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Preterm birth associated alterations in brain structure, cognitive functioning and behavior in children from the ABCD dataset

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Abstract

Background. Preterm birth is a global health problem and associated with increased risk of long-term developmental impairments, but findings on the adverse outcomes of prematurity have been inconsistent.

Methods. Data were obtained from the baseline session of the ongoing longitudinal Adolescent Brain and Cognitive Development (ABCD) Study. We identified 1706 preterm children and 1865 matched individuals as Control group and compared brain structure (MRI data), cognitive function and mental health symptoms.

Results. Results showed that preterm children had higher psychopathological risk and lower cognitive function scores compared to controls. Structural MRI analysis indicated that preterm children had higher cortical thickness in the medial orbitofrontal cortex, parahippocampal gyrus, temporal and occipital gyrus; smaller volumes in the temporal and parietal gyrus, cerebellum, insula and thalamus; and smaller fiber tract volumes in the fornix and parahippocampal-cingulum bundle. Partial correlation analyses showed that gestational age and birth weight were associated with ADHD symptoms, picvocab, flanker, reading, fluid cognition composite, crystallized cognition composite and total cognition composite scores, and measures of brain structure in regions involved with emotional regulation, attention and cognition.

Conclusions. These findings suggest a complex interplay between psychopathological risk and cognitive deficits in preterm children that is associated with changes in regional brain volumes, cortical thickness, and structural connectivity among cortical and limbic brain regions critical for cognition and emotional well-being.

Introduction

Preterm birth (live birth before 37 weeks of pregnancy) is a common global health problem with an estimated prevalence of about 11% (Chawanpaiboon et al., 2019), and it is the leading cause of death among children younger than 5 years worldwide (Liu et al., 2016). Although technological and medical advances have increased the survival rates from preterm birth in recent years (Horbar et al., 2012), survivors remain at risk for long-term neurological and cognitive dysfunction (Mwaniki, Atieno, Lawn, & Newton, 2012).

According to the United States Centers for Disease Control (CDC), the mortality rate of extremely preterm infants was 64%, and 43% of survivors had a neurodevelopmental disorder (Younge, Goldstein, Cotten, & Network, 2017), including emotion regulation disorders. Studies also reported that 31% of surviving preterm children have cognitive deficits, manifested by lower executive function, processing speed, visuospatial and sensorimotor functions, and academic outcomes (Hirschberger et al., 2018; Marlow, Hennessy, Bracewell, Wolke, & Group, 2007); and a 'preterm behavioral phenotype' characterized by a tendency toward internalizing features (anxiety, depression), externalizing behaviors (aggression), poor concentration, and social difficulties (Johnson & Marlow, 2011) has also been reported. However,

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findings regarding preterm birth association with anxiety and depression are not always consistent (Johnson & Wolke, 2013), and some studies also showed increases in survival with normal neurodevelopment in preterm children (Younge et al., 2017). A systematic review proposed that preterm birth associated structural brain alterations may affect later socio-emotional development, cognitive function and psychopathological risk, which required more comprehensive assessments for replication and supports (Montagna & Nosarti, 2016).

Neuroimaging studies have reported that preterm birth results in brain structural abnormalities of white matter (WM), including reduced WM volume and thinning of WM tracts in a variety of brain regions (Alexandrou et al., 2014), as well as underdevelopment of gray matter (GM) including cerebral and cerebellar cortex, thalamus, hippocampus and basal ganglia (Keunen et al., 2012; Loh et al., 2020; Nosarti et al., 2008). Prematurity-induced alterations in these structures might persist into adolescence and adulthood (Bjuland, Rimol, Lohaugen, & Skranes, 2014), impacting cognitive and emotion regulation. Alterations in GM/WM volumes in temporal and frontal regions, thalamus, corpus callosum and fornix were associated with scores in intelligence quotient (IQ), and in tests of memory and executive function in preterm children (Nosarti et al., 2014). One study reported that emotion processing difficulties were associated with volumetric changes in the orbitofrontal cortex and fusiform gyrus in preterm children (Healy et al., 2013). However, studies also suggested that preterm birth do not simply result in GM and WM tissue loss, but in complicated patterns of cortical and subcortical alterations, including increased GM probability and WM excesses in the cingulate gyrus, temporal and frontal lobes, fusiform gyrus and cerebellum. Increased tissue probabilities in preterm children could be due to less efficient or delayed programmed cell death in selective developing cortices, or might reflect delayed processes of synaptic pruning (Nosarti et al., 2008). There are also reports of functional and structural hyperconnectivity in temporoparietal areas in preterm children with good neurobehavioral performance (Barnes-Davis, Merhar, Holland, & Kadis, 2018; Barnes-Davis, Williamson, Merhar, Holland, & Kadis, 2020*a*), as well as greater structural connectivity in extracallosal pathways, relative to controls, which was positively correlated with language performance (Barnes-Davis, Williamson, Merhar, Holland, & Kadis, 2020*b*), perhaps reflecting adaptive mechanisms to overcome neurological impairment associated with prematurity. These findings warrant replication to investigate preterm birth-associated regional brain volume alterations and its potential long-term effects on neurodevelopment (Keunen et al., 2012).

Therefore, the current study aimed to investigate developmental impairments in preterm children in the Adolescent Brain Cognitive Development (ABCD) cohort, which provides an unprecedented opportunity to conduct research in a large-scale, long-term longitudinal neuroimaging dataset. We assessed preterm birth-associated brain structural and comprehensive behavioral changes in 1706 preterm children from the ABCD dataset and explored the association between these brain structural changes and behavioral measures. We took advantage of the relatively large sample size afforded by the ABCD and used an exploratory approach that involved regional metrics of whole brain without defining specific regions of interest. We hypothesized that preterm birth-associated brain structural alterations might underlie the psychopathological risk and cognitive deficits.

Materials and methods

Data source

The ABCD study is an ongoing nationwide prospective observational assessment of brain development which contains data of 11 875 children aged 9–11 years recruited from 21 centers throughout the United States with a diverse range of geographic, socioeconomic, ethnic, and health backgrounds (Casey et al., 2018; Hagler et al., 2019). The 21 centers obtained parents' full written informed consent and the children's assent, and research procedures and ethical guidelines were followed in accordance with the Institutional Review Boards. As the largest known investigation of brain development in children, the ABCD study is conceived with the goal of understanding how adverse experiences and exposures affect the developing brain and associate with cognitive, mental health, social, emotional and academic outcomes, which may facilitate interventions to mitigate the consequences of childhood stressors (Hoffman et al., 2019).

Participants

The data used in the present study were selected from the Annual Curated Data Release 3.0 from the ABCD consortium (https://abcdstudy.org/index.html). We excluded preterm children with a history of traumatic brain injury, contraindications to MRI and incomplete information on behavioral data; 1706 subjects remained in the Preterm group and we randomly selected 1865 matched individuals as a Control group [age, gender, race/ethnicity, household income, highest education of caregiver, prenatal tobacco/alcohol or cannabis expose, body mass index (BMI), intracranial volume (ICV) and sites] (online Supplementary Figure S1).

Structural neuroimaging

MRI acquisition

The experiments were conducted at 21 ABCD sites using 3.0 Tesla (T) scanner platforms (Siemens Prisma, General Electric 750 and Phillips). The ABCD imaging protocol was harmonized across data collection sites for three 3 T scanning systems (Siemens Prisma, Philips, General Electric 750), all of which used standard adult-size multi-channel head coils and multiband echo planar imaging acquisitions. The scanning sequences that yield structural data (Casey et al., 2018) include a localizer, T-1 weighted scan, diffusion tensor imaging (DTI), and T-2 weighted scans. Real-time motion detection and correction during acquisition are implemented by customized hardware and software, and imaging parameters were harmonized as much as possible between scanner manufacturers. The T1 weighted images were acquired using a three-dimensional magnetization-prepared rapid-acquisition gradient echo sequence with a voxel size of 1 mm^3 and a T2 weighted axial fast-spoiled gradient echo sequence (repetition time [TR] = 2400–2500 milliseconds, echo time [TE] = 2–2.9 milliseconds, matrix size = 256 × 256, field of view = 256 × 240–256 mm^2, flip angle = 8°, inversion delay = 1060 milliseconds, and 176–225 sections). The diffusion weighted imaging scan with a single-shot spin-echo echo-planar-imaging sequence, and diffusion sensitizing gradients were applied along 96 non-collinear directions (6 directions with $b = 500$ s/mm^2, 15 directions with $b = 1000$ s/mm^2, 15 directions with $b = 2000$s/mm^2, and 60 directions with $b = 3000$ s/mm^2) with 7 acquisitions without diffusion weighting ($b = 0$ s/mm^2). The imaging parameters

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were 81 continuous axial slices, TR = 4100–5300 milliseconds, TE = 81.9–89 milliseconds, matrix size = 140 × 140, and field-of-view = 240 × 240 mm^2, resulting in 1.7-mm isotropic voxels. Additional details on participants, data collection and imaging preprocessing parameters are provided in the ABCD website (https://abcdstudy.org/scientists/protocols/).

Image processing

We used MRI data in the 2020 ABCD Annual Curated Data Release 3.0. Briefly, T1-weighted and T2-weighted images were processed and corrected for gradient nonlinearity distortions to generate structure MRIs to ensure reliability across multiple imaging sites (Jovicich et al., 2006). Firstly, T1-weighted images were volume registered by adjusting and maximizing the relative position and orientation of mutual information among images. Then, images were intensity nonuniformity corrected based on tissue segmentation and sparse spatial smoothing, and resampled with 1 mm isotropic voxels into alignment within the brain atlas. FreeSurfer image analysis software (Version 5.3.0, http://surfer.nmr.mgh.harvard.edu/) was used to perform the cortical reconstruction and volumetric segmentation, and cortical or subcortical regions were parcellated and labeled with atlas classification. Major white matter tracts were labeled with Atlas Track which is a probabilistic atlas-based method for automated segmentation of white matter fiber tracts (Hagler et al., 2009). sMRI images for each subject were nonlinearly registered to the atlas using discrete cosine transforms, and DTI-derived diffusion orientations were compared to the atlas fiber orientations for each subject to refine a priori tract location probabilities, individualizing the fiber tract ROIs and minimizing the contribution from regions that were inconsistent with the atlas. All results were freely available within the ABCD data release and detailed data preprocessing procedures were described in the image processing paper of the ABCD team (Hagler et al., 2019).

All data used in the current study were processed by the ABCD team and provided within the ABCD data release. Morphometric measures consisting of cortical volumes and thickness (68 regions) (Desikan et al., 2006), subcortical volumes (22 regions) (Fischl et al., 2002) and white matter fiber tract volumes (37 major white matter tracts) (Hagler et al., 2009) were used in subsequent analyses.

Behavior measures

Preterm indicators

Preterm children were defined as children who were born before 37 weeks of pregnancy had been completed based on the parent's or caregiver's retrospective report. Gestational age was only provided in preterm children, and birth weight and the information of child prenatal tobacco/alcohol or cannabis exposure were reported in all children (Paul et al., 2021).

Cognitive assessments

Cognitive performance was assessed using the National Institutes of Health Toolbox (NIHTB) Cognition Battery, a readily available, validated, and computer-based objective assessment of cognitive function in children (Luciana et al., 2018). NIHTB contains measurements of seven domains including language vocabulary knowledge, attention, cognitive control, working memory, executive function, episodic memory, and language. The fluid cognition composite (Fluidcomp) consists of five domains (attention, working memory, episodic memory, cognitive control, and executive function), the crystallized cognition composite (Cryst) consists of the remaining 2 domains (language vocabulary knowledge and language), and the total cognition composite (Totalcomp) consists of all seven domains.

Mental health assessments

The Parent Child Behavior Checklist was used to assess the dimensional psychopathology and adaptive functioning of children in the ABCD cohort (Cheng et al., 2021), including 10 syndrome scales related to psychopathological status: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, aggressive behavior, internalizing broad band score, externalizing broad band score and a psychopathological total score. In addition, it contains six DSM-Oriented Scales calculated from the questionnaire.

Statistical analysis

The SPSS Statistics (Version 22, IBM) was used to analyze the differences in behavior measures [psychopathological risk (20 variables) and cognitive function (10 variables) scores] and morphometric measures [cortical thickness/volume (68 variables), subcortical volume (22 variables) and fiber tract volume (37 variables)] between the Preterm and Control groups. In addition, a two-way ANOVA was implemented to model the effects of group (Preterm, Control) and sex (female, male) on those behavior and morphometric measures. Children's age, gender, race/ethnicity, household income, highest education of caregiver, prenatal tobacco/alcohol or cannabis expose, BMI, ICV, family structures and sites were included as covariates, and all statistical results were corrected for multiple comparisons using Bonferroni correction: psychopathological risk [$p < 0.0025/(0.05/20)$], cognitive function [$p < 0.005/(0.05/10)$], cortical thickness/volume [$p < 0.0007/(0.05/68)$], subcortical volumes [$p < 0.0023/(0.05/22)$] and fiber tract volume [$p < 0.0014/(0.05/37)$]. Furthermore, a linear mixed-effect model (LME) was used to reperform the analyses. As recommended by the ABCD website and reports in many studies (Cheng et al., 2021; Saragosa-Harris et al., 2022), the covariates were modeled as fixed effects and the family structure nested within sites were modeled as random effects. The effect size (Cohen's d) was obtained for each LME model to reflect differences between preterm and control groups, and Bonferroni corrections were used for multiple comparison. We also conducted multiple imputation analysis using SPSS, based on five replications and a chained equation approach method for regression model estimation. In multiple imputations, the predictors included all variables in demographic and clinical characteristics and behavior measures. The consistent controls were used to repeat the analyses with complete cases and multiple imputed data in the preterm group to avoid bias and tested the robustness as suggested (Sterne et al., 2009). Due to the disproportionate number of twins in the preterm group (Table 1), we examined the impact of twin status on the findings by reducing the twin pairs of preterm children to match that of full-term (Maes et al., 2023).

Partial correlation analysis was used to evaluate the associations between significantly different psychopathological risk (12 variables) and cortical thickness (5 variables)/cortical volume (6 variables)/subcortical volume (3 variables)/fiber tract volume (3 variables) with the above identical covariates, and all statistical results were corrected for multiple comparisons using Bonferroni correction ($p < 0.0008/0.0007/0.0014/0.0014$). The same correlation analysis and multiple comparison correction

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Table 1. Demographic and clinical information of Preterm and Control group

	Preterm ($N = 1706$)		Control ($N = 1865$)		
	(Mean ± S.E.)	Range	(Mean ± S.E.)	Range	p value
Age, y	10.01 (0.02)	8.92–11.00	10.03 (0.01)	8.92–11.00	0.364
Gender, n (%)					
Female	811 (47.5)	N/A	882 (47.3)	N/A	0.883[a]
Male	895 (52.5)	N/A	983 (52.7)	N/A	
BMI, kg/m^2	18.51 (0.10)	11.47–38.22	18.42 (0.08)	13.75–37.30	0.426
ICV, cm^3	1524.24 (3.73)	1014.91–2061.95	1530.10 (3.36)	1023.35–2068.55	0.243
Gestational age, week	32.1 (0.06)	24–36	N/A	N/A	N/A
Birth weight, pounds	4.95 (0.03)	2–9	6.71 (0.03)	3–11	<0.001
Twin status, n (%)					
Twins	987 (57.9)	N/A	507 (27.2)	N/A	<0.001[a]
No Twins	719 (42.1)	N/A	1358 (72.8)	N/A	
Prenatal tobacco/alcohol expose, n (%)					
Expose	537 (31.5)	N/A	605 (32.4)	N/A	0.538[a]
Unexpose	1169 (68.5)	N/A	1260 (67.6)	N/A	
Prenatal cannabis expose, n (%)					
Expose	89 (5.2)	N/A	92(4.9)	N/A	0.699[a]
Unexpose	1617 (94.8)	N/A	1773 (95.1)	N/A	
Race/Ethnicity, n (%)					
White	1103 (64.7)	N/A	1180 (63.3)	N/A	0.857[a]
Black	205 (12.0)	N/A	233 (12.5)	N/A	
Hispanic	234 (13.7)	N/A	254 (13.6)	N/A	
Asian	80 (4.7)	N/A	97 (5.2)	N/A	
Other	84 (4.9)	N/A	101 (5.4)	N/A	
Household income, $, n (%)					
<50 K	398 (23.3)	N/A	443 (23.7)	N/A	0.560[a]
50 K–100 K	1077 (63.1)	N/A	1149 (61.6)	N/A	
>100 K	231 (13.6)	N/A	273 (14.7)	N/A	
Highest education of caregiver, n (%)					
<High school	61 (3.6)	N/A	82 (4.3)	N/A	0.779[a]
High school diploma or GED	130 (7.6)	N/A	141 (7.6)	N/A	
Some college or associate degree	540 (31.6)	N/A	578 (31.0)	N/A	
Bachelor's degree	544 (31.9)	N/A	585 (31.4)	N/A	
Postgraduate degree	431 (25.3)	N/A	479 (25.7)	N/A	

[a]χ^2 test.
Abbreviation: BMI, body mass index; ICV, Intracranial volume.

were conducted between the above morphometric measures and cognitive function (6 variables) ($p < 0.0017/0.0014/0.0028/0.0028$). Correlations between gestational age/birth weight and the above behavior and morphometric differences (psychopathological risk/cognitive function/cortical thickness/cortical volume/subcortical volume/fiber tract volume) were assessed by partial correlation analysis and Bonferroni correction for multiple comparisons correction ($p < 0.0042/0.0083/0.010/0.0083/0.017/0.017$). In addition, we also used same analysis to check the association between above fiber tract volume (3 variables) and integrated cortical volume (68 variables)/subcortical volume (22 variables) ($p < 0.0002/0.0008$).

Results

Demographic characteristics

There were no significant differences in age, sex, race/ethnicity, household income, highest education caregiver, prenatal

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tobacco/alcohol or cannabis expose, BMI, and ICV between the Preterm and Control groups ($p > 0.05$; Table 1), consistent with the matching procedure.

Differences in behavioral measures

Compared to the Control group, the Preterm group showed significantly lower cognitive function including picvocab, flanker, reading, Fluidcomp, Cryst and Totalcomp scores ($p < 0.005$; Figure 1A and online Supplementary Table S1.1); and higher dimensional psychopathology scores, including anxious/depressed, withdrawn, somatic, social, attention, internalizing, stress, total problems and 4 DSM-Oriented scores (depressive, anxiety, somatic and ADHD problems) ($p < 0.0025$; Figure 1A and online Supplementary Table S1.2). The LME analyses and twin pairs-matched tests showed consistent results (online Supplementary Table S1.3-1.6). In addition, there were no significant interaction effects (group × sex) on psychopathological risk and cognitive function (online Supplementary Table S1.7-1.8), and the complete cases and multiple imputed data in the preterm group showed consistent results (online Supplementary Table S1.9-1.10).

Differences in morphometric measures

Compared to the Control group, the Preterm group showed significantly greater cortical thickness in the medial orbitofrontal cortex (mOFC), left parahippocampal gyrus (PHG_L), right lateral occipital gyrus (LOG_R) and left pericalcarine cortex (PCC_L) ($p < 0.0007$; Figure 1B and online Supplementary Table S2.1); smaller cortical volumes in the inferior parietal lobule (IPL), right middle temporal gyrus (MTG_R), left postcentral gyrus (PoCG_L), right insula (INS_R), and right supramarginal gyrus (SMG_R) ($p < 0.0007$; Figure 1B and online Supplementary Table S2.2); smaller subcortical volumes in the cerebellum white matter and right thalamus (THA_R) ($p < 0.0023$; Figure 1B and online Supplementary Table S2.3); as well as lower fiber tract volume in the left parahippocampal-cingulum (PHC_L), right fornix (FORX_ R) and right fornix column (FORX column_R) ($p < 0.0014$; Figure 1B and online Supplementary Table S2.4). In addition, the LME analyses and twin pairs-matched tests showed consistent results (online Supplementary Table S2.5-2.12), and the two-way ANOVA analysis showed no significant interaction effects (group × sex) on cortical thickness/volume, subcortical volume and fiber tract volume (online Supplementary Table S2.13-2.16). The complete cases and multiple imputed data in the preterm group showed consistent results (online Supplementary Table S2.17-2.20).

Associations between preterm indicators and behaviors/morphometric measures

In the Preterm group, gestational age was negatively correlated with ADHD symptoms ($p < 0.0042$; Figure 2A and online Supplementary Table S3.1) and Cryst scores ($p < 0.0083$; Figure 2A and online Supplementary Table S3.2). In addition, birth weight was positively correlated with picvocab, reading, Fluidcomp, Cryst and Totalcomp scores ($p < 0.0083$; Figure 2A and online Supplementary Table S3.3-3.4). The gestational age showed no associations with morphometric differences in the preterm group (Fig. 2A and online Supplementary Table S4.1-4.4); and birth weight was negatively associated with cortical thickness in the LOG_R and mOFC_L/R ($p < 0.010$; Figure 2A and online Supplementary Table S4.5), and positively associated with cortical volume in the IPL_L/R, PoCG_L and MTG_R ($p < 0.0083$; Figure 2A and online Supplementary Table S4.6) and subcortical volume in cerebellum white matter and THA_R ($p < 0.017$; Figure 2A and online Supplementary Table S4.7), as well as fiber tract volume in the PHC_L and FORX column_R ($p < 0.017$; Figure 2A and online Supplementary Table S4.8).

Associations between behaviors and morphometric measures

Correlation analysis between behaviors and morphometric measures showed that cognitive function measures including picvocab, flanker, reading, Fluidcomp, Cryst and Totalcomp scores were all positively associated with cortical thickness in the PHG_L ($p < 0.0017$; Figure 2B and online Supplementary Table S6.1), and picvocab and Cryst scores were positively associated with fiber tract volume in the FORX_R ($p < 0.0028$; Figure 2B and online Supplementary Table S6.4). In addition, fiber tract volume in the right fornix were correlated with cortical volumes in the PHG, MTG, PoCG and IPL, rostral middle frontal gyrus (rMFG), superior frontal gyrus (SFG), ($p < 0.0002$; online Supplementary Table S7.1); and were also significantly correlated with all subcortical volumes except the caudate, though most of these subcortical regions showed no difference between the preterm and control group ($p < 0.0008$; online Supplementary Table S7.2). The strongest of the correlations between fiber tract volume in the fornix was with thalamic and cerebral white matter volumes.

Discussion

In the current study, we investigated preterm birth-associated brain structural changes in a large sample of children using the ABCD dataset, and explored the associations between these brain structural changes and behavioral measurements. Results showed abnormal neurodevelopment and behaviors (i.e. higher risk of psychopathological problems and cognitive deficits), which were associated with gestational age and birth weight in preterm children. In preterm children relative to controls, brain imaging data showed higher cortical thickness in the mOFC, PHG, LOG and PCC; smaller cortical/subcortical volume in the temporal and parietal gyrus, cerebellum, insula and thalamus; and smaller fiber tract volume in the FORX and PHC, which are part of large networks important for memory and cognitive function, and involved in 'social brain' networks that underly socioemotional, mental health and cognitive function. These results highlight the impact of preterm birth on abnormal brain structural development and cognitive and emotional function.

Our data showed smaller cortical/subcortical and fiber tract volume, and higher cortical thickness in multiple preterm birth-associated abnormal regions. LME analyses and twin pairs-matched tests showed consistent results though there were slightly diminished effect sizes, and the complete cases and multiple imputed data in the preterm group showed consistent results, demonstrating the robustness of our findings. The current results suggested global maturation delay in the brain development of preterm children as the usual developmental trajectories in children aged 9–11 years showed an increase in mean cortical volume and a decrease in mean cortical thickness (Bethlehem et al., 2022; Nosarti et al., 2008). The significant correlations between birth weight and cortical and subcortical brain measures suggest that

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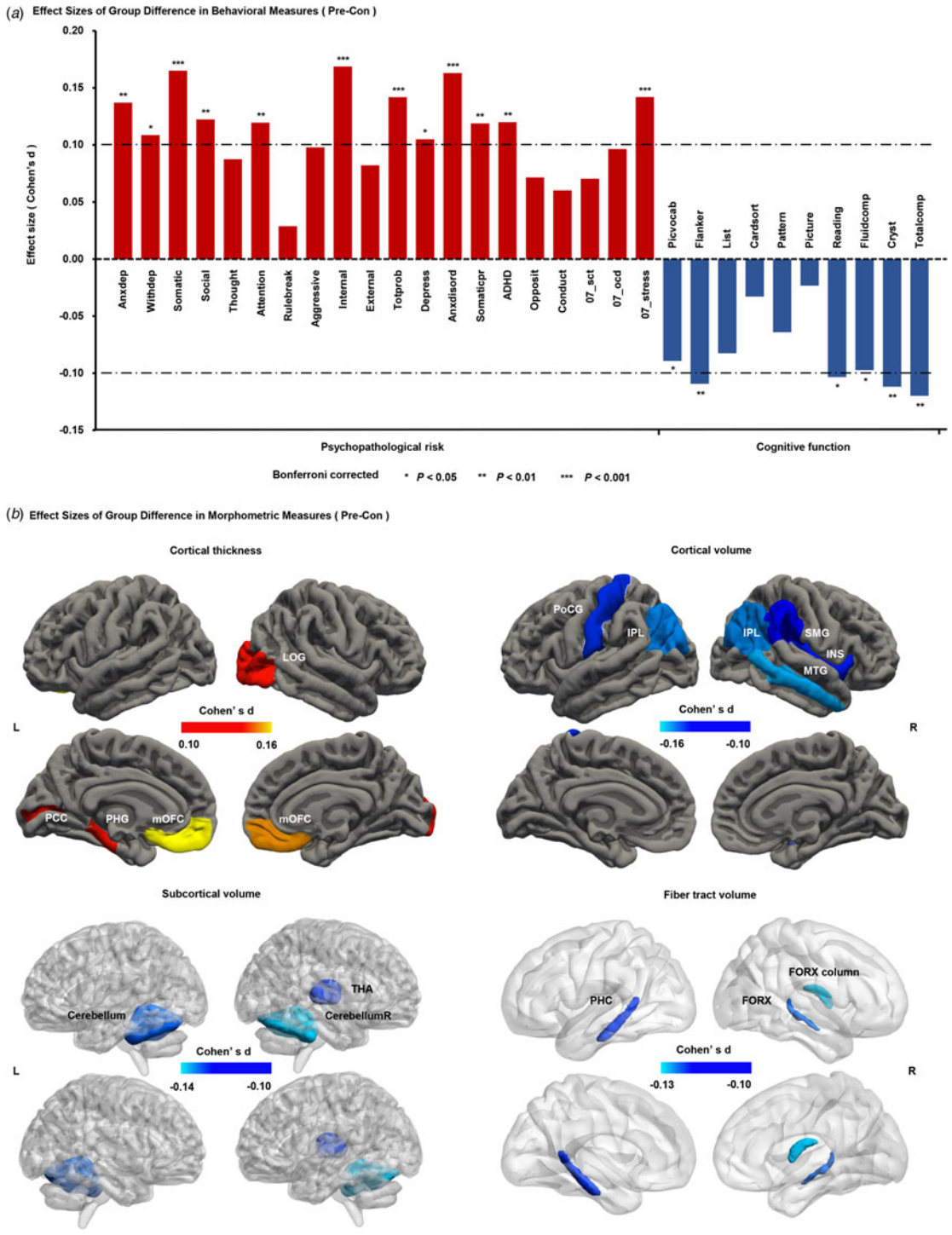

Figure 1. Group differences between the Preterm and Control group. (A) Effect sizes of group differences in behavioral measures (Bonferroni corrected, $p < 0.05$). (B) Effect sizes of group differences in morphometric measures (Bonferroni corrected, $p < 0.05$). The red color indicates Pre > Con and blue color indicates Pre < Con.Abbreviation: CBCL, Child Behavior Checklist; Anxdep, Anxious/Depressed CBCL Syndrome Scale; Withdep, Withdrawn/Depressed CBCL Syndrome Scale; Somatic, Somatic Complaints CBCL Syndrome Scale; Social, Social Problems CBCL Syndrome Scale; Thought, Thought Problems CBCL Syndrome Scale; Attention, Attention Problems CBCL Syndrome Scale; Rulebreak, Rule-Breaking Behavior CBCL Syndrome Scale; Aggressive, Aggressive Behavior CBCL Syndrome Scale; Internal, Internalizing Problems CBCL Syndrome Scale; External, Externalizing Problems CBCL Syndrome Scale; Totprob, Total Problems CBCL Syndrome Scale; Depress, Depressive Problems CBCL DSM-5 Scale; Anxdisord, Anxiety Problems CBCL DSM-5 Scale; Somaticpr, Somatic Problems CBCL DSM-5 Scale; ADHD, ADHD CBCL DSM-5 Scale; Opposit, Oppositional Defiant Problems CBCL DSM-5 Scale; Conduct, Conduct Problems CBCL DSM-5 Scale; 07_sct, Sluggish Cognitive Tempo (SCT) CBCL Scale2007 Scale; 07_ocd, Obsessive-Compulsive Problems (OCD) CBCL Scale2007 Scale; 07_stress, Stress Problems CBCL Scale2007 Scale; Nihtb, the National Institutes of Health Toolbox (NIHTB) Cognition Battery; Picvocab, Picture Vocabulary Test; Flanker, Flanker Inhibitory Control and Attention Test; List, List Sorting Working Memory Test; Cardsort, Dimensional Change Card Sort Test; Pattern, Pattern Comparison Processing Speed Test; Picture, Picture Sequence Memory Test; Reading, Oral Reading Recognition Test; Fluidcomp, Cognition Fluid Composite Score; Cryst, Crystallized Composite Language Score; Totalcomp, Cognition Total Composite Score; LOG, lateral occipital gyrus; PHG, parahippocampal gyrus; mOFC, medial orbitofrontal cortex; PCC, pericalcarine cortex; PoCG, postcentral gyrus; IPL, inferior parietal lobule; SMG, supramarginal gyrus; INS, insula; MTG, middle temporal gyrus; THA, thalamus; PHC, parahippocampal-cingulum; FORX, fornix.

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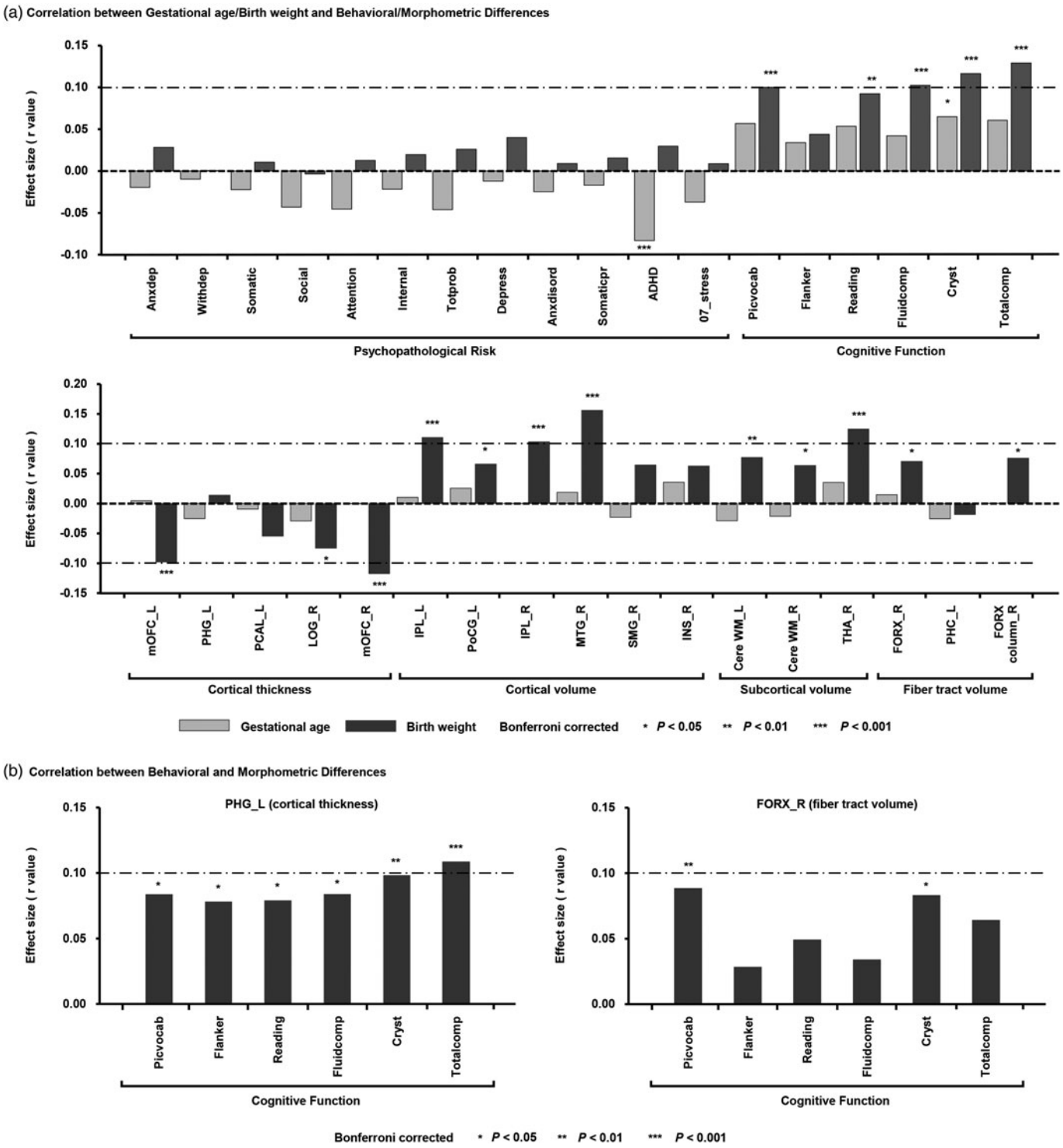

Figure 2. Correlation analysis in the Preterm group. (A) Partial correlation between gestational age/birth weight and behavioral/morphometric differences in the Preterm group (Bonferroni corrected, $p < 0.05$). (B) Partial correlation between behavioral and morphometric differences in the Preterm group (Bonferroni corrected, $p < 0.05$).Abbreviation: CBCL, Child Behavior Checklist; Anxdep, Anxious/Depressed CBCL Syndrome Scale; Withdep, Withdrawn/Depressed CBCL Syndrome Scale; Somatic, Somatic Complaints CBCL Syndrome Scale; Social, Social Problems CBCL Syndrome Scale; Attention, Attention Problems CBCL Syndrome Scale; Internal, Internalizing Problems CBCL Syndrome Scale; Totprob, Total Problems CBCL Syndrome Scale; Depress, Depressive Problems CBCL DSM-5 Scale; Anxdisord, Anxiety Problems CBCL DSM-5 Scale; Somaticpr, Somatic Problems CBCL DSM-5 Scale; ADHD, ADHD CBCL DSM-5 Scale; 07_stress, Stress Problems CBCL Scale2007 Scale; Nihtb, the National Institutes of Health Toolbox (NIHTB) Cognition Battery; Picvocab, Picture Vocabulary Test; Flanker, Flanker Inhibitory Control and Attention Test; Reading, Oral Reading Recognition Test; Fluidcomp, Cognition Fluid Composite Score; Cryst, Crystallized Composite Language Score; Totalcomp, Cognition Total Composite Score; LOG, lateral occipital gyrus; PHG, parahippocampal gyrus; mOFC, medial orbitofrontal cortex; PCC, pericalcarine cortex; PoCG, postcentral gyrus; IPL, inferior parietal lobule; SMG, supramarginal gyrus; INS, insula; MTG, middle temporal gyrus; THA, thalamus; PHC, parahippocampal-cingulum; FORX, fornix.

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there is an impact of preterm birth on long-term neurological development (Nosarti et al., 2008). In addition, lower fiber tract volumes in the fornix showed strong associations with cortical/subcortical WM and GM volumes. The fornix has structural connections with multiple brain regions (Catani, Howard, Pajevic, & Jones, 2002), thus a possible hypothesis is that developmental changes in the fornix may result in a cascade of alterations in many other regions (Hack & Taylor, 2000), which may be related to the timing of formation of axonal projections and primary connections between neurons. Abnormalities in neuronal migration may result in subsequent changes in axonal projections, WM and GM in preterm children (Nosarti et al., 2008). Furthermore, it is worth noting that brain measures were correlated with birth weight, but not gestational age. A recent study reported associations between continuously graded gestational stages and cortical volume in fronto-parieto-temporal areas by dividing the ABCD dataset into five groups based on gestational age (Ma et al., 2022). Critically, these findings of lower cortical volume and cognitive performance are consistent with our results, highlighting the reproducibility of our findings and the strength of open-source data in the ABCD study that allows researchers to approach similar questions from different perspectives.

The preterm group showed higher dimensional psychopathology risk and lower cognitive function scores compared to the controls. ADHD symptoms, picvocab, reading, Fluidcomp, Cryst and Totalcomp scores were significantly correlated with the gestational age and birth weight, suggesting the potential impact of preterm birth on long-term mental health and cognitive function development in preterm children (Arpi & Ferrari, 2013; Hutchinson, De Luca, Doyle, Roberts, & Anderson, 2013; Selten & Cantor-Graae, 2005). The altered brain developmental trajectories associated with preterm birth could also led to abnormal behaviors (Ball et al., 2015; Gimenez et al., 2006; Healy et al., 2013; Makinson & Huguenard, 2015; Pauly et al., 2008; Rogers et al., 2012). We speculate that smaller brain volumes in the orbitofrontal cortex, fornix, insula, temporal and parietal gyrus that may affect developing cognitive capacities resulting in poor performance in preterm children. In addition, preterm children had structural abnormalities in multiple brain regions related to ADHD problems, including frontal areas (dorsolateral prefrontal, orbitofrontal cortex), superior parietal areas, thalamus and caudate nucleus (Hart, Radua, Nakao, Mataix-Cols, & Rubia, 2013). Therefore we speculate that volumetric changes in these regions may contribute to persistent attentional deficits and impulsive behavior in preterm children (Durston, van Belle, & de Zeeuw, 2011).

Low cognitive scores were positively correlated with fiber tract volume in the FORX and PHC in the preterm children. The parahippocampal gyrus is part of a large network connecting temporal, parietal, and frontal cortical areas important for cognitive function including visuospatial processing (Stevens, Kahn, Wig, & Schacter, 2012) and episodic memory (Davachi, Mitchell, & Wagner, 2003). The fornix has multiple structural connections with the hippocampal formation, prefrontal cortex, anterior thalamus, as well as ventral striatum (Catani et al., 2002), which are associated with episodic memory, associative learning and visual recall functions (Aggleton & Brown, 1999, 2006). Studies showed activation in the hippocampal–fornix–anterior thalamus–prefrontal cortex recall network during learning (Aggleton & Brown, 1999, 2006), and there also reported the association between microstructural alterations in the fornix/cingulum and memory outcomes in preterm children (Caldinelli et al., 2017; Constable et al., 2008; Travis, Adams, Ben-Shachar, & Feldman, 2015). Furthermore, the positive associations between these cognitive scores and cortical thickness in the parahippocampal might reflect an adaptive mechanism for these preterm children (Barnes-Davis et al., 2020*a*). One study reported that when preterm birth was accompanied by severe brain injury, extensive plastic processes occurred in order to compensate for the effects of cell loss caused by the injury, demonstrating both specific deficits and adaptive developmental changes. These extra cells and synapses produced by the developing brain, which are normally later 'pruned', may provide the mechanism underlying enhanced early plasticity (Nosarti et al., 2008). Therefore, our findings may be related to the mechanism underlying enhanced early plasticity and global maturation delay in the brain development of preterm children. However, although studies suggested extensive compensatory processes in preterm infants with perinatal insult, our findings should be interpreted with caution due to lack of information on perinatal injuries.

Limitations

There were several limitations. Firstly, the prematurity, pregnancy or obstetrical variables, and newborn measures in the medical records were not provided in the ABCD study, which was a serious limitation and made our study more focused on whether preterm birth have brain structure and cognitive performance risk when the children reach aged 9–11 years old. In addition, the cross-sectional assessment limited the ability to make causal inferences. Therefore, the longitudinal component of ABCD will be essential to delineate causal longitudinal pathways. Furthermore, this study showed the impact of brain structural abnormalities on the risk of psychopathological problems and cognitive dysfunction in preterm children. Also, while we observed no differences in the prevalence between smoking and cannabis consumption between the mothers of premature and non-premature children, we cannot exclude the differences in the severity of exposure, which are associated with prematurity and neurodevelopment might have influenced our findings.

Conclusion

In summary, the current study investigated the impact of preterm birth on brain structure, cognitive performance and psychopathology in preterm children. Results showed that compared to controls, the preterm children exhibited higher risk of psychopathological problems and cognitive dysfunction, which were associated with brain structural changes in OFC, temporal gyrus, FORX and PHC.

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consortium investigators designed and implemented the study and/or provided data but did not necessarily participate in 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 NIMH Data Archive Digital Object Identifier (http://dx.doi.org/10.15154/1519007).

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