Global Brain Volume is Associated with General Psychopathology in Youth

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Background

- Childhood is an important time for brain development (Giedd et al., 1999).
- Mental disorders have high comorbidity rates, with many symptoms being dimensional, shared across disorders, and hierarchically organized (Conway et al., 2019; Caspi & Moffitt, 2018; Lahey et al., 2017).
- Despite the dimensional nature of psychopathology, most research surrounding the neural mechanisms of psychopathology has employed case-control designs with a focus on categorically-defined mental disorders.
- While some prior research has shown negative associations between dimensional factors of psychopathology and brain volume (Kaczkurkin, Park, et al., 2019; Romer et al., 2019; Snyder et al., 2017; Moore et al., 2019), the majority of these studies have used samples with large age ranges which may obscure developmental changes. Studies using more homogeneous ages are needed.
- The current research builds upon prior work through the investigation of associations between brain volume and psychopathology dimensions in a large sample of 9-10 year old children.
- **Hypotheses:** General psychopathology (as defined by a bifactor model) will be associated with smaller regional gray matter volume (GMV) throughout the brain.

Methods

Participants: Participants included the 9-10 year old children from Wave 1 (release 2.0.1) of the Adolescent Brain and Cognitive Development (ABCD) Study (Volkow et al., 2018), which provides a publicly available and fully de-identified dataset (*N* = 9,672, 51% male, 53% White).

Psychopathology measure: Psychopathology was measured with the Childhood Behavior Checklist (CBCL) for school-aged children (Achenbach, 2009) .

Brain volume measure: Regional gray matter volume (GMV) was defined by automated atlases for cortical (Desikan et al., 2006) and subcortical (Fischl et al., 2002) regions.

Procedure: Parents completed the CBCL to assess for psychopathology symptoms experienced by their children. The child participants completed MRI scanning sessions. Imaging data was acquired at 21 sites using Siemens (Prisma VE11B-C), Phillips (Achieva dStream, Ingenia), and GE (MR750, DV25-26) MRI scanners. Image processing was performed by the ABCD Data Analysis and Informatics Center using centralized protocols.

Bifactor analysis: Using 66 items from the Childhood Behavior Checklist (CBCL), an exploratory factor analysis identified three dimensions of psychopathology: internalizing, conduct problems, and ADHD. A confirmatory bifactor analysis was used to model these three factors plus a general factor of psychopathology (Moore et al., under review).

Brain volume analyses: Structural equation models (SEM) were then performed to evaluate associations between GMV of 68 cortical and 19 subcortical brain regions and the 4 psychopathology factors. Post-stratification weights were applied to account for stratification of the sample in the data sites. Data was clustered by family since the ABCD study includes twins and siblings. The model tested was as follows:

regional volume = age + sex + race/ethnicity + MRI manufacturer + general psychopathology + conduct problems + internalizing + ADHD

Correction for multiple comparisons: To control for multiple testing across many brain regions, we controlled the false discovery rate (q<.05). All factor analyses and SEM analyses were performed with Mplus (Muthén & Muthén, 2017).

Results

Bifactor Model

- A confirmatory bifactor analysis of the CBCL data yielded 4 orthogonal factors of psychopathology: general psychopathology which represents symptoms common across domains as well as specific internalizing, specific conduct problems, and specific ADHD factors.

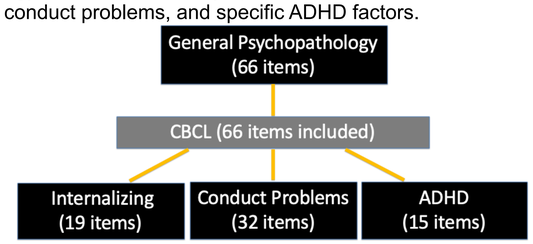

Figure 1. Bifactor model schematic

General Factor

- The general factor was inversely associated with GMV in 53 cortical and 19 subcortical regions

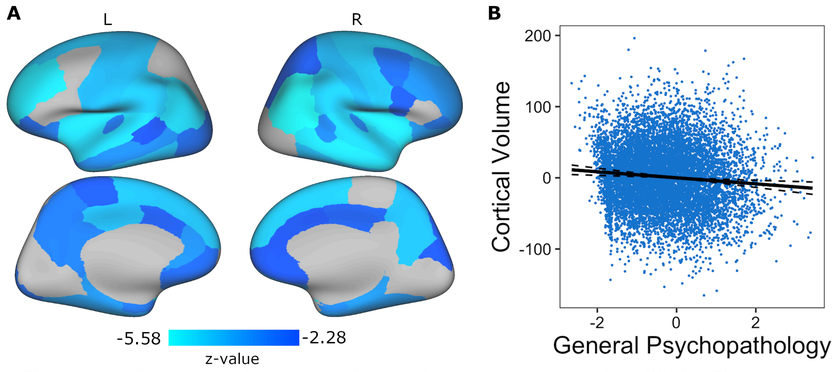

Figure 1. A) General psychopathology is associated with smaller cortical GMV in 53 regions (FDR corrected). **B)** As general psychopathology scores increase, whole brain volume decreases.

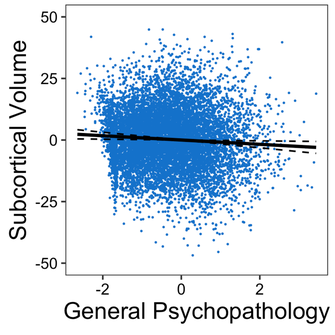

Figure 2. As general psychopathology scores increase, subcortical brain volume decreases.

Brain region	β	P_{fdr}
Left cerebellum cortex	-0.050	<.001
Left thalamus proper	-0.060	<.001
Left caudate	-0.053	<.001
Left putamen	-0.047	.001
Left pallidum	-0.055	<.001
Left hippocampus	-0.072	<.001
Left amygdala	-0.057	<.001
Left accumbens area	-0.056	<.001
Left ventral diencephalon	-0.061	<.001
Right cerebellum cortex	-0.049	<.001
Right thalamus proper	-0.059	<.001
Right caudate	-0.053	<.001
Right putamen	-0.045	.001
Right pallidum	-0.047	.001
Right hippocampus	-0.072	<.001
Right amygdala	-0.055	<.001
Right accumbens area	-0.059	<.001
Right ventral diencephalon	-0.044	.001
Brain stem	-0.053	<.001

Table 1. General psychopathology is associated with smaller subcortical GMV in 19 regions (FDR corrected).

Specific Factors

- The specific conduct problems factor was inversely associated with GMV in 53 cortical and 15 subcortical regions.
- The specific ADHD factor was inversely associated with GMV in 26 cortical and 8 subcortical regions.
- No regional GMVs were associated with the specific internalizing factor after FDR correction.

Discussion

- General psychopathology was associated with smaller cortical and subcortical gray matter volumes, consistent with previous work (Kaczkurkin, Park, et al., 2019; Romer et al., 2017; Snyder et al., 2017).
- The current study extends this prior work by showing that the association between smaller volumes and greater general psychopathology is apparent at a young age (9-10 years).
- This may suggest that reduced gray matter volume is a transdiagnostic risk factor across psychopathology domains.
- These findings can be related to prior research that found a general factor in childhood to be associated with an array of deficits, including deficits in self-control, emotion regulation, and executive functions (Caspi & Moffitt, 2018).
- These findings can be also related to prior research that has demonstrated reduced functional activity at the whole-brain level across multiple categories of disorders when performing tasks involving cognitive, social, and reward and threat processing (Sprooten et al., 2017).
- The current study also builds upon prior work by showing associations between smaller volumes and the specific psychopathology factors of conduct problems and ADHD.
- Interestingly, we found no association between volume and the specific internalizing factor in the current study.
- The lack of an association between volume and internalizing symptoms may be due to the later onset of these symptoms. Given that internalizing symptoms increase around adolescence, these symptoms may not be prominent yet in 9-10 year olds.
- A limitation of the current study includes assessing volume and psychopathology at a single time point. However, these results may serve as a baseline for which future waves of the ABCD dataset can be compared to determine whether the relationship between brain volume and psychopathology changes over the course of development.

Conclusions

- Consistent with the emerging notion that the general factor may relate to non-specific variation in the brain, the present analyses provide support that general psychopathology symptoms observed in childhood are inversely associated with global gray matter volume.
- Smaller brain volume may also represent a risk factor for ADHD and conduct problems specifically, with no evidence found for internalizing symptoms in the current study.
- While limited by a cross-sectional design, this study extends prior work by suggesting that the relationship between reduced gray matter volume and psychopathology is evident at an early age.
- The narrow age range used also allows us to overcome the difficulties in understanding developmental process using samples with very large age ranges.
- Considered together, these results support and expand upon prior work on the relationship between neurostructure and psychopathology in childhood.

Support & Disclosures

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