Journal of Psychopathology and Clinical Science

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Online First Publication, April 6, 2023. https://dx.doi.org/10.1037/abn0000820

AMERICAN PSYCHOLOGICAL ASSOCIATION

Journal of Psychopathology and Clinical Science

ISSN: 2769-7541

https://doi.org/10.1037/abn0000820

Associations With Youth Psychotic-Like Experiences Over Time: Evidence for Trans-Symptom and Specific Cognitive and Neural Risk Factors

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The current study examined whether impairments in cognitive and neural factors at baseline (ages 9–10) predict initial levels or changes in psychotic-like experiences (PLEs) and whether such impairments generalize to other psychopathology symptoms (i.e., internalizing and externalizing symptoms). Using unique longitudinal Adolescent Brain Cognitive Development Study data, the study examined three time points from ages 9 to 13. Univariate latent growth models examined associations between baseline cognitive and neural metrics with symptom measures using discovery ($n = 5{,}926$) and replication ($n = 5{,}952$) data sets. For symptom measures (i.e., PLEs, internalizing, externalizing), we examined mean initial levels (i.e., intercepts) and changes over time (i.e., slopes). Predictors included neuropsychological test performance, global structural MRI, and several a priori within-network resting-state functional connectivity metrics. Results showed a pattern whereby baseline cognitive and brain metric impairments showed the strongest associations with PLEs over time. Lower cognitive, volume, surface area, and cingulo-opercular within-network connectivity metrics showed associations with increased PLEs and higher initial levels of externalizing and internalizing symptoms. Several metrics were uniquely associated with PLEs, including lower cortical thickness with higher initial PLEs and lower default mode network connectivity with increased PLEs slopes. Neural and cognitive impairments in middle childhood were broadly associated with increased PLEs over time, and showed stronger associations with PLEs compared with other psychopathology symptoms. The current study also identified markers potentially uniquely associated with PLEs (e.g., cortical thickness). Impairments in broad cognitive metrics, brain volume and surface area, and a network associated with information integration may represent risk factors for general psychopathology.

General Scientific Summary

This study provides support for both shared and specific risk factors for psychopathology. Greater early psychosis spectrum symptoms over time showed specific associations with several lower brain metrics. Across all types of symptoms, there was also evidence for shared associations, including with lower cognitive functioning, with the strongest associations generally found for psychosis spectrum symptoms.

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We thank the families participating in the Adolescent Brain and Cognitive Development study. We greatly appreciate the consultations with Joshua Jackson regarding the development of the latent growth models.

Data used in the preparation of this article were obtained from the Adolescent Brain Cognitive Development (ABCD) Study (https://abcdstudy.org), held in the NIMH Data Archive (NDA). This is a multisite, longitudinal study designed to recruit more than 10,000 children aged 9–10 and follow them over 10 years into early adulthood. The ABCD Study is supported by the National Institutes of Health and additional federal partners under award numbers U01DA041022, U01DA041028, U01DA041048, U01DA041089, U01DA041106, U01DA041117, U01DA041120, U01DA041134, U01DA041148, U01DA041156, U01DA041174, U24DA041123, U24DA041147, U01DA041093, and U01DA041025. A full list of supporters is available at https://abcdstudy.org/federal-partners.html. A listing of participating sites and a complete listing of the study investigators can be found at https://abcdstudy.org/Consortium_Members.pdf. ABCD consortium investigators designed and implemented the study and/or provided data but did not necessarily participate in the analysis or writing of this report. This manuscript reflects the views of the authors and may not reflect the opinions or views of the NIH or ABCD consortium investigators. The ABCD data repository grows and changes over time. The ABCD data used in this report came from https://doi.org/10.15154/1523041.

This work was supported by the National Institute on Drug Abuse (U01 DA041120 to Deanna M. Barch) and the National Institute of Mental Health (K23MH121792-01 and L30 MH120574-01 to Nicole R. Karcher, T32 MH126368 to Brent I. Rappaport).

Nicole R. Karcher, Jaisal Merchant, Brent I. Rappaport, and Deanna M. Barch report no biomedical financial interests or potential conflicts of interest.

The manuscript contains original work that has not been published or submitted for publication elsewhere. All procedures were approved by the institutional review board at each Adolescent Brain Cognitive Development collection site (WUSTL IRB: 201708123; https://abcdstudy.org/study-sites/).

Data and research materials are available at https://doi.org/10.15154/1523041. Analyses from this manuscript were presented at Flux 2021 Congress.

Nicole R. Karcher served as lead for conceptualization, data curation, formal analysis, visualization, writing–original draft, and writing–review and editing. Deanna M. Barch provided supervision. Jaisal Merchant contributed toward writing–original draft. Jaisal Merchant, Brent I. Rappaport, and Deanna M. Barch contributed toward writing–review and editing.

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Keywords: psychotic-like experiences, internalizing, externalizing, Adolescent Brain Cognitive Development study, trans-symptom

Supplemental materials: https://doi.org/10.1037/abn0000820.supp

The development of childhood psychopathology symptoms over time can be at least partially understood within a multilevel developmental psychopathology perspective (e.g., Calkins & Fox, 2002; Cicchetti et al., 2008), which posits that multiple contributors from different levels of biological and environmental influence interact in the development of psychopathology symptoms. However, symptoms often show a lack of stability across childhood psychopathology domains and can wax and wane over a period of months and years prior to the development of psychiatric disorders (Costello & Angold, 2016), including psychotic disorders (Lieberman & First, 2018). Furthermore, cognitive and neural risk factors often do not correspond to established diagnostic boundaries, but instead frequently correlate with several psychopathology domains (McTeague et al., 2016).

It is important to understand factors associated with variation in symptoms over time, especially prior to the onset of diagnosable disorders. It is critical to examine risk factors in middle childhood, prior to changes (e.g., neurological, hormones, etc.) that occur during adolescence that may further alter etiological pathways (Costello et al., 2007). Understanding the unique and overlapping ways in which risk factors are associated with various forms of psychopathology during this age would further our understanding of symptoms and aid in early identification and intervention efforts (Okuzawa et al., 2014; van der Gaag et al., 2013). The current study therefore utilized three waves of the unique longitudinal Adolescent Brain Cognitive Development (ABCD) Study data to examine factors associated with trajectories of psychopathology symptoms in middle childhood and early adolescence.

The current study focused on examining psychotic-like experiences (PLEs), internalizing, and externalizing symptoms, as previous research using factor analyses suggests the structure of psychopathology may be best fit in terms of a three-factor model that encompasses these three psychopathology domains (Kotov et al., 2011; Wright et al., 2013). PLEs are commonly experienced by the general population, especially in childhood, with some evidence that as many as 61% of children report at least one PLE (Karcher, Loewy, et al., 2020). There are several reasons that it may be important to examine PLEs over time, especially in childhood and adolescence. There is evidence that PLEs decrease in prevalence from childhood to adulthood, as these experiences transition from being somewhat developmentally normative to more indicative of psychopathology (Downs et al., 2013). Persistence of PLEs over time may distinguish between developmentally normative PLEs and those that are associated with the later onset of psychiatric disorders (Dominguez et al., 2011). Recent research also indicates that PLEs may be a transdiagnostic marker of psychopathology (Guloksuz et al., 2020; van Os & Reininghaus, 2016), as opposed to being uniquely associated with psychosis.

Internalizing symptoms (i.e., depression, anxiety) and externalizing symptoms (i.e., attention deficit hyperactivity, conduct problems), can also represent significant forms of psychopathology with onsets often in childhood and adolescence (Kessler et al., 2007). Internalizing symptoms in childhood and adolescence can constitute a significant mental health difficulty that may interfere with social and school functioning (Merikangas et al., 2010; Ramsawh et al., 2010). Furthermore, for a subset of youth, these symptoms persist and can be associated with the development of both internalizing and other related disorders (Fergusson et al., 2005; Hirshfeld-Becker et al., 2019). For many youth externalizing symptoms peak in adolescence and then decline, although for a subset they persist through adulthood (Moffitt et al., 2001). As with PLEs, it may be critical to understand how these symptoms change over the course of late childhood into early adolescence, as there is evidence that symptoms that persist may be associated with a later transition to more severe and clinical forms of externalizing problems (Beauchaine & McNulty, 2013). While previous studies have examined PLEs, (Kalman et al., 2019; Zhang et al., 2019), internalizing (Kuang & Flouri, 2020; Nivard et al., 2017; Papachristou & Flouri, 2020; Whittle et al., 2020), and externalizing symptoms (Flouri et al., 2019; Kuang & Flouri, 2020; Nivard et al., 2017; Papachristou & Flouri, 2020) over time, the current study is the first examining whether PLEs over time show stronger associations with baseline cognitive and neural correlates compared with the other symptom domains.

Several cognitive and neural risk factors likely interact in the development of psychopathology. Presumably many biological markers are both equifinal (i.e., many risk factors can result in the same psychopathology domain) and multifinal (e.g., the same risk factor can result in the development of multiple domains of psychopathology; Cicchetti & Rogosch, 1996). For example, brain volume may be a multifinal risk factor, whereby reduced volumes are associated with a range of psychopathology, including PLEs, internalizing, and externalizing symptoms. On the other hand, factors such as reduced cortical thickness, cortical volume, and a range of cognitive indices may all be equifinal antecedents of PLEs (Alkan et al., 2021; Ehrlich et al., 2012). The current study therefore examined associations between cognitive and neural risk factors with PLEs, internalizing symptoms, and externalizing symptoms to begin to elucidate whether any factors are uniquely associated with changes in PLEs, versus whether any factors represent broader trans-symptom markers of psychopathology.

Consistent with the multilevel developmental psychopathology perspective, there is evidence that PLEs, as well as internalizing and externalizing symptoms are all associated with several cognitive and neural correlates. Each of these symptom domains has been associated with lower overall cognitive functioning (Papachristou & Flouri, 2020; Racz et al., 2017; Sheffield et al., 2018), including executive functioning deficits in particular (Fusar-Poli et al., 2012; Sheffield et al., 2018; Weyandt et al., 2014). Longitudinal studies have also suggested that changes in symptoms are associated with cognitive functioning (Flouri et al., 2019; Kuang & Flouri, 2020). Further, all three symptom domains are associated with structural

neural impairments (e.g., reduced cortical volume and thickness), with some evidence for longitudinal associations between increased symptoms and increased structural impairments (Cannon et al., 2015; Whittle et al., 2020). There is also evidence that each symptom domain, as well as psychopathology in general (Karcher, Michelini, et al., 2020), is associated with resting state functional connectivity impairments in several networks, including default mode (i.e., a network associated with attention to internal states; Chabernaud et al., 2012; Karcher et al., 2019), frontoparietal (i.e., a network engaged in attention-demanding tasks; Fair et al., 2012; Whitfield-Gabrieli et al., 2020), ventral attention (i.e., a network associated with bottom-up attention; Dong et al., 2018; Sanefuji et al., 2017; Sylvester et al., 2013), and cingulo-opercular (i.e., a network associated with information integration and salience attribution; Karcher et al., 2019; Satterthwaite et al., 2015) networks. Further, changes in internalizing and externalizing symptoms are associated with altered connectivity to frontal regions (Barch et al., 2018; Chahal et al., 2020) and ventral attention networks (Afzali et al., 2020).

The current study examine whether risk factors during middle childhood, specifically cognition and neural metrics at baseline, are associated with PLEs, internalizing symptoms, and externalizing symptoms over time, using three ABCD Study time points from ages 9 to 13. It was expected that in general, the cognitive and neural metrics would show a gradient of impairment, whereby initial levels and changes over time for each symptom domain would show associations with lower cognitive scores and neural metrics at baseline, but that changes in PLEs would be associated with the greatest impairments in these risk factors.

Method

Participants

The ABCD Study is a large-scale study tracking 9–10-years-olds recruited from 21 research sites across the United States. The current data release, ABCD Data Release 4.0 (https://doi.org/10.15154/1523041) includes three full waves of data: baseline ($N = 11{,}878$), 1-year follow-up ($N = 11{,}235$), and 2-year follow-up ($N = 10{,}416$; Table 1 in the online supplemental materials for sample characteristics). These data were accessed from the National Institutes of Mental Health Data Archive (described in the author note; see online supplemental materials for study-wide exclusion details). All available data were used in analyses and missing data were handled using maximum likelihood estimation.

Measures

Symptom Measures

As a measure of PLEs, youth completed the Prodromal Questionnaire-Brief Child Version (PQ-BC), a 21-item self-report questionnaire previously validated for use with school-age children using the ABCD sample (Karcher et al., 2018; Karcher, Loewy, et al., 2020), which asks about positive PLEs (e.g., unusual, thought content, perceptual abnormalities) in the past month (see online supplemental materials for additional information). Consistent with this previous research (Karcher et al., 2018), distress scores were calculated as the total number of endorsed questions weighted by level of distress (i.e., 0 = *no*, 1 = *yes* [but no distress], 2–6 = *yes* [1 + score on distress scale]).

The current study also utilized the internalizing and externalizing scale raw scores from an abbreviated form of the Youth Self Report, the youth-rated Brief Problem Monitor (BPM; Achenbach et al., 2011). The BPM is administered at the 6-month follow-up (and every 6 months after including the 2-year follow-up) and asks youth to rate 19 items assessing current psychopathology (i.e., within the past 6 months) on a 0 (*not true*) to 2 (*very true or often true*) scale.

The PQ-BC was completed at baseline and the BPM was completed at 6-month follow-up (PLE $\omega = 0.83$; BPM $\omega = 0.67$), 1-year follow-up (PLE $\omega = 0.84$; BPM $\omega = 0.81$), and 2-year follow-up (PLE $\omega = 0.81$; BPM $\omega = 0.80$).

Neuropsychological Test Battery

Analyses examined the seven individual National Institutes of Health Toolbox Cognitive Battery (NIHTB-CB) and both fluid and crystalized composite scores at baseline (Weintraub et al., 2013). The current study utilized uncorrected NIHTB-CB scores, but all analyses include age and sex as covariates.

Structural MRI Measures

For the current study, baseline structural MRI measures include total volume (intracranial, cortical, and subcortical; Fischl et al., 1999), surface area (Chen et al., 2012), and cortical thickness (Fischl & Dale, 2000). All data were acquired on a 3T scanner (Siemens, General Electric, or Phillips) with a 32-channel head coil and completed T1-weighted and T2-weighted structural scans (1 mm isotropic). Structural neuroimaging processing was completed using FreeSurfer version 5.3.0 through standardized processing pipelines (Hagler et al., 2019; see the online supplemental materials for additional details). Participants that did not pass FreeSurfer Quality Control measures (i.e., at least one T1 scan that passed all quality control metrics) were excluded from analyses ($n = 142$).

Resting State Functional Connectivity

Participants completed four 5-min resting-state BOLD scans, with their eyes open and fixated on a crosshair (see the online supplemental materials for additional information). Resting-state image parameters varied by 3T scanner and have been previously detailed (https://abcdstudy.org/images/Protocol_Imaging_Sequences.pdf). The current study utilized the baseline tabulated ABCD Study resting state functional connectivity (RSFC) data, created by calculating correlation values between each pair of functionally defined parcels within predefined networks (Gordon et al., 2016; Figure 1 in the online supplemental materials). Consistent with previous research (Cortese et al., 2012; Karcher et al., 2019; Sylvester et al., 2013), we examined the cingulo-opercular (CON), default mode (DMN), frontoparietal (FPAR), and ventral attention (VAN) within-network connectivity data. Participants were removed from analyses in the current study for not having at least one resting state scan that passed quality assurance criteria ($n = 605$).

Statistical Analysis

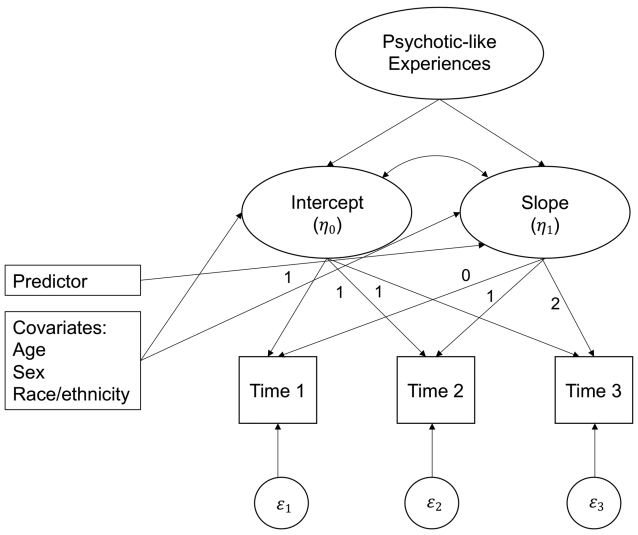
We first examined how best to model symptoms over the three time points (i.e., baseline, 1-year follow-up, 2-year follow-up). Using univariate latent growth curve models, we examined models that estimated the slope, intercept, variance, and covariance for each individual symptom domain (i.e., each symptom domain was estimated separately). For each symptom domain, we first examined a series of stepwise tests. We examined several common model fit indices including the Comparative Fit Index (CFI), Tucker–Lewis Index (TLI), Bayesian Information Criterion (BIC), and root mean square error of approximation (RMSEA) for four progressively less restrictive models (i.e., by progressively freely estimating the slope latent factor mean, slope variance, and slope-intercept covariance; see online supplemental materials for details). As can be seen in Table 2 in the online supplemental materials, for all symptoms, the freely estimated/least restrictive model provided the best fit, showing improvements in CFI, TLI, BIC, and RMSEA (see Figure 1 for an example model). Of note, when including all three symptom indices in the same model to examine general psychopathology models, models showed poor fit (see Table 2 in the online supplemental materials).

For the best-fitting models for each symptom type, we examined whether mean changes in symptoms (i.e., as indexed by the slope of the symptom across the three time points) as outcomes were associated with baseline indices of cognition and neural metrics as predictors. Models then examined whether mean initial baseline symptoms (i.e., as indexed by the intercept) as outcomes were associated with baseline indices of cognition and neural metrics modeled as predictors. We examined the fluid and crystallized cognitive composites, as well as the seven individual NIH Toolbox tests. We examined global structural metrics: ICV, total cortical and subcortical volume, total surface area, and total cortical thickness. Based on previous research (Chabernaud et al., 2012; Dong et al., 2018; Fair et al., 2012; Karcher et al., 2019; Sanefuji et al., 2017; Satterthwaite et al., 2015; Sylvester et al., 2013; Whitfield-Gabrieli et al., 2020), models investigated within-network CON, DMN, FPAR, and VAN. We also examined whether the results remained consistent when including other symptoms, by analyzing whether results with PLEs remained significantly associated with these metrics when including either internalizing or externalizing symptoms. Results generally remained consistent when including only individuals with complete symptom data ($n = 8{,}355$; see Tables 3–4 in the online supplemental materials; also see Table 5 in the online supplemental materials for comparison of complete and missing samples).

All analyses included sex, race/ethnicity (i.e., a 5-level variable with Asian, Black, Hispanic, Multiracial/Multiethnic, and White categories, factor coded with the largest group [White] as the reference group), and age at baseline as time-invariant covariates (RSFC metric models additionally included head motion), with family unit and the 21 ABCD Study sites included as random intercepts. We used ComBat harmonization (https://github.com/ncullen93/neuroCombat), with age and sex added as biological covariates to the design matrix, to estimate and remove individual scanner effects (i.e., using Siemens, Phillips, and GE device serial numbers) from MRI measures prior to entry into models.

We first randomly split the data into discovery ($n = 5{,}926$) and replication ($n = 5{,}952$) data sets. All analyses were first conducted in the discovery data set. Results from the discovery data set were false discovery rate (FDR) corrected across all models within a symptom type (e.g., 18 FDR corrections for PLEs), separately for slopes and intercepts. We then examined whether the results replicated in the replication data set. Results were considered to replicate if: (a) they were FDR$p < .05$ in the discovery data set and (b) $p < .05$ in the replication data set (Tables 6–7 in the online supplemental materials). Follow-up analyses examined interactions with sex (Tables 8–10 in the online supplemental materials) and models covarying for either intracranial value in other structural MRI metric models or inclusion of caregiver years of education in cognitive metric models (Tables 11–12 in the online supplemental materials).

Figure 1
Example Univariate Latent Growth Curve (LGC) Model Examining Psychotic-Like Experiences



Note. This LGC modeled slope and intercept, and examined whether slope as outcome was associated with a predictor of interest (e.g., fluid cognition), when accounting for age, sex, and race/ethnicity as covariates. LGC = latent growth curve.

Transparency and Openness

Sample size determinations, data exclusions, and all included measures are reported above. Data and research materials are available at https://doi.org/10.15154/1523041. Data were analyzed using R Version 3.6.1. Analyses were conducted using the lavaan package in R (Rosseel, 2012). The study design and analysis were not preregistered.

Results

Model estimates indicated that PLEs and internalizing symptoms on average decreased over time, whereas externalizing symptoms slightly increased over time. For all symptom types, there was a negative association between initial values and symptom changes over time (see Table 13 in the online supplemental materials). See Table 1 in the online supplemental materials for baseline sample characteristics and symptom measure descriptive statistics across all three waves (see Figure 2 in the online supplemental materials for symptoms across

Table 1

Associations Between Initial Individually Modeled Symptoms (i.e., Intercepts) and Indices of Function, Cognition, and Neural Metrics in the Discovery Data Set[a]

	PLEs				Externalizing symptoms				Internalizing symptoms			
Model predictor	Estimate	*SE*	*Z*	FDR*p*	Estimate	*SE*	*Z*	FDR*p*	Estimate	*SE*	*Z*	FDR*p*
					Cognition							
Fluid (n = 11,630)	**−1.311**[b,c]	**0.107**	**−12.218**	**1.29E−05**	**−0.185**	**0.025**	**−7.516**	**2.00E−05**	**−0.23**	**0.025**	**−9.106**	**2.25E−05**
Crystallized (n = 11,686)	**−1.303**[b,c]	**0.106**	**−12.315**	**1.29E−05**	**−0.129**	**0.024**	**−5.351**	**2.00E−05**	**−0.2**[d]	**0.025**	**−7.95**	**2.25E−05**
Picture vocabulary (n = 11,718)	**−1.286**[b,c]	**0.106**	**−12.15**	**1.29E−05**	**−0.092**	**0.024**	**−3.911**	**1.38E−04**	**−0.17**[d]	**0.025**	**−6.802**	**2.25E−05**
List sorting (n = 11,669)	**−1.188**[b,c]	**0.109**	**−10.855**	**1.29E−05**	**−0.163**	**0.024**	**−6.713**	**2.00E−05**	**−0.227**[d]	**0.025**	**−9.008**	**2.25E−05**
Card sorting (n = 11,713)	**−0.97**[b,c]	**0.11**	**−8.858**	**1.29E−05**	**−0.172**	**0.025**	**−7.014**	**2.00E−05**	**−0.181**	**0.025**	**−7.108**	**2.25E−05**
Pattern (n = 11,694)	**−0.71**[c]	**0.096**	**−7.421**	**1.29E−05**	**−0.112**	**0.023**	**−4.881**	**2.00E−05**	**−0.124**	**0.023**	**−5.289**	**2.25E−05**
Picture (n = 11,706)	**−0.801**[b,c]	**0.1**	**−8.034**	**1.29E−05**	**−0.096**	**0.023**	**−4.197**	**4.86E−05**	**−0.11**	**0.024**	**−4.58**	**2.25E−05**
Flanker (n = 11,712)	**−0.503**[b,c]	**0.104**	**−4.846**	**1.29E−05**	**−0.07**	**0.025**	**−2.855**	**5.54E−03**[f]	**−0.089**	**0.026**	**−3.425**	**1.64E−03**
Reading (n = 11,704)	**−0.938**[b,c]	**0.101**	**−9.308**	**1.29E−05**	**−0.128**	**0.024**	**−5.39**	**2.00E−05**	**−0.172**	**0.025**	**−6.931**	**2.25E−05**
					MRI							
Structural MRI												
ICV (n = 11,486)	**−0.525**[b,c]	**0.111**	**−4.714**	**1.29E−05**	**−0.103**[e]	**0.026**	**−4.006**	**1.01E−04**	**−0.068**	**0.027**	**−2.479**	**.01**[f]
Cortical volume (n = 11,486)	**−0.726**[b,c]	**0.111**	**−6.527**	**1.29E−05**	**−0.144**[e]	**0.026**	**−5.594**	**2.00E−05**	**−0.067**	**0.026**	**−2.53**	**.01**[f]
Subcortical volume (n = 11,486)	**−0.671**[b,c]	**0.111**	**−6.031**	**1.29E−05**	**−0.131**[e]	**0.025**	**−5.201**	**2.00E−05**	**−0.091**	**0.027**	**−3.327**	**1.64E−03**
Cortical thickness (n = 11,486)	**−0.263**[b,c]	**0.097**	**−2.715**	**8.40E−03**	0.027	0.024	1.136	.28	0.033	0.025	1.309	.21
Surface area (n = 11,486)	**−0.679**[b,c]	**0.113**	**−6.006**	**1.29E−05**	**−0.176**[e]	**0.026**	**−6.805**	**2.00E−05**	**−0.093**	**0.027**	**−3.431**	**1.64E−03**
					RSFC							
CON (n = 10,943)	**−0.568**[b,c]	**0.126**	**−4.501**	**1.29E−05**	**−0.073**	**0.03**	**−2.402**	**.02**[f]	**−0.092**	**0.029**	**−3.116**	**3.00E−03**[f]
DMN (n = 10,947)	**−0.246**[b,c]	**0.11**	**−2.229**	**.03**[f]	−0.023	0.027	−0.851	.40	−0.01	0.026	−0.389	.70
FPAR (n = 10,950)	−0.13	0.12	−1.085	.29	0.056	0.031	1.812	.08	0.035	0.028	1.235	.23
VAN (n = 10,946)	−0.143[b]	0.141	−1.019	.31	−0.042	0.026	−1.61	.12	−0.044	0.028	−1.549	.15

Note. PLEs = psychotic-like experiences; $Z = Z$ statistic; FDRp = false discovery rated-corrected p-value; Y2 = 2-year follow-up; MRI = magnetic resonance imaging; ICV = intracranial volume; CON = cingulo-opercular; DMN = default mode network; FPAR = frontoparietal; VAN = ventral attention network; RSFC = resting state functional connectivity.

[a] Findings that replicate in the replication data set are in bold. Follow-up analyses examined whether standardized estimates significantly differed from one another using Meng's Z test (Meng et al., 1992). [b] Follow-up analyses indicated PLEs were significantly stronger than externalizing symptoms. [c] Follow-up analyses indicated PLEs were significantly stronger than internalizing symptoms. [d] Follow-up analyses indicated internalizing symptoms were significantly stronger than externalizing symptoms. [e] Follow-up analyses indicated externalizing symptoms were significantly stronger than internalizing symptoms. [f] If using Bonferroni ($p < .002$) instead of FDR for multiple comparison correction, this test would no longer survive multiple comparison correction.

the three waves). Below we present findings that passed FDR$p < .05$ in the discovery data set (Tables 1 & 2) and were $p < .05$ in the validation data set (Tables 6–7 in the online supplemental materials). See Table 14 in the online supplemental materials for associations with covariates, and Tables 15–16 in the online supplemental materials for results when examining models without covariates.

Cognition

As can be seen in Tables 1 & 2, lower scores on all cognitive composites and individual tests were associated with higher initial (i.e., intercept) PLEs, and externalizing and internalizing symptoms. These metrics were only associated with greater PLEs symptoms over time (i.e., slope), and not externalizing or internalizing symptoms over time (Figure 2). However, *higher* crystallized cognition composite, as well as the picture vocabulary and reading individual tests, at baseline was associated with greater internalizing symptoms over time. As can be seen in Tables 1 and 2, PLEs generally showed the strongest associations compared to both internalizing and externalizing symptoms, with internalizing symptoms showing stronger associations compared to externalizing symptoms for several metrics (e.g., slopes with crystalized metrics).

For initial levels of internalizing symptoms, follow-up analyses revealed there was an interaction between sex and several cognitive indices (crystallized composite, as well as picture vocabulary and reading tests; see Table 8 in the online supplemental materials), whereby the association between lower cognitive scores and greater initial internalizing symptoms was weaker for females than males (Table 10 in the online supplemental materials). After the inclusion of caregiver years of education in follow-up analyses, many results remained consistent, although notably several results changed for externalizing symptoms with crystalized cognitive metrics (Table 11–12 in the online supplemental materials).

MRI Metrics

Lower intracranial, cortical, and subcortical volume, and surface area at baseline were associated with higher initial PLEs, externalizing, and internalizing symptoms (Table 1; Figure 3). Structural MRI metrics were only associated with higher PLEs over time, and not externalizing or internalizing symptoms over time (Figure 2). Further, lower cortical thickness was only associated with PLEs, including greater initial PLEs. After accounting for ICV, several associations with volume, especially subcortical

Table 2

Associations Between Changes Over Time in Individually Modeled Symptoms (i.e., Slopes) and Indices of Function, Cognition, and Neural Metrics in the Discovery Data Set[a]

Model predictor	PLEs				Externalizing symptoms				Internalizing symptoms			
	Estimate	*SE*	*Z*	FDR*p*	Estimate	*SE*	*Z*	FDR*p*	Estimate	*SE*	*Z*	FDR*p*
Cognition												
Fluid (n = 11,630)	**−0.427**[b,c]	**0.058**	**−7.311**	**3.00E−05**	−0.016	0.014	−1.171	.43	0.013	0.015	0.876	.46
Crystallized (n = 11,686)	**−0.385**[b,c]	**0.061**	**−6.362**	**3.00E−05**	0.007	0.013	0.527	.68	**0.08**[d]	**0.016**	**5.171**	**9.00E−05**
Picture vocabulary (n = 11,718)	**−0.417**[b,c]	**0.058**	**−7.151**	**3.00E−05**	0.01	0.013	0.802	.58	**0.078**[d]	**0.015**	**5.149**	**9.00E−05**
List sorting (n = 11,669)	**−0.328**[b,c]	**0.059**	**−5.566**	**3.00E−05**	−0.007	0.014	−0.524	.68	0.006	0.015	0.405	.73
Card sorting (n = 11,713)	**−0.361**[b,c]	**0.058**	**−6.194**	**3.00E−05**	−0.023	0.014	−1.698	.29	0.009	0.014	0.661	.57
Pattern (n = 11,694)	**−0.209**[b]	**0.052**	**−4.007**	**1.57E−04**	−0.033	0.013	−2.598	.08	0.002	0.014	0.123	.90
Picture (n = 11,706)	**−0.248**[b,c]	**0.051**	**−4.831**	**3.00E−05**	0.007	0.012	0.587	.68	0.016	0.014	1.165	.33
Flanker (n = 11,712)	**−0.206**[b,c]	**0.057**	**−3.593**	**5.35E−04**	0.014	0.014	0.976	.50	0.021	0.015	1.391	.28
Reading (n = 11,704)	**−0.224**[b,c]	**0.058**	**−3.832**	**2.54E−04**	0.001	0.013	0.105	.92	**0.06**[d]	**0.015**	**3.975**	**4.20E−04**
MRI												
Structural MRI												
ICV (n = 11,486)	**−0.152**[b]	**0.059**	**−2.581**	**.01**[e]	−0.014	0.014	−1.044	.49	0.031	0.016	1.94	.13
Cortical volume (n = 11,486)	**−0.205**[b]	**0.059**	**−3.494**	**7.14E−04**	−0.027	0.014	−1.945	.23	**0.041**[d]	**0.016**	**2.624**	**.04**[e]
Subcortical volume (n = 11,486)	**−0.229**[b,c]	**0.06**	**−3.799**	**2.61E−04**	−0.021	0.014	−1.54	.29	0.03	0.016	1.83	.16
Cortical thickness (n = 11,486)	−0.097[b]	0.05	−1.941	.06	0.002	0.013	0.181	.91	0.031	0.015	2.094	.13
Surface area (n = 11,486)	**−0.187**[b]	**0.058**	**−3.218**	**1.38E−03**	−0.037	0.014	−2.642	.08	0.025	0.016	1.524	.26
RSFC												
CON (n = 10,943)	**−0.225**[b,c]	**0.059**	**−3.789**	**1.71E−04**	−0.025	0.017	−1.445	.30	−0.03	0.015	−1.987	.13
DMN (n = 10,947)	**−0.127**	**0.057**	**−2.222**	**.03**[e]	−0.024	0.016	−1.51	.29	−0.02	0.014	−1.359	.28
FPAR (n = 10,950)	−0.105	0.061	−1.711	.09	0.04	0.017	2.375	.11	0.019	0.015	1.229	.33
VAN (n = 10,946)	−0.054	0.081	−0.663	.51	−0.024	0.015	−1.633	.29	−0.013	0.014	−0.939	.45

Note. PLEs = psychotic-like experiences; $Z = Z$ statistic; FDRp = false discovery rated-corrected p-value; MRI = magnetic resonance imaging; ICV = intracranial volume; CON = cingulo-opercular; DMN = default mode network; FPAR = frontoparietal; VAN = ventral attention network; RSFC = resting state functional connectivity.

[a] Findings that replicate in the replication data set are in bold. Follow-up analyses examined whether standardized estimates significantly differed from one another using Meng's Z test (Meng et al., 1992). [b] Follow-up analyses indicated PLEs were significantly stronger than externalizing symptoms. [c] Follow-up analyses indicated PLEs were significantly stronger than internalizing symptoms. [d] Follow-up analyses indicated internalizing symptoms were significantly stronger than externalizing symptoms. [e] If using Bonferroni ($p < .002$) instead of FDR for multiple comparison correction, this test would no longer survive multiple comparison correction.

volume, were reduced, most strongly for externalizing and internalizing symptoms (Tables 11–12 in the online supplemental materials), indicating results may be more attributable to whole brain volume. Effects were generally strongest for PLEs compared with both internalizing and externalizing symptoms, especially for intercepts, with externalizing symptoms showing stronger associations compared with internalizing symptoms for volume metrics (Tables 1 and 2).

Resting State Functional Connectivity

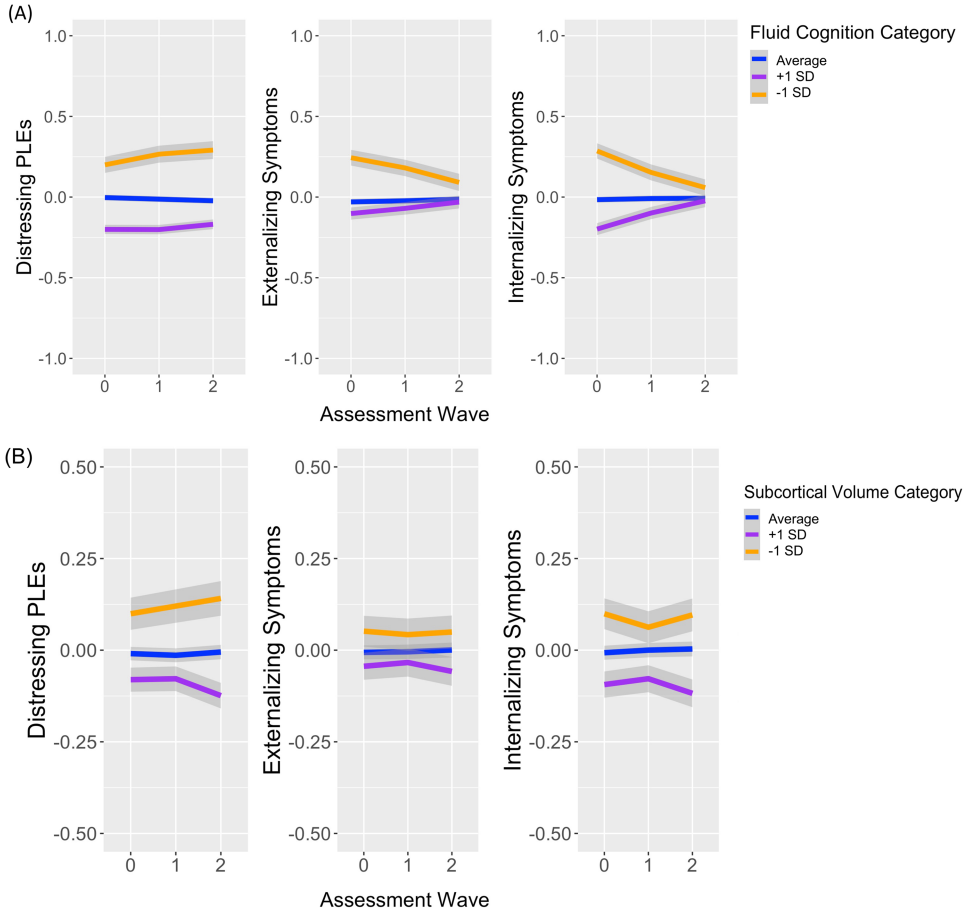
As can be seen in Table 1 and Figure 3, lower CON within-network connectivity at baseline was associated with higher initial levels of PLEs, externalizing, and internalizing symptoms, but were only associated with greater PLEs over time. Additionally, lower DMN within-network connectivity at baseline was only associated with greater PLEs over time. When comparing the magnitude of these effects, effects were stronger for PLEs than for both internalizing and externalizing symptoms.

Discussion

The current study provides several novel and important insights about cross-sectional and longitudinal associations between symptoms with a number of cognitive and neural metrics. The results contribute to the ongoing conversation about unique and overlapping risk factors for psychopathology, highlighting the importance of examining symptoms over time (Nivard et al., 2017). Several patterns emerged across cognitive and neural markers. Across the board, PLEs showed the strongest and broadest associations with impairments across both cognitive and neural markers. A number of these markers also showed evidence of trans-symptom associations (i.e., associations with more than one symptom domain), including each of the cognitive composites and individual tests, volume and surface area metrics, and within-network cingulo-opercular connectivity. However, these markers generally showed the *strongest* associations with PLEs, including PLEs over time (i.e., slopes), as well as initial (i.e., intercepts) internalizing and externalizing symptoms. The current study also found several markers uniquely associated with PLEs. Specifically, only PLEs slopes were associated with lower within-network DMN connectivity, and only initial PLEs were associated with lower cortical thickness. These results are generally consistent with a multilevel developmental psychopathology perspective (Calkins & Fox, 2002; Cicchetti et al., 2008), suggesting several equifinal metrics are associated with PLEs slopes as well as initial externalizing and internalizing symptoms. Further, many cognitive and structural neural metrics showed evidence of multifinality, as they were associated with multiple domains of psychopathology. Below, more in-depth discussion of these findings is organized from risk factors showing the broadest symptom associations to

Figure 2

Depictions of Associations Between Symptom Changes Over the Three Assessment Waves for PLEs, Internalizing, and Externalizing Symptoms (Standardized Within Assessment Wave) With Baseline (panel A) Fluid Cognition and (panel B) Subcortical Volume



Note. For the purpose of this figure, fluid cognition and subcortical volume metrics are partitioned into low (−1 *SD*), average, and high (+1 *SD*) groups. PLE = psychotic-like experience. See the online article for the color version of this figure.

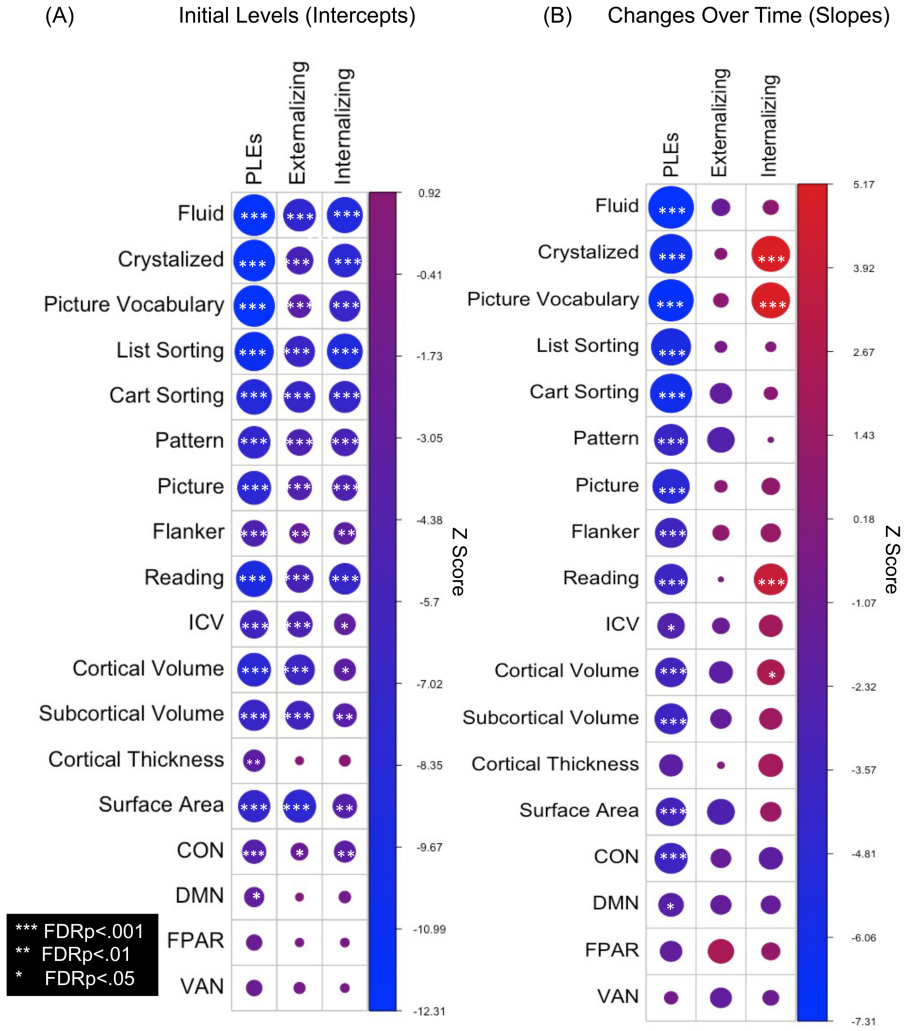
cognitive and neural factors showing more specific associations with symptoms.

There were a number of cognitive and structural metrics that showed trans-symptom impairments. Specifically, these metrics showed evidence of associations with changes in PLEs over time and initial levels of internalizing and externalizing symptoms. First, all cognitive metrics showed this pattern of trans-symptom impairment. This supports previous literature finding broad deficits across cognitive domains among clinical populations (McTeague et al., 2016; Snyder et al., 2015), as well as in individuals with attenuated symptoms (Romanowska et al., 2018; Tickell et al., 2019). This has led to a recent review underscoring the possibility of a "c" factor, or a generalized, transdiagnostic cognitive deficit (Abramovitch et al., 2021). Although the current sample included youth-endorsing symptoms and not necessarily diagnosable mental health concerns, the current study indicates that these broad trans-symptom cognitive deficits are apparent in youth aged 9–13. When comparing the relative size of the effects between symptom domains, while each cognitive composite and test showed evidence of trans-symptom impairments, the magnitude of these effects was largest for PLEs, consistent with previous work (Abramovitch et al., 2021). Additionally, if comparing the relative size of the effects across predictors (i.e., cognitive and neural metrics), fluid cognitive metrics, including executive functioning, were the largest, consistent with previous research (McTeague et al., 2016; Snyder et al., 2015). This information may help inform models of psychopathology development, whereby a foundational aspect of many disorders is cognitive deficits.

Indices of neural volume and surface area were also broadly associated with trans-symptom impairments. Specifically, structural MRI metrics were associated with both PLEs over time and initial externalizing and internalizing symptoms, with the exception of cortical thickness, which was only associated with initial levels of PLEs. These structural neural findings support research finding broad structural neural impairments across psychiatric disorders (Goodkind et al., 2015; McTeague et al., 2016). Although future

Figure 3

Summary of Results



Note. (Panel A) *Z*-score estimates for associations between initial (i.e., intercepts) PLEs, externalizing, and internalizing symptom with baseline cognitive and neural metrics. (Panel B) *Z*-score estimates for associations between PLEs, externalizing, and internalizing symptoms over time (i.e., slopes) with baseline cognitive and neural metrics. PLE = psychotic-like experience. See the online article for the color version of this figure.

research will need to examine whether these impairments show regional specificity (e.g., frontal, temporal), the current study is an important step in confirming broad volumetric and surface area impairments as markers of general psychopathology. The current study also found evidence for trans-symptom impairments in within-network cingulo-opercular connectivity, specifically associations with both PLEs over time and initial externalizing and internalizing symptoms. This network has been linked to information integration and associated with cognitive control abilities (Dosenbach et al., 2008), as well as evidence this network is associated with trans-diagnostic impairments (McTeague et al., 2016). More indirect evidence comes from previous meta-analyses finding that regions implicated in the cingulo-opercular network, including the dorsal anterior cingulate and insula, are associated with a broad range of psychiatric diagnoses (Goodkind et al., 2015).

These findings point to several broad pathophysiological impairments across domains of psychopathology. Speculatively, for individuals at risk for the development of psychopathology, genetics in combination with early impairments in cortical gyrification may lead to broad volumetric and surface area impairments (Garcia et al., 2018), as well as specifically impairments in within-network cingulo-opercular connectivity, which in turn may lead to broad cognitive impairments (Romer & Pizzagalli, 2021). Alternatively, it is impossible to rule out that environmental factors, including traumatic life events and deprivation, may have contributed to both psychopathology and the development of these pathophysiological impairments (Barch et al., 2018; McLaughlin et al., 2020). The results from this general population non-help-seeking sample also provide the opportunity for comparison with high-risk samples. The results show similarities to clinical high-risk for psychosis

studies (Lam et al., 2018; Seidman et al., 2016), including evidence for widespread cognitive and structural neural metric deficits in high-risk populations. Studies examining the risk for depression have often relied on samples with a family history of depression and have found evidence for smaller subcortical structures, including in the ABCD Study (Pagliaccio et al., 2020). Overall, these results are generally consistent with previous research and theory, indicating that there are consistent multifinal metrics that are associated with a range of psychopathology (Cicchetti & Rogosch, 1996; Elliott et al., 2018; Gibson et al., 2016).

Only changes in PLEs over time, as opposed to internalizing or externalizing slopes, were generally associated with cognitive and neural impairments. The findings are largely consistent with research indicating impairments in executive functioning, processing speed, and memory are associated with greater psychosis spectrum symptoms over time, even transition to psychotic disorders (Fusar-Poli et al., 2012; Sheffield et al., 2018). Findings also indicate that changes in psychosis spectrum symptoms over time are associated with a variety of structural abnormalities (Andreou & Borgwardt, 2020), including in volume metrics and thickness. Importantly, and consistent with previous research (Cannon et al., 2015), only PLEs were associated with lower cortical thickness. This adds to the growing evidence that cortical thickness may be a particularly important marker for the worsening of psychosis spectrum symptoms (Cannon et al., 2015; Ramanathan et al., 2017). Additionally, only PLEs over time were associated with lower DMN within-network connectivity, consistent with other psychosis spectrum research (Karcher et al., 2019; Satterthwaite et al., 2015) and potentially pointing to the importance of impairments in regions related to self-referential thoughts and internally generated thinking (Raichle, 2015) in the development of early psychosis spectrum symptoms. Associations between DMN with PLEs slopes were substantively reduced when simultaneously modeling either internalizing or externalizing symptoms, although associations between DMN with initial PLEs (i.e., intercepts) remained.

There may be several possible explanations for the limited findings for associations with internalizing and externalizing symptoms over time compared with PLEs over time. First, it may be the case that increased PLEs over time represent a more severe form of psychopathology, and this is reflected in the associations with a wide array of cognitive and neural metrics. Second, it is difficult to rule out the possibility that the results are partially attributed to other factors, including greater variability in PLE scores over time compared with the other symptom domains (Figure 2 in the online supplemental materials), with PLEs showing generally showing a decrease from baseline to 2-year follow-up. Third, it is possible that internalizing and externalizing symptoms may generally represent more stable trait-like phenomena, and therefore associations are generally found with intercepts instead of slopes, whereas PLEs are more variable phenomena and therefore show associations with both intercepts and slopes.

There were also several unique findings with internalizing symptoms. First, in contrast to findings for PLEs, better performance on several metrics including crystallized cognition and specifically picture vocabulary and reading were associated with *increased* youth-reported internalizing symptom slopes. The finding may reflect the possibility that increased cognitive functioning lends itself toward certain maladaptive thought patterns (e.g., rumination; Karpinski et al., 2018) that are associated with greater internalizing symptoms over time (Abela & Hankin, 2011; Liu et al., 2019). Further, it cannot be ruled out that individuals higher in crystallized intelligence may better articulate internal states related to internalizing symptoms (although interestingly, after accounting for caregiver education, increased externalizing symptom slopes were also associated with higher picture vocabulary scores). Second, when examining interactions with sex, findings indicated that for several cognitive indices, females compared with males showed a weaker association between increased initial internalizing symptoms and lower cognitive scores (Table 10 in the supplemental materials). Finding associations between lower crystallized cognitive metrics and higher initial internalizing symptoms are stronger for males compared with females is in line with previous findings of associations between cognition and depressive symptoms in males (Zammit et al., 2004). It may point to possible alternate factors (e.g., hormones) that may influence these relationships differently in males and females (Conley & Rudolph, 2009).

Limitations

It is possible that some results may be in part attributable to other factors, including variability in the reliability of measures or to factors such as head motion, although the use of a validation data set and inclusion of head motion as a covariate diminish these possibilities. Furthermore, the measure of PLEs was a self-report measure that was read to participants, rather than a clinician-rated interview. Additionally, the ABCD Study 4.0 data release did not contain information about meeting diagnostic criteria for mental disorders. Other limitations include that since there are only three waves of data, only certain types of longitudinal analyses can be conducted. More data are required to examine leading and lagging associations between symptoms with neural metrics and cognition. Future research will examine how longitudinal changes in neural and cognition markers are associated with symptoms. We did not examine this for several reasons, including that we were specifically interested in how symptoms over time related to baseline metrics. However, it is also the case that neural metrics were only measured every 2 years and the cognition battery exhibited some additions and deletions over time compared to the baseline assessment in the ABCD study, limiting some of the analyses that we can conduct. Future research should also examine multivariate approaches to examine the strongest cognitive and neural predictors of symptoms. Although the analyses utilized all available data, follow-up analyses comparing the individuals with complete versus missing data generally found similar results (see Tables 3–4 in the online supplemental materials) although found evidence that individuals with missing data on average showed higher symptoms scores, perhaps reflective of bias in the data which may have affected our results.

Overall, the current study provides important new information about the associations between various indices of psychopathology over time with cognitive and neural metrics. Perhaps most clearly, greater PLEs over time were associated with impairments across most metrics. For cognition, volume, surface area, and cingulo-opercular connectivity metrics, there was a gradient by which PLEs showed the greatest impairments, followed by initial levels of externalizing and internalizing symptoms. These results point to multiple cognitive and neural risk factors as potential contributors to the development of psychopathology in general,

with PLEs representing a more severe form of psychopathology. Other risk metrics appeared more consistent with specific markers for elevated PLEs over time, including lower cortical thickness. Overall, the research enhances our understanding of the nature of psychopathology in middle childhood and early adolescence. Different psychopathology domains showed far more shared risk factors than unique, although PLEs generally showed the broadest and greatest impairments across risk factors. These results are potentially supportive of early transdiagnostic identification and prevention efforts, with additional efforts working toward capitalizing on unique risk factors to aid in diagnostic specificity.

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Received February 18, 2022
Revision received December 21, 2022
Accepted January 6, 2023 ■