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ARTICLE

Association between parental age, brain structure, and behavioral and cognitive problems in children

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OBJECTIVE: To investigate the relation between parental age, and behavioral, cognitive and brain differences in the children.
METHOD: Data with children aged 9–11 of 8709 mothers with parental age 15–45 years were analyzed from the Adolescent Brain Cognitive Development (ABCD) study. A general linear model was used to test the associations of the parental age with brain structure, and behavioral and cognitive problems scores.
RESULTS: Behavioral and cognitive problems were greater in the children of the younger mothers, and were associated with lower volumes of cortical regions in the children. There was a linear correlation between the behavioral and cognitive problems scores, and the lower brain volumes ($r > 0.6$), which was evident when parental age was included as a stratification factor. The regions with lower volume included the anterior cingulate cortex, medial and lateral orbitofrontal cortex and amygdala, parahippocampal gyrus and hippocampus, and temporal lobe (FDR corrected $p < 0.01$). The lower cortical volumes and areas in the children significantly mediated the association between the parental age and the behavioral and cognitive problems in the children (all $p < 10^{-4}$). The effects were large, such as the 71.4% higher depressive problems score, and 27.5% higher rule-breaking score, in the children of mothers aged 15–19 than the mothers aged 34–35.
CONCLUSIONS: Lower parental age is associated with behavioral problems and reduced cognitive performance in the children, and these differences are related to lower volumes and areas of some cortical regions which mediate the effects in the children. The findings are relevant to psychiatric understanding and assessment.

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INTRODUCTION

Throughout the world, the trend in recent years has been for more parents to have a higher childbearing age [1]. However, it is estimated that ~16 million adolescents (15–19-years old) contribute to nearly 11% of all child births worldwide [2, 3]. There is some evidence that higher parental age at the time the children are born is associated with fewer behavioral conduct problems and better cognitive performance in the children [4]. There is also some evidence that a higher parental age can be associated with psychiatric problems such as schizophrenia and autism [5–8]; and low parental age with behavioral and emotional disorders [8]. Parental age at the birth of a child has also been found to be associated with children's brain development, with lower gray matter volumes in children of younger and older parents [9], with lower total brain volume in children of older fathers [10], and with higher volumes of the hippocampus and inferior frontal gyrus with higher paternal age [11]. However, most investigations did not analyse brain differences in the children of different parental ages, and how any such differences may be related to the cognitive and behavioral problems in the children.

The current investigation focuses on the relationship between parental age and children's behavioral problems and cognitive performance, and assesses whether there are differences in the brain volumes and cortical areas of different brain regions, and whether these endophenotypic factors mediate the individual variability in behavioral and cognitive problems. The hypotheses that we were able to investigate tested the following in this large-scale study: (1) There is a relationship between parental age, and cognitive performance and behavioral problems scores in the children. (2) There is a relation between parental age and brain structure in children. (3) Grouping the children based on their parental age as a stratification approach can help to reveal the association between brain structure, and the cognitive performance and behavioral problems scores in the children. (4) Some brain regions of the children have structural differences that mediate the association between parental age and the children's behavior. It is of importance to understand which brain regions are involved, as this may provide evidence relevant to understanding any differences in behavior found. We used a large sample of more than 11,000 children aged 9–11 from the Adolescent Brain Cognitive

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Developmental (ABCD) study and showed clear relations not only between the parental age and behavioral problems of children, but also between the parental age and cognitive performance, and how the cortical area and brain volume are different in the children of different parental ages. We also controlled for several characteristics that might be relevant, such as the children's age, gender, body mass index, race, neuroimaging scanning site, and parents' income and academic performance. A strength of the current investigation is the much larger number of participants than previous investigations, and also the analysis of brain differences at the voxel level.

MATERIALS AND METHODS

Participants and data preprocessing

This study used the data from the ABCD Study annual release 2.01 (https://abcdstudy.org/scientists/data-sharing/), held in the NIMH Data Archive (NDA). A total of 11,897 participants aged between 9 and 11 years was involved in release 2.01 of the ABCD study, which was a large longitudinal study that recruited children across 21 research sites across the US [12]. The ABCD investigators obtained written and oral informed consent from all the parents and children, respectively [13]. More details of the subjects, and the collection and preprocessing parameters of the data are provided at the ABCD website (https://abcdstudy.org/scientists/protocols/) and elsewhere [14]. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All the details of the ethics principles and process of the ABCD cohorts are described here [15]. The details of the participants and data preprocessing of this study are described in the Supplementary Methods. Data of 8709 children were used in our analysis. The demographic characteristics of these participants are summarized in Table S1. The distribution of the number of participants in each age group shown separately for maternal and paternal age are shown in Fig. S1.

Behavioral measures

Maternal and paternal ages assessments. Maternal and paternal ages were defined as the age of the biological mother and father at the time of the child's birth, which is available in the ABCD Developmental History Questionnaire (dhx01).

Cognitive performance assessments. We investigated the relationship between parental age and cognitive performance. Cognitive abilities were assessed by the ABCD *Youth NIH TB Summary Scores* (abcd_tbss01) which consists of 10 validated and reliable psychometric test scores: Picture Vocabulary Test Score; Flanker Inhibitory Control and Attention Test Score; List Sorting Working Memory Score; Dimensional Change Card Sort Test Score; Pattern Comparison Processing Speed Test Score; Picture Sequence Memory Test Score; Oral Reading Recognition Test Score; Cognition Fluid Composite Score; Crystallized Composite Score; Cognition Total Composite Score [16, 17]. A high score means better cognitive ability. More details of the cognitive performance scores can be found in Table S2.

Behavioral problems assessments. We also investigated the relationship between parental age and behavioral problems. The Parent Child Behavior Checklist Scores (abcd_cbcls01) contains eight empirically based syndrome scales related to psychiatric problems: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior. Internalizing and externalizing scores were derived from the following syndrome scores: anxious/depressed, withdrawn/depressed, somatic complaints, rule-breaking behavior and aggressive behavior. The behavioral problems total score is calculated by the sum of these sub-scores. A high score indicates dimensional psychopathology. The scores are useful in evaluating many aspects of the mental health of children and have been widely used in previous ABCD studies [18–20]. More details of the behavioral scores can be found in Table S2.

Association analysis

A general linear model (GLM) was used to test the association of the maternal and paternal age with the brain morphometric measurements, and with the cognitive performance and behavioral problems scores noted above that are provided by ABCD. Although a linear mixed effect model was recommended by the ABCD and used in other studies [14, 21], in the analysis of vertex-wise brain imaging data, the linear mixed effect model was computationally infeasible for such high-dimensional data. Instead, we selected the first child per family to eliminate any possible effects of correlations in the observations if they were from the same family, and used a computationally feasible GLM to perform the vertex-level association analysis. Specifically, a generalized linear regression model, $y = \beta_1 x + \beta_2 x^2 + \varepsilon$, was used to test whether the measures of interest (y) of the children were associated with the maternal and paternal age (x). A brain morphometry measurement or behavioral score was modeled as the dependent variable, and the nuisance covariates to be regressed out were modeled as fixed effects. Similarly, we used the GLM model to test the association of maternal age and paternal age with the ASEG [22] subcortical brain volume. The following variables were used as nuisance covariates of no interest: children's age, sex, body mass index, race (coded as 3-column dummy variables as provided in ABCD, namely White, Black, and American Indian and others), parents' income, parents' number of years of education, the scanning site of the structural neuroimaging, parental relationship status (coded as 0/1), and whether the child was born prematurely (coded as 0/1, as set out in the 'ABCD Developmental History Questionnaire'). These confounding variables were regressed out in all analyses. Any missing data of continuous variables were replaced with the mean value of the available data. The information on missing data is provided in Table S3. An F-statistic was obtained for each GLM to reflect the association of the parental age and the brain morphometric measurements or behavioral score. False discovery rate (FDR) was used to correct for multiple comparisons across all vertices. It should be noted that the maternal age and paternal age were modeled independently in the analysis.

Stratified analysis

Since both brain structure and behavioral problems are associated with parental age, we further investigated whether the difference of behavioral problems of children with different parental age can be related to the difference of brain structure of children. In a stratification approach, the children in this investigation were divided into 14 groups to test the hypothesis that grouping the children based on their parental age can increase the association between brain structure, and cognitive performance and the behavioral problems scores in the children. The 14 groups contain data for mothers in year groups of 2 years each starting at age 18. (For the groups at each end the numbers of mothers with age <18 and with age >41 are small, and so the first group contained mothers aged 15–17 and the last group contained mothers aged 42–45.) These groups were used for statistical comparisons except where stated. With the children divided into 14 groups based on the children's maternal age, we averaged the brain measures and behavioral problems scores and cognitive performance scores within each group, and then investigated the associations at the group level between the brain measures of the children and the behavioral problems and cognitive performance scores. To test the hypothesis that the children of teenaged mothers have lower cognitive performance and higher behavioral problems scores than the children of older mothers, we combined the first two groups 15–17 years and 18–19 years (based on the guidelines of CDC [23] who grouped 15–19-year-old mothers as teenaged mothers) and compared the cognitive performance, the behavioral problems scores, and brain area and volume of the children to the children of those with older maternal age. The nuisance covariates of no interest described above were also incorporated in this stratified analysis, so that these factors of no interest did not contribute to the results of the stratified analysis. The distributions of the numbers of children in each group separated by maternal age are shown in Fig. S1.

Mediation analysis

A standard mediation analysis was performed using the Mediation Toolbox developed by Tor Wager's group (https://github.com/canlab/MediationToolbox), which has been widely used in many neuroimaging studies [24–26]. A standard 3-variable path model was used here [27], with the detailed methodology description in the supplementary material of [24]. Briefly, mediation analysis tests whether the association between two variables can be explained by a third variable (the mediator). The hypothesis tested here was whether the mean cortical area and volume of the significant brain regions were mediators between the parental age and cognitive measure total score (NIH TB Summary Score) and the behavioral problems total score (TotProb CBCL Syndrome Scale). Confounding variables as in the association analysis were regressed out in the mediation model. The mediation analysis was performed at the level

of the individual child in the 8709 participants. The significance of the mediation was estimated by the bias-corrected bootstrap approach (with 10,000 random samplings).

RESULTS

Maternal and paternal ages were associated with behavioral problems and cognitive performance

Figure 1 shows the relationship between the behavioral problems and cognitive performance of the children and the maternal and paternal ages at the time of the child's birth. The generalized linear regression model test showed that the behavioral problems of the children showed a relationship with the maternal age ($F = 20.5$, $p = 1.3 \times 10^{-9}$), and also with the paternal age ($F = 22.6$, $p = 1.7 \times 10^{-11}$). We note that the maternal age and the paternal age are correlated, $r = 0.78$, so these are not presented as being independent of each other. Figures 1A and 2 show that the behavioral problems total score was significantly higher for the maternal ages of 15–17 and 18–19 compared to the groups with older maternal age. The results for different behavioral problems sub-scores are shown in Fig. 1C and show that all sub-scores in children with maternal age between 15–17 and 18–19 were significantly higher compared with the groups with older maternal age. For example, the measure of rule-breaking in the children (cbcl_scr_syn_rulebreak) of the mothers aged 15–17 was 27.7% higher compared with the 32–33 year group ($t = 4.0$, $p = 7.8 \times 10^{-5}$, Cohen's $d = 0.31$, significant after FDR correction); and 28.3% higher compared with the 34–35 year old group ($t = 4.0$, $p = 7.3 \times 10^{-5}$, Cohen's $d = 0.32$, significant after FDR correction). The depressive symptom score (cbcl_scr_syn_withdep) in the children of the mothers aged 18–19 was 71.8% higher compared with the group with mothers aged 34–35 ($t = 4.3$, $p = 2.0 \times 10^{-5}$, Cohen's $d = 0.27$, significant after FDR correction); and was 56.9% higher compared with the group with mothers aged 32–33 ($t = 3.7$, $p = 2.1 \times 10^{-4}$, Cohen's $d = 0.23$, significant after FDR correction). The effects were large, such as the 71.4% higher depressive problems score, and 27.5% higher rule-breaking score, in the children of mothers aged 15–19 than the mothers aged 34–35 (Fig. 1), with these differences very significant (Fig. 2).

The cognitive performance total scores of children showed a very significant relationship with both the maternal age ($F = 13.4$, $p = 1.5 \times 10^{-6}$) and paternal age ($F = 9.5$, $p = 7.8 \times 10^{-5}$) at the time of the child's birth, see Table S4. Figures 1B and 2 show that the children's cognitive performance total score was significantly lower for maternal ages of 15–17 and 18–19 compared to all the groups older than 24 years except the oldest group. For example, the cognitive performance total score of children with 15–17 maternal age was 6.4% lower compared with the 30–31 year group ($t = -3.6$, $p = 3.4 \times 10^{-4}$, Cohen's $d = -0.28$, significant after FDR correction). The cognitive performance total score of children with 18–19 maternal age was 5.2% lower compared with the 30–31 year maternal age group ($t = -3.8$, $p = 1.7 \times 10^{-4}$, Cohen's $d = -0.23$, significant after FDR correction). The most significant item, the picture vocabulary test score (nihtbx_picvocab), in the children of the teenaged mothers (15–17) was 5.6% lower compared with the group with mothers aged 36–37 ($t = -4.1$, $p = 3.7 \times 10^{-5}$, Cohen's $d = -0.35$, significant after FDR correction); and 6.5% lower compared with the group with mothers aged 38–39 ($t = -4.6$, $p = 4.9 \times 10^{-6}$, Cohen's $d = -0.40$, significant after FDR correction).

A similar association pattern was also identified in the analysis between behavioral and cognitive problems and the paternal age (Fig. 1). Further, we note that the parent's income and education were also associated with parental age with r values ranging from 0.13 to 0.17 (all $p < 0.001$). A stratified analysis showed that a similar association pattern was found for groups separated by high vs low income, and high vs low number of years of education (Fig. S2). We further note that the associations shown in Fig. 1 were made clear by the use of stratification into groups by age.

Maternal and paternal ages associated with cortical area and volume

The generalized linear model showed that maternal age also showed a significant relationship with both the total cortical volume ($F = 10.6$, $p = 2.6 \times 10^{-5}$) and area ($F = 6.4$, $p = 1.7 \times 10^{-3}$) of the children (Fig. 1E). The total cortical volume and area were significantly lower in the children of the younger mothers. As shown in Fig. 3A, the lower areas were especially of the medial temporal lobe (parahippocampal gyrus and hippocampus) and temporal pole, medial and lateral orbitofrontal cortex and amygdala, anterior cingulate cortex and adjoining medial prefrontal cortex, and postcentral cortex (FDR corrected $p < 0.01$). Similar brain regions had cortical volumes that were associated with the maternal age (FDR corrected $p < 0.01$, Fig. S3A). A similar association pattern was also identified in the analysis between brain structure and the paternal age (Fig. 3B and Fig. S3B). The subcortical volume associated with maternal age is shown in Table S5.

We also investigated the association between maternal and paternal age, and brain structure adjusted for the age of the other parent (Fig. S4). As shown in Fig. S4, the relationship was similar to Fig. 3. The maternal age was still associated with lower area of the anterior temporal lobe, antero-medial prefrontal cortex and lateral orbitofrontal cortex when the paternal age was regressed out. The paternal age was no longer associated with cortical area if the maternal age was regressed out.

In addition, we also analyzed the linear (parental age) and quadratic (parental age*parental age) effects between parental age and brain structure. As shown in Figs. S5 and S6, the pattern of linear and quadratic effects were very similar, including the medial temporal lobe, temporal pole, medial and lateral orbitofrontal cortex and anterior cingulate cortex, etc., which is also consistent with the findings shown in Fig. 3.

Correlation between behavioral and cognitive problems, and low cortical volume and area, in the children of different maternal ages

With the children divided into 14 groups based on children's maternal age, both the behavioral problems and the cognitive performance were significantly correlated with both the cortical area and the cortical volume of the children. Fig. 4A shows that there was a linear negative correlation between the behavioral problems total score and the mean cortical area ($r = -0.61$, FDR corrected $p < 0.05$) and the mean cortical volume ($r = -0.60$, FDR corrected $p < 0.05$) with grouping across different maternal ages. Figure 4B shows that there was also a significant positive correlation between the cognitive total score and the mean cortical area ($r = 0.69$, FDR corrected $p < 0.05$) and cortical volume ($r = 0.67$, FDR corrected $p < 0.05$) with grouping across different maternal ages. That is, there is an approximately linear relationship between the high behavioral problems and low cognitive performance scores in the children with cortical area and volume in the children, using grouping across different maternal ages. What is shown in Fig. 4A can be understood by the high negative correlation between behavioral problems and cortical area ($r = -0.81$, $p = 4.3 \times 10^{-4}$) in the children shown in Fig. S7 when the data are grouped by cortical area into 14 groups, and the finding that behavioral problems are related to maternal age shown in Fig. 1. What is shown in Fig. 4B can be understood by the high positive correlation between cognitive total score and cortical area ($r = 0.90$, $p = 9.5 \times 10^{-6}$) in the children shown in Fig. S7 when the data are grouped by cortical area into 14 groups, and the finding that cognitive score is related to maternal age shown in Fig. 1. For comparison, the correlations with cortical area and volume without grouping across the 8709 participants are shown in Fig. S8. Figure S9 shows that it is particular brain regions in which the cortical areas are related to behavioral problems and cognitive performance.

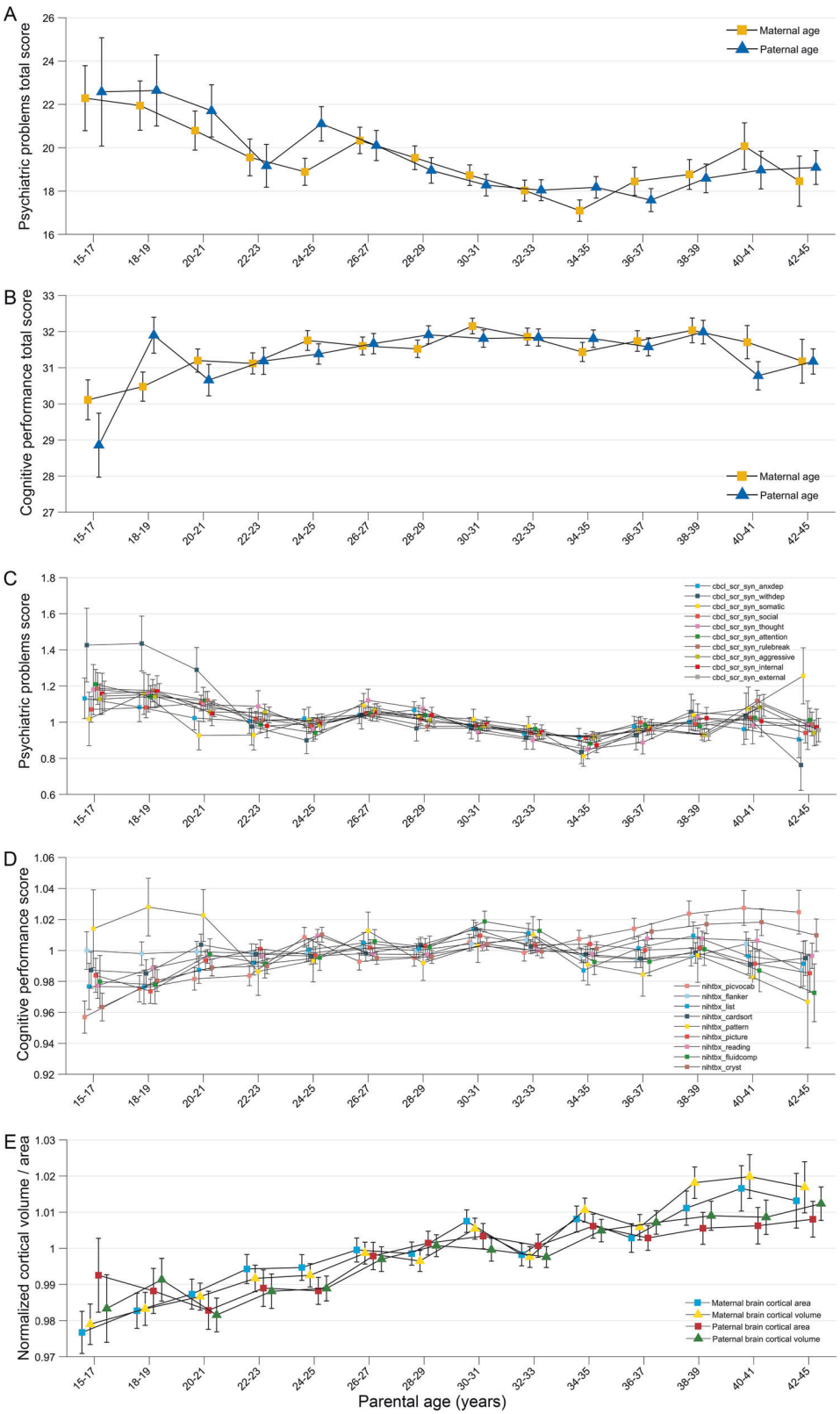

Fig. 1 The relationship between the behavioral problems and cognitive performance of the children and the maternal and paternal ages. **A** The behavioral problems total score of the children is significantly associated with parental age (i.e., a lower parental age is associated with behavioral problems). **B** The cognitive performance total score of the children is significantly associated with parental age. **C** The normalized behavioral problems sub-scores of the children are significantly associated with parental age. **D** The normalized cognitive performance sub-scores are significantly associated with parental age. **E** The relation between parental age, and normalized cortical area and volume in the children. A description of the variables in this figure is provided in Table S1.

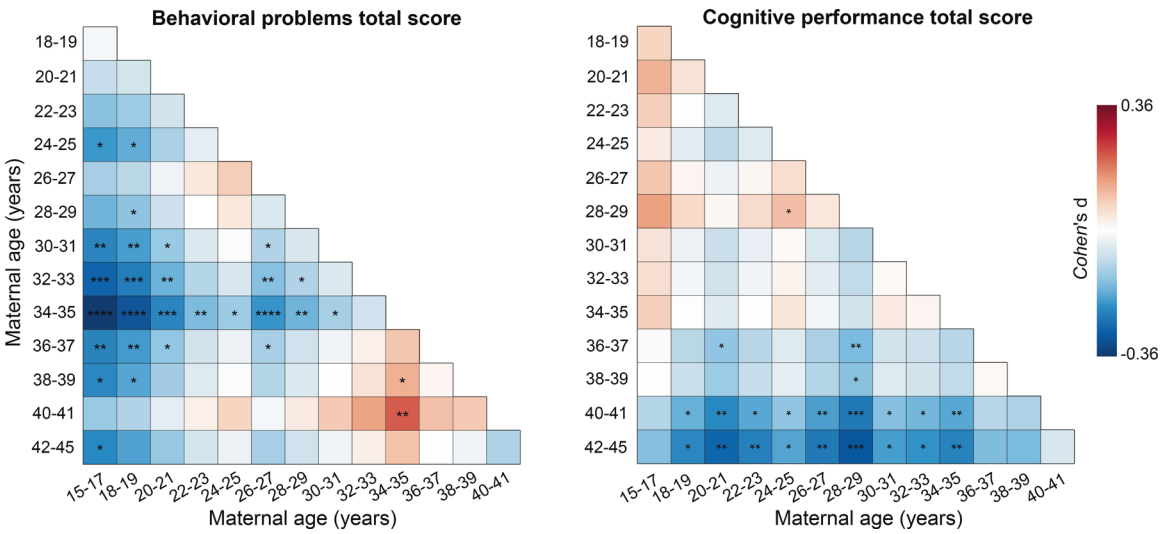

Fig. 2 The statistical differences of the children's behavioral problems total score (Left triangle matrix) and cognitive performance total score (right triangle matrix) between the groups with mothers of different ages. The matrix shows the Cohen's *d* effect size for the comparison between maternal age groups. Each entry in the matrix compares the measures for row minus column. A higher behavioral problems score indicates more behavioral problems; and a higher cognitive performance score indicates higher cognitive performance. (*$p <$ 0.05, **$p < 0.01$, ***$p < 0.001$, ****$p < 0.0001$.).

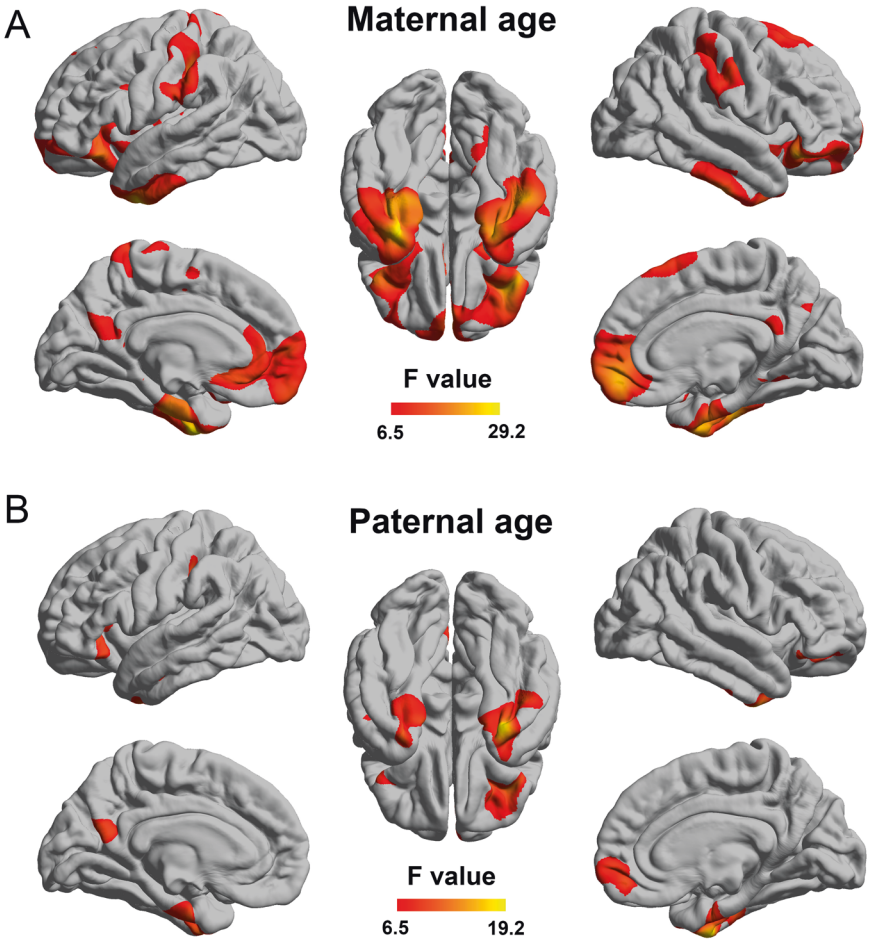

Fig. 3 The brain regions with their cortical areas in the children correlated with maternal and paternal age. A Brain regions in the children with their area significantly related to maternal age (FDR corrected $p < 0.01$, vertex-wise regression). A high cortical area in the children is associated with the maternal age, as can be inferred from Fig. 1. **B** Brain regions in the children with their area significantly related to paternal age (FDR corrected $p < 0.01$).

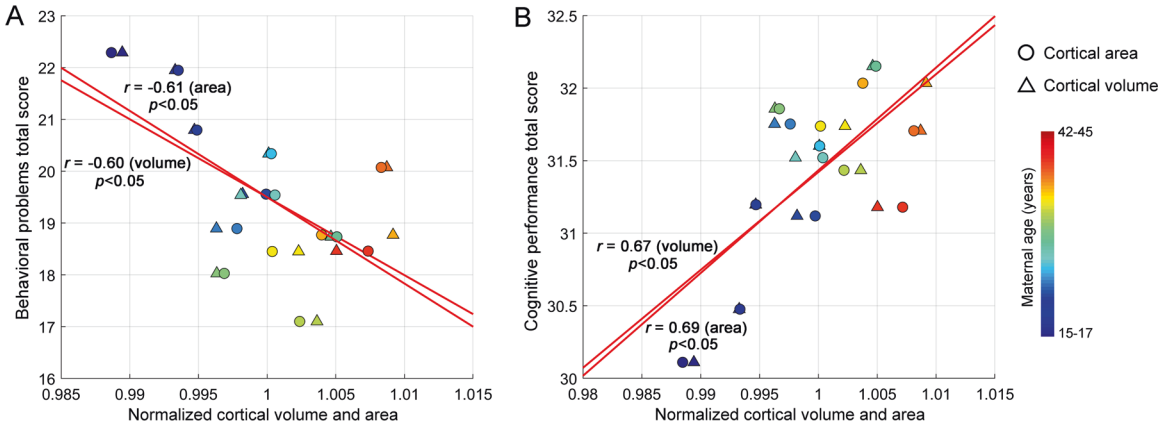

Fig. 4 The relation between the behavioral and cognitive problems in the children and their normalized cortical volume and area. A The relation between the behavioral problems total score and total cortical area and volume in the children. The participants were divided into 14 groups for this stratified analysis, with each group containing data for 2 years starting at age 18, and with the first group containing mothers aged 15–17 and the last group containing mothers aged 42–45. Each group is represented by a different data point in the figure, with the colorbar showing the maternal age. **B** The relation between the cognitive performance total score and total cortical area and volume in the children. Note that the cortical volume and area are normalized by dividing by their own mean value for visualization.

Mediation analysis

The mediation analysis showed that the mean cortical area and volume of the significant brain regions shown in Fig. 3 significantly mediated the relationship between maternal age and the behavioral problems total score and cognitive performance total score. The indirect association between the maternal age and the behavioral problems (total score) was significantly mediated by cortical area (7.7% of the total effect size measured by the variance explained (VE), $p = 3.3 \times 10^{-5}$, $\beta = -0.004$, 95% CI = −0.006 to −0.002, Fig. 5A). The indirect association between the maternal age and the cognitive performance total score was significantly mediated by cortical area (VE = 21.4%, $p = 1.3 \times 10^{-7}$, $\beta = 0.007$, 95% CI = 0.005 to 0.010, Fig. 5B). The indirect association between the maternal age and the behavioral problems (total score) mediated by cortical volume was significant (VE = 9.5%, $p = 2.4 \times 10^{-5}$, $\beta = -0.005$, 95% CI = −0.008 to −0.003, Fig. 5C). The indirect association between the maternal age and the cognitive performance (total score) mediated by cortical volume was significant (VE = 26.0%, $p = 5.6 \times 10^{-9}$, $\beta = 0.008$, 95% CI = 0.006 to 0.011, Fig. 5D). Given the non-linear relationship between the behavioral problems and cognitive scores of the children and the maternal ages (Fig. 1), a complementary mediation analysis that restricted the maternal age to be <36 years old was also performed. Figure S10 shows that the above mediation results remained significant.

DISCUSSION

This research shows that for younger mothers, the children when aged 9–11 tend significantly to have lower cortical volume and area, and that these are associated with behavioral and cognitive problems (Fig. 1). Indeed, a linear relationship was shown between the behavioral problems and cognitive performance and the total cortical volume and area in these children of the mothers with different ages (Fig. 4). The main cortical regions with lower area in the children of the younger mothers included the temporal lobe, medial and lateral orbitofrontal cortex and amygdala, anterior cingulate cortex, nucleus accumbens, and hippocampus (Fig. 3). The lower volumes and areas found for some cortical regions in parents of different ages were shown to significantly mediate the association between the parents' age and the behavioral and cognitive problems (Fig. 5).

We found that a range of behavioral problems of the children were associated with the maternal and paternal ages at the time of the child's birth, consistent with previous reports but in a much larger sample [8]. The behavioral problems in the children that we found to be closely associated with parental age included psychiatric problems such as depressive symptoms, as well as rule-breaking (Fig. 1). In the mothers with younger ages, the brain regions with lower volumes in the children with behavioral problems included the anterior cingulate cortex, orbitofrontal cortex, parahippocampal gyrus and hippocampus, precuneus, and temporal cortical areas. All of these regions are related to a range of mental disorders, including depression [28], schizophrenia [29, 30], and autism [31]. For example, functional connectivities involving the lateral orbitofrontal cortex and anterior cingulate cortex, precuneus and temporal cortical areas are higher in patients with depression [28, 32] consistent with the theory that the lateral orbitofrontal cortex by responding to non-reward is involved in depression [33]. Rule-breaking and conduct disorders were also significantly found in these children, and may relate to functions of the orbitofrontal cortex and anterior cingulate cortex [34, 35]. The mechanisms may include the following, with the underlying premise that an altered volume or area of a brain region may reflect less effective functioning. The human lateral orbitofrontal cortex and a region to which it projects the supracallosal part of the anterior cingulate cortex [36, 37] respond to punishments and not receiving expected rewards [35, 38, 39], both of which normally change behavior so that that behavior is performed less in future. If these brain regions have a different volume and area, then punishment and non-reward might lead to more rule-breaking due to insensitivity to these reinforcement contingencies, consistent with previous studies that smaller lateral orbitofrontal cortex volume is associated with impulsive behavior [40] and externalizing behavior [41]. A cycle of rule-breaking and other difficult behaviors may result in fewer rewards being obtained, and that could contribute to depression [42]. Further, given that the medial orbitofrontal cortex projects to the pregenual anterior cingulate cortex [36, 37], and that both brain regions are activated by rewards and that their volume is associated with reward-learning, [43] a different area and volume of the pregenual anterior cingulate cortex (Fig. 3) in children could be associated with less reward and a tendency thereby to depression [39, 42]. This is also supported by a recent study that found that the medial orbitofrontal cortex volume is negatively associated with depressive symptoms [44]. Consistent with this, the functional connectivity of the medial orbitofrontal cortex and anterior cingulate cortex are lower in depression [28, 39, 45], and activations of the medial orbitofrontal cortex to winning a reward in the monetary incentive delay task are lower in children at risk of depression [46]. The sequential mediation analysis

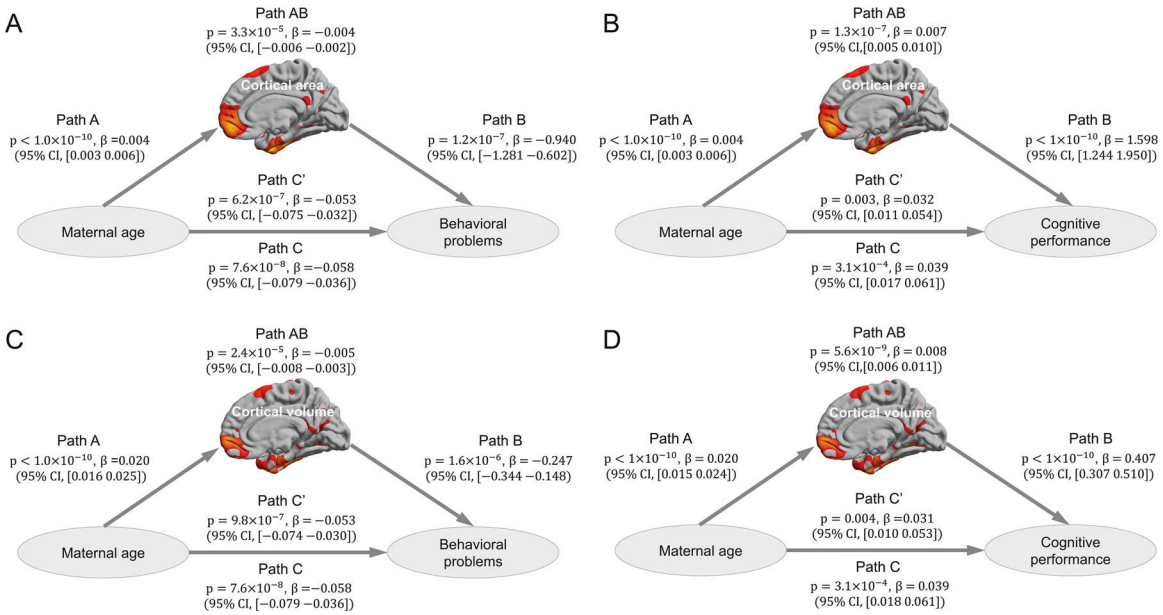

Fig. 5 Mediation analyses showing that cortical volume and area in the children are mediators in the relation between maternal age and behavioral problems and cognitive performance in the children. A Mediation analysis: the mediation implemented by cortical area in the children from maternal age on the behavioral problems total score was significant ($\beta = -0.004$, $p = 3.3 \times 10^{-5}$). Path A: the association between maternal age and the mediator (cortical area); Path B: the association between the mediator (cortical area) and the outcome (behavioral problems total score); Path C shows that the regression coefficient (beta value) of the maternal age on the behavioral problems total score was high when the cortical area was not considered. The beta values show the regression coefficient of the effect of the independent variable (maternal age) on the dependent variable (the behavioral problems total score). Path C′ indicates the direct association between the maternal age and the outcome (the behavioral problems total score) controlling for the mediator (cortical area). Path C′ shows some reduction in the regression coefficient when the effect of cortical area was removed. Path AB indicates the extent to which taking the cortical area into account can explain the 7.7% association between the maternal age and the behavioral problems total score, which is significant as noted above at $p = 3.3 \times 10^{-5}$. **B** Mediation analysis: the mediation implemented by cortical area from maternal age on cognitive performance is significant ($\beta = 0.007$, $p = 1.3 \times 10^{-7}$). **C** Mediation analysis: the mediation implemented by cortical volume from maternal age on behavioral problems total score is significant ($\beta = -0.005$, $p = 2.4 \times 10^{-5}$). **D** Mediation analysis: the mediation implemented by cortical volume from maternal age on cognitive performance is significant ($\beta = 0.008$, $p = 5.6 \times 10^{-9}$).

provided additional evidence that differences in brain structure may partly mediate the relationship between maternal age and the behavioral problems scores.

Beyond the behavioral problems, the investigation draws particular attention to the association between cognitive performance in children and parental age (Fig. 1). The brain areas involved in these cognitive performance differences include the superior medial prefrontal cortex and the anterior cingulate cortex which are key regions involved in executive function [47] and emotion [34, 45], the anterior temporal cortex which is involved in semantic memory [48], and the parahippocampal gyrus and hippocampus which are involved in episodic memory [49]. The mechanisms by which reduced efficacy of these brain regions may impair cognitive functions are considered elsewhere [50]. Previous research has shown that the area of some brain regions is related to cognition [51], and there is some overlap of those regions with the regions identified here, including the anterior temporal lobe and the anterior cingulate cortex. Some previous research, though with much smaller sample sizes, has found cognitive differences such as in attention in children that are related to maternal age. For example, the children of mothers <20 years old had a 78% increased risk of attention-deficit hyperactivity disorder (ADHD) [52]. Other studies have reported that younger maternal age at childbirth was associated with ADHD [53, 54]. In another study, advanced maternal age was associated with fewer behavioral problems, including social and emotional difficulties in children at 7 and 11 years of age [55].

The linear relationship between the behavioral problems and cognitive performance, and the total cortical volume and area, in these children of the mothers with different ages is striking. This can be understood by inspection of Fig. 1 which shows that the curves as a function of maternal age for cognitive performance and cortical volume have the same form. Thus selecting data by age provides a linear relation between cognitive performance and brain volume. The same applies to behavioral problems and brain volume, except that the correlation is reversed, which is what is shown in Fig. 4.

Both maternal and paternal age were associated with the behavioral and cognitive problems in the children, but the maternal age and the paternal age are correlated, $r = 0.78$, so these associations are not presented as being independent of each other. When maternal age was regressed out, it was found that paternal age was no longer associated with differences in total cortical area in the children. Maternal age remained associated with differences in total cortical area when paternal age was regressed out (Fig. S4). The implication is that maternal age is more important than paternal age in the association between parental age and behavioral and cognitive problems in children.

The findings described here are associations. Although they show that brain volume or area significantly mediate the association between the parents' age and behavioral and cognitive problems, there are important issues about the origin of some of the relationships described that need to be the subject of future research. The youngest two maternal age groups 15–17 y and 18–19 y shown in Fig. 1 were considered as teenaged mothers based on the guidelines of the CDC [23]. For example, it could be that the mothers who are 15–19 and tend to have a higher incidence of children with behavioral problems might before they became mothers have had behavioral problems, so the effects found could be related to genetic effects, or to the environment in which the children were brought up. For example, it has been

shown that the functional connectivity between brain regions has a genetic component [56], and genetic components are one way in which the brain structural and the related behavioral and cognitive differences described here in children could be related to possible differences in the mothers, though environmental effects are also likely to be important, and psychosocial and cultural factors should be considered [57]. For example, younger parents are often associated with lower socioeconomic status, which may provide a less supportive and unstable home environment for the offspring [58]. An adverse family environment can affect brain development especially during the fetal stage which leads to suboptimal outcomes including neurodevelopmental disorders and developmental delays in offspring [59]. In addition, younger parents are more likely to be smokers and heavy alcohol users [60], and growing evidence indicates that exposure to prenatal smoking and alcohol could affect epigenetic modifications [61], which may account for the increased risks of behavioral problems in offspring. Another factor is that delaying first births may enable mothers to complete more years of education [62]. To cast light on the mechanisms, measures from the parents of their behavioral problem status and cognitive performance before they have children, or from their relatives, could be valuable. We were careful to regress out some socioeconomic factors such as the parents' income and the parents' number of years of education, but there are clearly a number of factors that may underlie some of the associations described here. Indeed, we note that we describe here important associations between parental and especially maternal age and behavioral and cognitive problems in the children, and that the findings point towards the importance of further research with the aim of investigating causal factors.

The new findings presented here are based on associations, that is on correlations, and do not identify causal factors. We took care to remove effects related to parental income and education, but addressing the extent to which the observed effects are related to sociodemographic factors or genetic differences or other factors that are likely to be associated with parental age needs more research in the future. However, we were able to show that similar results to those shown in Fig. 3 were obtained when the following further factors were included as possible confounds of no interest in the model: the psychopathology history of the biological father, the psychopathology history of the biological mother, parental monitoring, family conflict, and the scanning machine used.

In summary, this investigation revealed associations between the parental age and behavioral and cognitive problems in their children aged 10 years old. Moreover, this study showed that the volume and area of a number of brain regions were lower in the children of the younger mothers, and partly mediated the association between the maternal age and the behavioral and cognitive problems. The paternal age was not associated with these brain differences if the maternal age was regressed out. The effects were statistically robust, with a large sample size of 8709 participants. It is an important finding that differences in the brain volume of the children mediate in part the association between the maternal age when the child is born, and behavioral and cognitive problems. These findings are relevant to psychiatric practice as part of the possible background when assessing children with behavioral or cognitive problems.

DATA AVAILABILITY

The data that support the findings of this study are openly available in the ABCD Dataset Data Release 2.01 at https://nda.nih.gov/abcd.

CODE AVAILABILITY

The data preprocessing software FreeSurfer v6.0 can be obtained from https://surfer.nmr.mgh.harvard.edu/. Qoala-T v1.2 for automatic quality control can be obtained from: https://github.com/Qoala-T/QC. The scripts used for these analyses will be made available upon publication at the following url: https://osf.io/qdb23/. Software for the mediation analysis can be obtained from https://github.com/canlab/MediationToolbox.

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AUTHOR CONTRIBUTIONS

JD and WC designed the research. JD, ETR, WG and WC analyzed the data. JD and WC made the figures. JD, ETR, MC, DV, JZ, JK, JF and WC wrote and edited the manuscript. All authors approved the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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