalizing-specific		**−0.25 [−0.45, −0.05]**	**0.10**	**−2.44**	**.015** *
Externalizing-specific		−0.05 [−0.18 0.09]	0.07	−0.67	.504
p factor		−0.11 [−0.24, 0.01]	0.06	−1.77	.077
Internalizing-specific	Insula	**−0.35 [−0.55, −0.15]**	**0.10**	**−3.46**	**.001** *
Externalizing-specific		−0.04 [−0.15, 0.07]	0.07	−0.63	.529
p factor		−0.07 [−0.20, 0.09]	0.06	−1.17	.241
Internalizing-specific	Occipital Cortex	−0.09 [−0.32, 0.14]	0.12	−0.77	.440
Externalizing-specific		−0.03 [−0.15, 0.08]	0.07	−0.46	.645

Note.

* $p < .05$

Table 3

Follow-up Individual ROI Regressions

Psychopathology Factor	Region	Brain ROI	β [95% CI]	SE	*Z*	*p*
p factor	DPFC	**L SFG**	**−0.14 [−.26 – −.02]**	**0.06**	**−2.31**	**.021** **
		R SFG	**−0.13 [−.25 – −.01]**	**0.06**	**−2.05**	**.040** *
		L rostral MFG	**−0.19 [−.31 – −.07]**	**0.06**	**−2.91**	**.004** **
		R rostral MFG	**−0.15 [−.27 – −.03]**	**0.06**	**−2.35**	**.019** **
		L caudal MFG	−0.04 [−.18 – .10]	0.07	−0.62	.533
		R caudal MFG	−0.09 [−.23 – .05]	0.07	−1.25	.211
	VLPFC	L IFG pars opercularis	−0.10 [−.23 – .04]	0.07	−1.53	.125
		R IFG pars opercularis	−0.04 [−.18 – .10]	0.07	−0.64	.522
		L IFG pars triangularis	**−0.13 [−.27 – .00]**	**0.07**	**−1.98**	**.048** *
		R IFG pars triangularis	−0.02 [−.16 – .12]	0.07	−0.30	.761
		L IFG pars orbitalis	−0.13 [−.27 – .01]	0.07	−1.90	.057
		R IFG pars orbitalis	**−0.18 [−.30 – −.06]**	**0.06**	**−2.77**	**.006** **
	OFC	**L lateral OFC**	**−0.17 [−.29 – −.05]**	**0.06**	**−2.70**	**.007** **
		R lateral OFC	**−0.16 [−.28 – −.04]**	**0.06**	**−2.44**	**.015** **
		L medial OFC	**−0.15 [−.29 – −.01]**	**0.07**	**−2.38**	**.018** **
		R medial OFC	**−0.17 [−.29 – −.05]**	**0.06**	**−2.69**	**.007** **
Internalizing-Specific	MTL	**L hippocampus**	**−0.25 [−.47 – −.03]**	**0.11**	**−2.33**	**.020** **
		R hippocampus	**−0.33 [−.55 – −.11]**	**0.11**	**−2.88**	**.004** **
		L parahippocampus	−0.01 [−.23 – .21]	0.11	−0.08	.936
		R parahippocampus	−0.08 [−.34 – .18]	0.13	−0.67	.506
		L entorhinal cortex	−0.18 [−.40 – .04]	0.11	−1.61	.107
		R entorhinal cortex	−0.09 [−.33 – .15]	0.12	−0.74	.460
	Amygdala	**L amygdala**	**−0.20 [−.40 – −.00]**	**0.10**	**−2.00**	**.045** *
		R amygdala	**−0.27 [−.47 – −.07]**	**0.10**	**−2.71**	**.007** **

Psychopathology Factor	Region	Brain ROI	β [95% CI]	SE	Z	*p*
	Insula	**L insula**	**−0.31 [−.57 – −.05]**	**0.13**	**−2.45**	**.014****
		R insula	**−0.36 [−.56 – −.16]**	**0.10**	**−3.74**	**<.001****

Note. L = left, R =right

* p < .05 uncorrected

** p < .05 with FDR correction