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Sleep duration, brain structure, and psychiatric and cognitive problems in children

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Abstract

Low sleep duration in adults is correlated with psychiatric and cognitive problems. We performed for the first time a large-scale analysis of sleep duration in children, and how this relates to psychiatric problems including depression, to cognition, and to brain structure. Structural MRI was analyzed in relation to sleep duration, and psychiatric and cognitive measures in 11,067 9-11 year-old children from the Adolescent Brain Cognitive Development (ABCD) Study, using a linear mixed model, mediation analysis, and structural equation methods in a longitudinal analysis. Dimensional psychopathology (including depression, anxiety, impulsive behavior) in the children was negatively correlated with sleep duration. Dimensional psychopathology in the parents was also correlated with short sleep duration in their children. The brain areas in which higher volume was correlated with longer sleep duration included the orbitofrontal cortex, prefrontal and temporal cortex, precuneus, and supramarginal gyrus. Longitudinal data analysis showed that the psychiatric problems, especially the depressive problems, were significantly associated with short sleep duration one year later. Further, mediation analysis showed that depressive problems significantly mediate the effect of these brain regions on sleep. Higher cognitive scores were associated with higher volume of the prefrontal cortex, temporal cortex, and medial orbitofrontal cortex. Public health implications are that psychopathology in the parents should be considered in relation to sleep problems in children. Moreover, we show that brain structure is associated with sleep problems in children, and that this is related to whether the child has depressive problems.

Introduction

Sleep is necessary for maintaining cognitive and emotional abilities. Lack of sleep has been associated with health-related and cognitive consequences¹⁻⁴. Population-based studies show that individuals with short sleep duration or insomnia are at significantly greater risk for cerebrovascular diseases⁵, mental disorders^{6, 7} and metabolic disorders^{8, 9}. A meta-analysis of 91 studies found that sleep alterations, such as sleep depth and altered rapid eye movement (REM) sleep, were present in many mental disorders including schizophrenia, anxiety, affective, eating and autistic disorders¹⁰. A previous study in adults revealed a high association between sleep quality and the depressive problems score that was mediated by functional connectivities involving the lateral orbitofrontal cortex, anterior cingulate cortices, hippocampus, and precuneus⁷. Moreover, the impact of sleep and insomnia on brain structure and function is striking. For example, the functional connectivity in the resting state of the default mode, dorsal attention, and hippocampal networks was different after sleep deprivation.¹¹ In adults aged ≥ 55 y, self-reported short sleep duration was associated with faster expansion of the ventricles and faster decline in cognitive performance in the following two years¹². However, most studies on the relation between sleep and brain structure and function have used relatively small numbers of participants (e.g. 1972 participants in 24 studies in a recent meta-analysis¹³), indicating the need for a robust large-scale study such as the present one that included 11,067 participants.

Sleep states are active processes that may function to support reorganization of brain circuitry¹⁴, which makes sleep especially important for children at this stage of brain development. A recent meta-analysis showed a high correlation between sleep and cognitive functioning and behavioral problems in school-age children. Shorter sleep duration was associated with poorer cognitive functioning and worse school performance, and also was related to behavioral problems¹⁵. Although many studies have identified associations between sleep and cognitive performance and adverse mental health outcomes in children, only a few imaging studies have examined the association between low sleep duration and brain structure¹⁶

and development^{17, 18}, and the neural mechanisms underlying the association between sleep and cognition and mental health in children are still unknown.

A large-scale multimodal neuroimaging study tracking over 11,000 children in the Adolescent Brain Cognitive Development (ABCD) cohort provides an unprecedented opportunity to investigate the neural differences in children with short sleep duration, and the possible neural mechanisms underlying the association between sleep and various mental health disorders and cognitive performance¹⁹. The ABCD dataset has been shown useful in investigating the relationship between children's behavior and brain structure^{20, 21}. In the present investigation, we analyzed in the ABCD cohort the relation between brain structure, and sleep duration, cognitive performance and mental health by measuring brain morphometric information of different brain regions, and then using a mediation analysis to assess the underlying mechanisms. The main hypothesis that we investigate is that the relation between brain structure and sleep is mediated by psychiatric problems related to brain structure. The second hypothesis that we investigate in another mediation analysis is the extent to which the relation between brain structure and cognition is mediated by sleep duration. Strengths of the present investigation are the longitudinal data with a large number of child participants (baseline 11,067; one year follow up 4,696) leading to robust findings; the mediation analysis; linking the findings to recent advances in understanding brain mechanisms related to mental disorders, cognition, and sleep; and the inherent interest of the relation between sleep, cognition and psychiatric problems to a wide readership.

Materials and Methods

Participants and data preprocessing

The dataset used for this investigation was selected from the Annual Curated Data Release 2.01 from the ABCD consortium (<https://abcdstudy.org/index.html>) which contains over 11,000 children aged 9 to 11 years recruited from 21 centers throughout the United States with a diverse range of geographic, socioeconomic, ethnic, and health backgrounds^{19, 22}. The 21 centers

obtained parents' full written informed consent and the childrens' assent, and research procedures and ethical guidelines were followed in accordance with the Institutional Review Boards (IRB). Our sample includes 11,067 subjects (ages 9–11 years, 5301 females) scanned with three 3 Tesla (T) scanner platforms: Siemens Prisma, General Electric 750 and Phillips. 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 also are described elsewhere^{19, 23}.

We obtained preprocessed structural imaging data (T1 and T2) using the ABCD pipeline, with all the data preprocessing procedures performed by the ABCD team as described in their image processing paper²³ and in the Supplementary Material. Morphometric measures consisting of the cortical area, volume and thickness of 68 cortical regions²⁴ and 40 subcortical regions²⁵ from the ABCD preprocessing were used in the following analyses. The imaging data were only available for baseline (11,067 participants).

The quality control of the processed images was done by the ABCD team and 481 participants who failed to pass the quality control of the ABCD team were removed from subsequent analysis. In addition, 3 participants who did not contain the full information of both the sleep behavior measures and the structural images were excluded. Finally, 11,067 participants were left for this study and the demographic characteristics of these participants are summarized in Table 1.

Behavioral measures

Sleep assessments

The sleep disturbances scale for children is based the ABCD Parent Sleep Disturbance Scale for Children (abcd_sds01) which is useful for assessing the sleep-wake rhythm of a child and of any problems in his/her sleep behavior²⁶. In the current study, we focus on an important measure of sleep, sleep duration, which is question 1 of the above scale, namely "How many hours of sleep does your child get on most nights" (with further details in the Supplementary

Material). We note that a high sleep duration score in this measurement system indicates short sleep duration. In this paper, we use 'sleep duration' as the descriptor, where a high sleep duration indicates a large number of hours of sleep. The data were available for baseline (11,067 participants) and one year follow up (4,696 participants).

Cognitive assessments

To investigate the relationship between sleep duration and cognitive performance, the NIH Cognition Battery Toolbox (abcd_tbss01) was used to evaluate the cognitive performance of children²⁷. The summary score of the NIH Cognition Battery Toolbox contains seven components: language vocabulary knowledge, attention, cognitive control, working memory, executive function, episodic memory and language. These data were only available for baseline (11,067 participants).

Mental health assessments

We also investigated the relationship between sleep duration and psychiatric problems. The Parent Child Behavior Checklist Scores (abcd_cbcls01) were used to assess the dimensional psychopathology and adaptive functioning in children²⁸. It contains ten empirically-based syndrome scales related to psychiatric problems: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, aggressive behavior, internalizing broad band score and externalizing broad band score; and a psychiatric problems total score. Six DSM-Oriented Scales were also calculated based on the questionnaire. A high score indicates dimensional psychopathology. The data were available for baseline (11,067 participants) and one year follow up (4,696 participants).

More details of these behavior assessments are provided in the Supplementary Material (Table S1) and also can be found at the ABCD website (<https://abcdstudy.org/scientists-protocol.html>).

Statistical Analysis

Association analysis: A linear mixed-effect model (LMM) was used to test the associations of the sleep duration with the brain morphometric measures and with the children's cognitive scores from the NIH Cognitive Toolbox and the psychiatric problems scores from the Child Behavior Checklist noted above that are provided by ABCD. As recommended by the ABCD and used in many studies^{29, 30}, a linear mixed-effect model was used to take account of the correlated observations within families due to twins and siblings and at sites. In this way, the LMM was specified to model family nested within site. The LMM was implemented using the MATLAB function *fitlme*. A morphometry measurement or behavioral score was modelled as the dependent variable, and the sleep duration and the nuisance covariates were modelled as fixed effects, while the family structures nested within sites were modelled as random effects. To ensure that the following variables did not influence the results, they were used in the LMM as covariates of no interest: children's age, sex, body mass index, puberty score, race (coded as 3-column dummy variables), and parents' income and number of years of education. A t-statistic and the effect size Cohen's d were obtained for each LMM model to reflect the association between sleep duration and the dependent variable. Finally, false discovery rate (FDR) and Bonferroni corrections to correct the results for multiple comparisons were performed³¹. All brain measurements and behavioral variables used in the association analysis were collected at the ABCD baseline time when the average age was 119 months.

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 neuroimaging studies^{32, 33}. A standard 3-variable path model was used here³⁴, with the detailed methodology described in the supplementary material of³². Briefly, mediation analysis tests whether the covariance between two variables can be explained by a third variable (the mediator). The two hypotheses investigated the relation of cortical morphometry with psychiatric and cognitive problems and sleep duration. For the first hypothesis, the independent (predictor) variable was a morphometry measure and the dependent

(predicted) variable was sleep duration. The proposed mediator (in the indirect path) was the depressive score. (The proposed mediator in another test in the Supplementary Material was the psychiatric problems total score.) For the second hypothesis, the independent (predictor) variable was a morphometric measure and the dependent (predicted) variable was the Cognition Total Composite Score. The proposed mediator was sleep duration. Confounding variables as in the association analysis were regressed out in the mediation model. The significance of the mediation was estimated by the bias-corrected bootstrap approach (with 10,000 random samplings). All brain measurements and behavioral variables used in the mediation analysis were collected at the ABCD baseline time. We note that significant mediation effects show how much of the correlation between independent and dependent variables is related to another variable termed the mediator, and is strictly a measure of association, which does not prove causality.

Longitudinal data analysis: For the above-mentioned measurements, it was possible to perform a longitudinal analysis for approximately half the participants (4,696) using the sleep duration and psychiatric problems scores which were obtained in the follow up 1 year after the baseline time. The neuroimaging was available only at the baseline time. A classic two-wave cross-lagged panel model (CLPM, implemented by Mplus (version 7.4)³⁵) based on structural equation modelling was implemented to investigate the longitudinal associations between sleep duration and each of the psychiatric problems scores, using the longitudinal panel data in ABCD^{36,37}. Specifically, let x_t and y_t be the de-meaned baseline sleep duration score and a psychiatric problem score of a subject, and x_{t+1} and y_{t+1} be their one year follow up. The CLPM models them as:

$$x_{t+1} = \alpha_t x_t + \beta_t y_t + \eta_1 z_t + \varepsilon_1$$

$$y_{t+1} = \delta_t y_t + \gamma_t x_t + \eta_2 z_t + \varepsilon_2$$

where α_t , β_t , δ_t , γ_t , η_1 and η_2 are the coefficients of the model, z_t is the confounding variable, and ε_1 and ε_2 are the error term. The model was estimated by using maximum likelihood estimation with robust standard errors that also take clustering of cases

into account. The standardized regression coefficients and their standard errors of variables of interest (namely, α_t , β_t , δ_t , γ_t) are reported throughout. Confounding variables, as in the association analysis, were regressed out in the CLPM analysis.

Results

The correlation between sleep duration and other measures in the ABCD dataset

The dimensional psychopathology measures (abcd_cbcl01, abcd_ksad501, abcd_ksad01) were significantly negatively correlated with the sleep duration (that is, pathology was positively associated with short sleep durations) (Fig. 1 and Table 2). 82 out of 119 individual items (119 questions in the CBCL questionnaire, abcd_cbcl01) were significant after Bonferroni correction ($p < 0.05$). Indeed, all the psychiatry problems scores (abcd_cbcls01) were negatively correlated with the sleep duration with r values ranging from -0.062 to -0.208 (Bonferroni corrected, $p < 0.05$, Table 2 and Fig. 1C). The depressive problems score was the score most significantly negatively correlated with the sleep duration ($r = -0.208$, Cohen's $d = -0.425$, $p < 1 \times 10^{-10}$). Thus the children with shorter sleep duration tended to have higher psychiatric problems scores. What is also interesting is that many parent dimensional psychopathology measures (including abcd_asrs01 and pasr01) were significantly negatively correlated with the sleep duration of the child. As shown in Fig. 1, the screen time utilization (e.g. the use of mobile phones, TV, internet, and video games, abcd_stq01) was negatively correlated with sleep duration, which is consistent with previous studies^{38,39}. Interestingly, the environmental risk (abcd_rhds01) related measures were also correlated with sleep duration, suggesting that a sense of safety (low risk) may be associated with children's sleep duration. These, and also the other sleep component scores (abcd_sds01), were negatively correlated with sleep duration with r values ranging from -0.07 to -0.21 (Bonferroni corrected, $p < 0.05$). In addition, subsyndromal mania (abcd_pgbi01); school, family, and social relations (dibf01); monitoring of children's functioning (abcd_ssbpmtf01); and cultural values (macv01) were negatively correlated with sleep duration in the children (Fig. 1A).

Eight out of 10 of the cognitive summary scores (abcd_tbss01) were positively correlated with the sleep duration (Bonferroni corrected, $p < 0.05$, Fig. 1B). The range of r values between the sleep duration and cognitive measurements was between 0.032 and 0.069, and these were highly significant (Table 2 and Fig. 1B). Further, 15 out of 49 individual items within neurocognition (abcd_tbss01) were positively correlated with long sleep durations (Bonferroni corrected, $p < 0.05$, Fig. 1A and Table 2). Thus children with long sleep duration have better cognitive performance.

Short sleep duration, poor cognition, and psychiatric problems are associated with low cortical area and volume

Both cortical area and volume of the whole brain were significantly positively correlated with sleep duration ($r = 0.046$, Cohen's $d = 0.093$, $p = 1.0 \times 10^{-6}$ and $r = 0.047$, $d = 0.095$, $p = 6.2 \times 10^{-7}$ respectively). Specifically, in children with short sleep, the cortical areas / volumes were lower of the lateral and medial orbitofrontal cortex, superior and middle frontal gyrus and medial superior frontal, inferior and middle temporal gyrus, precuneus and posterior cingulate cortex, ventromedial prefrontal cortex, supramarginal gyrus, and some motor cortical areas (FDR corrected, $p < 0.005$, Fig. 2A and Fig. S1A), and volumes were lower of the thalamus, caudate, and the pallidum (FDR corrected, $p < 0.005$, Table S2). (Cortical thickness was not associated with sleep duration or with most of the other measures, and for brevity is not described further.). Given the significant association between sleep duration, and cognition and the other sleep component scores, we also performed a complementary analysis with these variables (cognitive total score and all 5 sleep component scores) as covariates, and found a high correlation between the associated brain patterns with and without these variables regressed out in the analysis of the association between cortical area (or volume) and sleep duration ($r > 0.95$, $p < 1 \times 10^{-10}$). This shows that the results are robust and consistent and do not depend on these other variables.

Total cortical area and volume were significantly positively correlated with the cognition

total composite score ($r=0.13$, $d=0.27$, $p < 1 \times 10^{-10}$ and $r=0.11$, $d=0.23$, $p < 1 \times 10^{-10}$ respectively). The brain areas with significant correlations with the cognition score included the prefrontal and anterior cingulate cortex, medial orbitofrontal cortex, temporal cortex, insula, inferior parietal gyrus, thalamus, caudate, and putamen (FDR corrected, $p < 0.005$, Fig. 2B, Fig. S1B and Table S2).

Total cortical area and volume were significantly negatively correlated with the psychiatric problems total score ($r=-0.07$, $d=-0.15$, $p=1.3 \times 10^{-14}$ and $r=-0.07$, $d=-0.14$, $p=2.9 \times 10^{-14}$ respectively). The significant brain regions after FDR correction ($p < 0.005$) are shown in Fig. S2. Given the high correlation between depression and sleep problems, we next focus on the depressive problems score. We found that both cortical area and volume were significantly negatively correlated with the depressive problems score ($r=-0.05$, $d=-0.09$, $p=8.1 \times 10^{-7}$ and $r=-0.05$, $d=-0.09$, $p=6.4 \times 10^{-7}$ respectively). Fig. 2C shows that the brain areas with lower area in participants with high depressive problems scores included the lateral and medial orbital frontal cortex, temporal cortex, precuneus, superior and middle frontal gyrus and superior medial frontal cortex, angular and supramarginal gyrus, hippocampus, thalamus, caudate and motor areas (FDR corrected, $p < 0.005$, Fig. 2C, Fig. S1C and Table S2).

The brain areas with correlations with both sleep duration and cognitive performance are shown in Fig. 2D and Fig. S1D; and with both sleep duration and depressive problems in Fig. 2E and Fig. S1E.

Next, we performed two complementary analyses to determine whether the present brain structure findings were regionally specific. Firstly, we included the intracranial volume as a covariate, which is a useful normalization procedure used in morphometric analyses⁴⁰. As shown in Fig. S5, the association patterns with brain regions were similar between the cases with and without regression of the intracranial volume for all behavioral measures including sleep duration, depressive score, and cognitive score. The regions associated with sleep duration included the orbitofrontal cortex, superior, middle and medial superior frontal gyrus, inferior and middle temporal gyrus, precuneus, and posterior cingulate cortex, all of which remained

significant after regressing out the effect of the intracranial volume (FDR $p < 0.05$). Secondly, we also performed the same analysis using the total cortical volume or area as covariates. Although no region was significant in this case, the association patterns with and without regression of the total cortical volume or area were highly correlated (r ranging from 0.66 to 0.85, all $p < 1.0 \times 10^{-5}$).

The longitudinal association between sleep duration and the psychiatric problems scores

The structural equation modelling path estimates were used to analyze the changes that occurred between the baseline ages of around 10 and one year later. These showed that psychiatric problems at the baseline age including the depressive problems and total psychiatric problems scores were significantly associated with decreased sleep duration at the one-year follow-up (Fig. 3A and Fig. S3). The reverse was not found. It should be noted that the depressive problems score is the top contribution from the different psychiatric measures to the association with decreased sleep duration ($\beta = -0.081$, $SE = 0.016$, $p < 1 \times 10^{-4}$); and the reverse was not found ($\beta = -0.018$, $SE = 0.013$, $p = 0.17$). The model accounted for 23.8% of the variance in sleep duration, and 40.1% of the variance in the depressive problems score in children aged around 11, by taking into account the measures of sleep and depressive problems one year earlier.

Mediation Analysis

The two main hypotheses are defined above. First, the depressive problems significantly mediated the relationship between the mean cortical area of the significant brain regions shown in Fig. 2E and sleep duration (Fig. 3B, path AB, 25.9% of the total effect size, $\beta = 0.015$, $p = 2.5 \times 10^{-10}$; 95% CI, 0.011 to 0.020, FDR corrected, $p < 0.005$). The brain regions with areas related to both sleep and depressive problems, and involved in the mediation analysis just described, are shown in Fig. 2E and include the medial and lateral orbitofrontal cortex, dorsolateral prefrontal cortex, precuneus, and angular gyrus. The interpretation is that

depressive problems significantly mediate the effect of brain structure on sleep. (Similar findings for brain volume are provided in Fig. S4A.)

Similar results were also found for the total psychiatric problems score (Fig. S4B and C). The interpretation is that psychiatric problems taken together significantly mediate the effect of brain structure on sleep.

The second hypothesis investigated is the extent to which the relation between brain structure and cognition is mediated by sleep duration. Fig. 3C shows that the relation between brain structure (the mean cortical area of the significant brain regions shown in Fig. 2D) and cognition was significantly mediated by sleep duration (path AB, 2% of the total effect size, $\beta=0.032$, $p=1.5\times 10^{-4}$; 95% CI, 0.018 to 0.053, FDR corrected, $p<0.005$). (The result for brain volume was similar as shown in Fig. S4D.)

Third, in addition, we showed that brain structure mediated some of the effects found. For example, the mediation implemented by cortical area from depressive problems on sleep duration was significant ($\beta=-0.0009$, $p=7.8\times 10^{-4}$; 95% CI, -0.0014 to -0.0004, FDR corrected, $p<0.005$) (Fig. S6). In addition, the mediation implemented by cortical area from sleep duration on cognition was significant ($\beta=0.065$, $p=1.5\times 10^{-6}$; 95% CI, 0.04 to 0.092, FDR corrected, $p<0.005$) (Fig. S6). These analyses provide evidence that the brain structure differences described here that are associated with sleep duration are closely related to the cognitive and depressive problems present in the children. We note that these analyses show partial mediation effects. Further, we note that the brain is a significant mediator in all these models, and that the brain in all these models also has a significant effect as an independent variable.

Discussion

We found that dimensional psychopathology (including depression, anxiety, impulsive behavior) in the children aged 9-11 was negatively correlated with sleep duration (Fig. 1 and Table 2). Very interestingly, dimensional psychopathology in the parents was also correlated with short sleep duration in their children (Fig. 1). The brain areas in which higher volume was

correlated with longer sleep duration included the superior and middle frontal gyri and superior medial frontal areas, inferior and middle temporal gyrus, precuneus, supramarginal gyrus, thalamus, caudate, and the lateral and medial orbital frontal cortex. Longitudinal data analysis showed that the psychiatric problems, especially the depressive problems, were associated with lower sleep duration measured one year later. The reverse association was not significant. Further, mediation analysis showed that depressive problems mediate considerably the effect of brain structure (Fig. 2E) on sleep. The areas we suggest include the orbitofrontal cortex because of its functions in depression and other psychiatric problems^{41, 42}, and the dorsolateral prefrontal cortex, because of their importance in cognitive functions such as episodic memory and working memory⁴³.

The mediation analyses showing that depressive problems mediate considerably the effect of low brain area or volume on low sleep duration implicated the lateral orbitofrontal cortex. Part of what was found was that low volume in the orbitofrontal cortex was associated with a high depressive problems score (Fig. 2C). This is of interest, for the lateral orbitofrontal cortex is implicated in depression^{41, 44}. A possible hypothesis is that reduced volume of the medial orbitofrontal cortex related to reward processing, and of the lateral orbitofrontal cortex related to non-reward processing, is related to depression⁴⁴. Further, if the orbitofrontal cortex is not yet well developed as reflected in its volume, then problems related to depression and thereby poor sleep may occur (as shown by the mediation analysis in Fig. 3B). Many of the other brain areas with structure related to sleep duration and psychiatric problems especially depression including other frontal cortical areas, and the precuneus, are also implicated by functional connectivity analyses in depression and have different connectivity with the orbitofrontal cortex^{41, 44-46}. There is also evidence for a role of the thalamus, especially the “nonspecific” intralaminar and midline thalamic nuclei, and the reticular nuclei, in sleep^{47, 48}.

The brain areas in which higher cognitive scores were associated with higher volume included the prefrontal cortex (involved in working memory), the temporal cortex (involved in perception and semantic representation), and the medial orbitofrontal cortex and pregenual

cingulate cortex (involved in reward^{44, 49}) (Fig. 2B), and it was of interest that high sleep duration was also associated with high volume of similar areas (Fig. 2D). Sleep had a small effect in mediating the relationship between brain structure and cognition (Fig. 3C).

One of the interesting possibilities raised by this research is that children who are developmentally advanced for their age may have more brain volume in some of the areas identified in this investigation including the orbitofrontal cortex and precuneus, and may thereby be developing cognitive and behavioral capacities that enable them to perform better. Another point is the finding that dimensional psychopathology in the parents was positively correlated with short sleep durations in their children (and with the children's brain volumes and problems). This could be due to inherited characteristics, or could be due to the influences of the environment produced by the parents, or an interaction between the two. Further research will be of interest to address these issues, including genetic mediation analyses.

Research on the role of brain development in children as a factor to help understand the links between sleep, psychiatric problems and brain structure has not provided clear answers yet. One study showed that sleep disturbances in the first 6 years are associated with smaller grey matter volumes and thinner dorsolateral prefrontal cortex at age 7⁵⁰. A recent study also showed that sleep problems in children at 1.5, 2, and 6 years of age were associated with lower fractional anisotropy values at 10 years⁵¹. Although these studies with sleep measures at different times in children potentially reflect the effect of sleep problems on neurodevelopment, the long-term effect of sleep on brain development remains unknown, partly due to the lack of longitudinal neuroimaging studies. A recent systematic review concluded that "Although the research presented supports and offers more insight into the importance of sleep for the developing brain of children and adolescents, no firm conclusions that apply broadly may be drawn"¹³. The present study involved more than a magnitude more participants than these previous studies, and a much wider range of measures. It will be useful to explore the causal relationship between sleep and brain structure and function when the follow-up brain imaging data are available in the ABCD dataset in the future.

Several strengths of the research described here are 1) the very large sample size (11,067) with many behavioral measures of children of almost the same age thereby controlling for age effects; 2) the longitudinal design of the study that enabled us to analyze the relation between psychiatric problems, and sleep duration measured one year later; 3) the mediation analysis providing evidence that the psychiatric problems mediated the relationship between brain structure and sleep.

In summary, we show that that dimensional psychopathology (including depression, anxiety, and impulsive behavior) is negatively correlated with sleep duration in a large cohort of 11,067 children. Importantly, dimensional psychopathology in the parents was also correlated with short sleep duration in their children. Further, this is the first large-scale investigation of how brain regions contribute to sleep problems in children. We show that psychiatric problems mediate these effects to a considerable extent, via brain regions that include the orbitofrontal cortex, frontal including medial cortical areas, inferior and middle temporal gyrus, precuneus, and supramarginal gyrus (Fig. 2E). We also show that sleep duration mediates a small part of the relation between high brain volume and good cognition.

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Declaration of interests.

All authors declare no competing interests.

Table 1. The demographic characteristics of the ABCD participants.

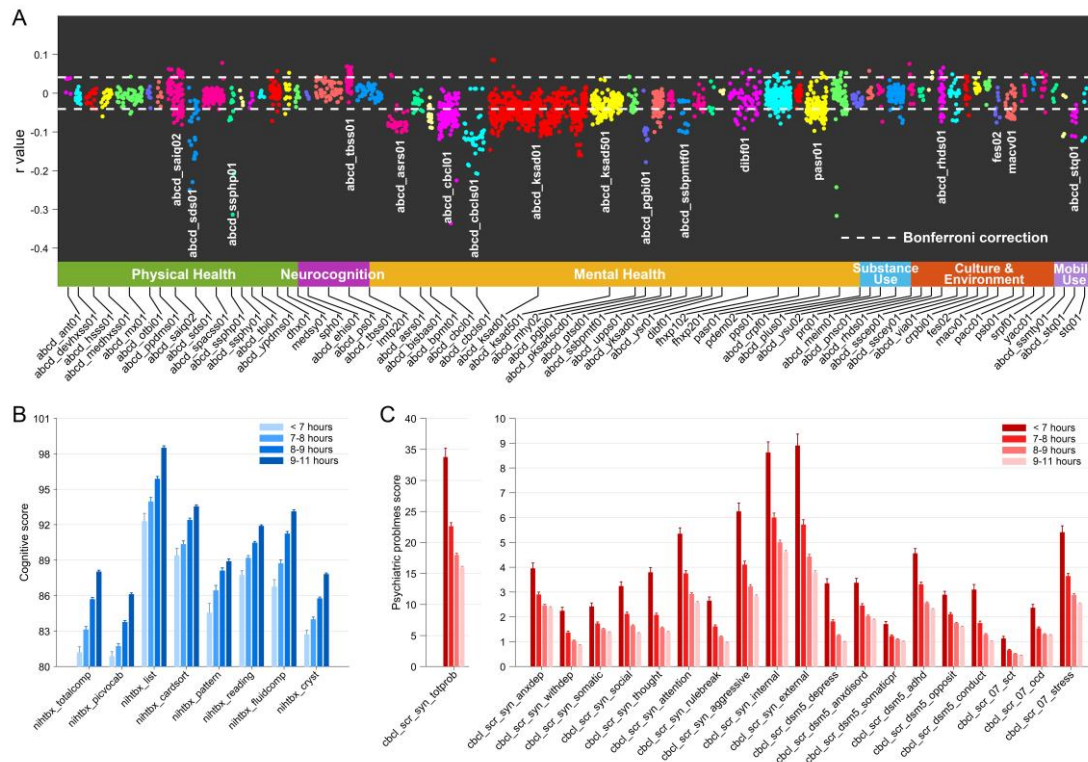
Basic information						
Age (month)	Gender (Male / Female)	BMI	Parents income	Parents education	puberty	Race (White/Black/Indian/Others)
119.0 ± 7.47	5766 / 5301	18.79 ± 4.17	7.56 ± 2.53	16.63 ± 2.75	1.61 ± 0.49	8279/2298/366/124
Cognitive measurement						
nihbtb_picvocab	nihbtb_flanker	nihbtb_list	nihbtb_cardsort	nihbtb_pattern	nihbtb_picture	nihbtb_reading
84.55 ± 8.10	94.09 ± 9.05	96.80 ± 12.00	92.61 ± 9.45	88.18 ± 14.56	102.94 ± 12.08	90.91 ± 6.87
nihbtb_fluidcomp	nihbtb_cryst	nihbtb_totalcomp				
91.70 ± 10.58	86.43 ± 7.04	86.36 ± 9.08				
Psychiatric problem measurement						
cbcl_scr_syn_anxdep	cbcl_scr_syn_withdep	cbcl_scr_syn_somatic	cbcl_scr_syn_social	cbcl_scr_syn_thought	cbcl_scr_syn_attention	cbcl_scr_syn_rulebreak
2.52 ± 3.08	1.03 ± 1.71	1.50 ± 1.96	1.61 ± 2.27	1.61 ± 2.19	2.94 ± 3.47	1.18 ± 1.84
cbcl_scr_syn_aggressive	cbcl_scr_syn_internal	cbcl_scr_syn_external	cbcl_scr_syn_totalprob	cbcl_scr_dsm5_depress	cbcl_scr_dsm5_anxdisord	cbcl_scr_dsm5_somaticpr
3.25 ± 4.33	5.05 ± 5.54	4.43 ± 5.82	18.09 ± 17.89	1.26 ± 2.01	2.06 ± 2.44	1.09 ± 1.51
cbcl_scr_dsm5_adhd	cbcl_scr_dsm5_opposite	cbcl_scr_dsm5_conduct	cbcl_scr_07_sct	cbcl_scr_07_ocd	cbcl_scr_07_stress	
2.59 ± 2.95	1.76 ± 2.03	1.27 ± 2.34	0.52 ± 1.00	1.34 ± 1.82	2.89 ± 3.35	

Note: **nihbtb_picvocab:** NIH Toolbox Picture Vocabulary Test Age 3+ v2.0 Uncorrected Standard Score; **nihbtb_flanker:** NIH Toolbox Flanker Inhibitory Control and Attention Test Ages 8-11 v2.0 Uncorrected Standard Score; **nihbtb_list:** NIH Toolbox List Sorting Working Memory Test Age 7+ v2.0 Uncorrected Standard Score; **nihbtb_cardsort:** NIH Toolbox Dimensional Change Card Sort Test Ages 8-11 v2.0 Uncorrected Standard Score; **nihbtb_pattern:** NIH Toolbox Pattern Comparison Processing Speed Test Age 7+ v2.0 Uncorrected Standard Score; **nihbtb_picture:** NIH Toolbox Picture Sequence Memory Test Age 8+ Form A v2.0 Uncorrected Standard Score; **nihbtb_reading:** NIH Toolbox Oral Reading Recognition Test Age 3+ v2.0 Uncorrected Standard Score; **nihbtb_fluidcomp:** Cognition Fluid Composite Uncorrected Standard Score; **nihbtb_cryst:** Crystallized Composite Uncorrected Standard Score; **nihbtb_totalcomp:** Cognition Total Composite Score Uncorrected Standard Score; **cbcl_scr_syn_anxdep:** Anxious/Depressed CBCL Syndrome Scale; **cbcl_scr_syn_withdep:** Withdrawn/Depressed CBCL Syndrome Scale; **cbcl_scr_syn_somatic:** Somatic Complaints CBCL Syndrome Scale; **cbcl_scr_syn_social:** Social Problems CBCL Syndrome Scale; **cbcl_scr_syn_attention:** Attention Problems CBCL Syndrome Scale; **cbcl_scr_syn_rulebreak:** Rule-Breaking Behavior CBCL Syndrome Scale; **cbcl_scr_syn_aggressive:** Aggressive Behavior CBCL Syndrome Scale; **cbcl_scr_syn_internal:** Internalizing Problems CBCL Syndrome Scale; **cbcl_scr_syn_external:** Externalizing Problems CBCL Syndrome Scale; **cbcl_scr_dsm5_depress:** Depressive Problems CBCL DSM5 Scale; **cbcl_scr_dsm5_anxdisord:** Anxiety Problems CBCL DSM5 Scale; **cbcl_scr_dsm5_somaticpr:** Somatic Problems CBCL DSM5 Scale; **cbcl_scr_dsm5_adhd:** ADHD CBCL DSM5 Scale; **cbcl_scr_dsm5_opposite:** Oppositional Defiant Problems CBCL DSM5 Scale; **cbcl_scr_dsm5_conduct:** Conduct Problems CBCL DSM5 Scale; **cbcl_scr_07_sct:** Sluggish Cognitive Tempo (SCT) CBCL Scale2007 Scale; **cbcl_scr_07_ocd:** Obsessive-Compulsive Problems (OCD) CBCL Scale2007 Scale; **cbcl_scr_07_stress:** Stress Problems CBCL Scale2007 Scale.

Table 2. The correlation between the sleep duration and the cognitive and psychiatric problems scores. A high cognitive score means better performance, and a high psychiatric score means a worse mental state. All cognitive measures were positively correlated with sleep duration and all psychiatric problems scores were negatively correlated with sleep duration (Bonferroni corrected, $p < 0.05$), indicating that the children with short sleep duration tend to have poor cognitive performance, and psychiatric problems. Positive t values indicate positive correlations; negative t values indicate negative correlations.

NIH Toolbox Cognition Battery Scores							
Cognitive measurement	r value	Cohen's d	p value	Cognitive measurement	r value	Cohen's d	p value
nihtbx_picvocab	0.060	0.121	3.2×10^{-10}	nihtbxreading	0.051	0.103	8.3×10^{-8}
nihtbx_list	0.038	0.077	6.5×10^{-5}	nihtbx_fluidcomp	0.049	0.099	2.6×10^{-7}
nihtbx_cardsort	0.039	0.077	5.8×10^{-5}	nihtbx_cryst	0.069	0.138	5.9×10^{-13}
nihtbx_pattern	0.032	0.063	9.3×10^{-4}	nihtbx_totalcomp	0.069	0.139	5.8×10^{-13}
Parent Child Behavior Checklist Scores							
Psychiatric measurement	r value	Cohen's d	p value	Psychiatric measurement	r value	Cohen's d	p value
cbcl_scr_syn_anxdep	-0.100	-0.201	$< 1 \times 10^{-10}$	cbcl_scr_dsm5_depress	-0.208	-0.425	$< 1 \times 10^{-10}$
cbcl_scr_syn_withdep	-0.120	-0.242	$< 1 \times 10^{-10}$	cbcl_scr_dsm5_anxdisord	-0.114	-0.229	$< 1 \times 10^{-10}$
cbcl_scr_syn_somatic	-0.079	-0.159	$< 1 \times 10^{-10}$	cbcl_scr_dsm5_somaticpr	-0.062	-0.124	$< 1 \times 10^{-10}$
cbcl_scr_syn_social	-0.118	-0.237	$< 1 \times 10^{-10}$	cbcl_scr_dsm5_adhd	-0.128	-0.258	$< 1 \times 10^{-10}$
cbcl_scr_syn_thought	-0.187	-0.380	$< 1 \times 10^{-10}$	cbcl_scr_dsm5_opposit	-0.108	-0.217	$< 1 \times 10^{-10}$
cbcl_scr_syn_attention	-0.134	-0.270	$< 1 \times 10^{-10}$	cbcl_scr_dsm5_conduct	-0.113	-0.227	$< 1 \times 10^{-10}$
cbcl_scr_synulebreak	-0.118	-0.238	$< 1 \times 10^{-10}$	cbcl_scr_07_sct	-0.099	-0.200	$< 1 \times 10^{-10}$
cbcl_scr_syn_aggressive	-0.119	-0.240	$< 1 \times 10^{-10}$	cbcl_scr_07_ocd	-0.104	-0.209	$< 1 \times 10^{-10}$
cbcl_scr_syn_internal	-0.120	-0.242	$< 1 \times 10^{-10}$	cbcl_scr_07_stress	-0.146	-0.295	$< 1 \times 10^{-10}$
cbcl_scr_syn_external	-0.126	-0.254	$< 1 \times 10^{-10}$	cbcl_scr_syn_totprob	-0.156	-0.315	$< 1 \times 10^{-10}$

Figure 1. Sleep duration, and cognitive and psychiatric problems scores. A) The correlation between sleep duration and a wide variety of measurements including physical and mental health, neuro-cognition, substance use, culture, environment and mobile technology, etc. Here we highlight the 17 measurements that are significantly correlated with sleep duration. For example, the positive r value for the cognition scores indicates that long sleep duration is positively correlated with good cognition. The full names for these measurements are shown below and the details for each item are provided in Table S1. **B) A histogram showing the relation between the number of hours of sleep and cognitive measures.** The Y axis is the cognitive score and the error bar is the SEM. There was a significant correlation between the cognitive score and the number of hours of sleep (Bonferroni corrected, $p < 0.05$). The children with long sleep duration tended to have good cognitive performance. **C) A histogram showing the relation between the number of hours of sleep and the psychiatric problems scores.** The Y axis is the psychiatric problems score and the error bar is the SEM. There was a significant negative correlation between the psychiatric problems scores and the number of hours of sleep (Bonferroni corrected, $p < 0.05$). The children with short sleep duration tended to have high psychiatric problems scores.



Note: **abcd_saiq02:** ABCD Parent Sports and Activities Involvement Questionnaire (SAIQ); **abcd_sds01:** ABCD Parent Sleep Disturbance Scale for Children; **abcd_ssp01:** ABCD Sum Scores Physical Health Parent; **abcd_tbss01:** ABCD Youth NIH TB Summary Scores; **abcd_asrs01:** Adult Self Report summary scores; **abcd_cbcl01:** ABCD Parent Child Behavior Checklist Raw Scores Aseba (CBCL); **abcd_cbcls01:** Child Behavior Check List summary scores; **abcd_ksad01:** ABCD Parent Diagnostic Interview for DSM-5 Full; **abcd_ksad01:** ABCD Parent Diagnostic Interview for DSM-5 Full (KSADS-5); **abcd_ksad501:** ABCD Youth Diagnostic Interview for DSM-5 (KSADS-5); **abcd_pgbi01:** ABCD Parent Parent General Behavior Inventory-Mania; **abcd_ssbpmtf01:** ABCD Summary Scores Brief Problem Monitor-Teacher Form for Ages 6-18; **dibf01:** ABCD Parent Diagnostic Interview for DSM-5 Background Items Full; **pasr01:** ABCD Parent Adult Self Report Raw Scores Aseba; **abcd_rhds01:** Residential History Derived Scores; **fes02:** ABCD Parent Family Environment Scale-Family Conflict Subscale Modified from PhenX; **maev01:** ABCD Parent Mexican American Cultural Values Scale Modified; **abcd_stq01:** ABCD Youth Screen Time Survey.

Figure 2. Brain regions with their area significantly related to sleep duration, cognitive scores, and depressive scores. A) Brain regions with their cortical area significantly associated with sleep duration (FDR corrected, $p < 0.005$). The red color indicates brain regions with high area positively associated with longer sleep duration. B) Brain regions with their area significantly associated with the cognitive total score (FDR corrected, $p < 0.005$). The red color indicates brain regions where high area is positively correlated with a higher cognitive score. Here, we only show the regions with Cohen's d larger than 0.15. C) Brain regions with their area significantly associated with the depressive problems score (FDR corrected, $p < 0.005$). Blue indicates brain regions with a negative correlation between area and the depressive problems score (i.e. a low cortical area is associated with depressive problems). The brain regions shown here were confirmed using a non-parametric approach that utilized a permutation test (with 5,000 random samplings). D) Brain regions with their area associated with both sleep duration and the cognitive total score. The regions shown are the overlap of what is shown in A and B. E) Brain regions with their area associated with both sleep duration and the depressive problems score. The regions shown are the overlap of what is shown in A and C.

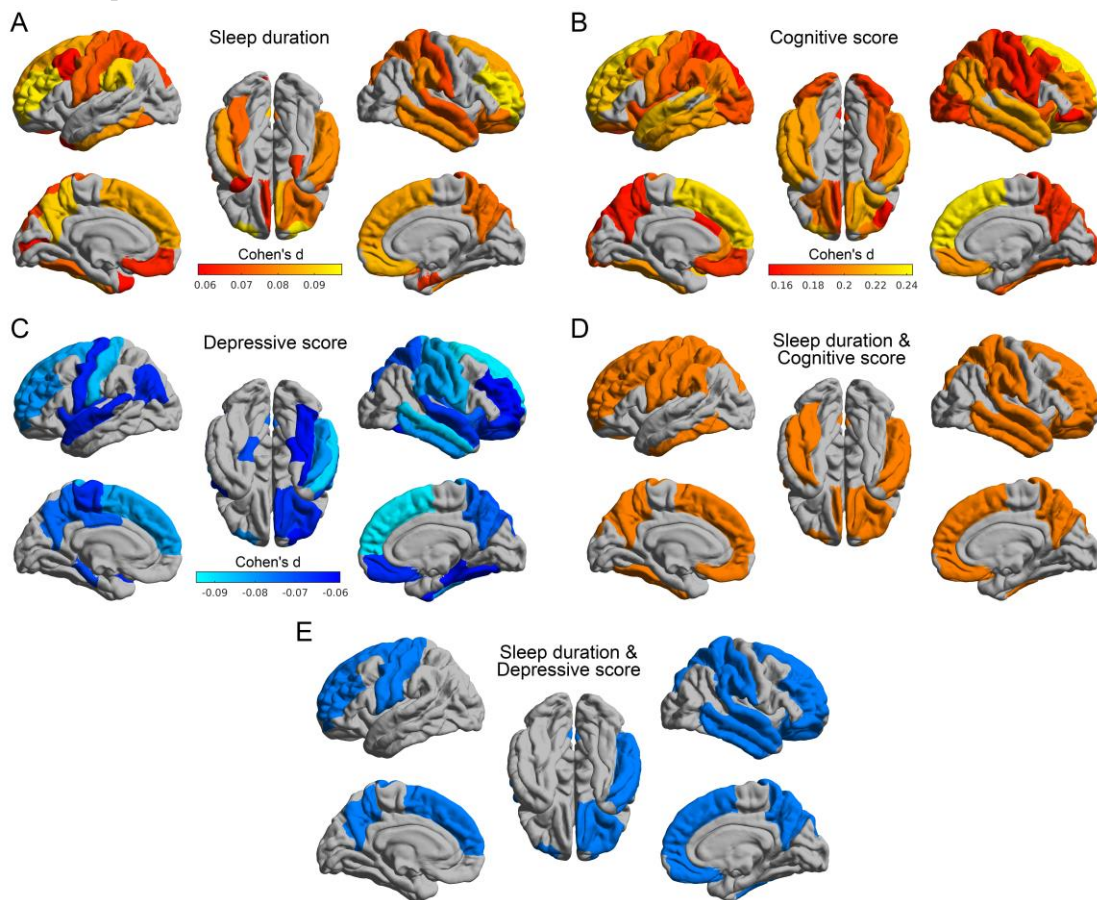
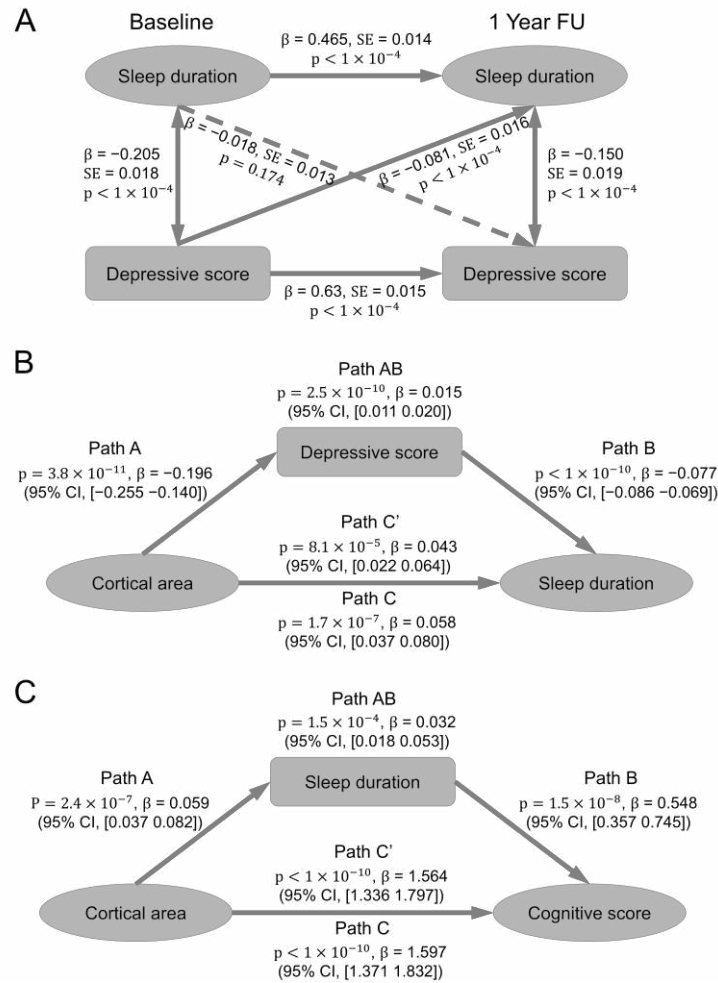


Figure 3. The relation between depressive problems scores and sleep duration. A) The longitudinal association between the depressive problems score and the sleep duration revealed by structural equation modelling (using a two-wave cross-lagged panel model). The depressive problems score was significantly associated with lower sleep duration measured one year later ($\beta = -0.081$, $SE = 0.016$, $p < 1 \times 10^{-4}$); and the reverse (dashed line) was not true ($\beta = -0.018$, $SE = 0.013$, $p = 0.174$). **B) Mediation analysis:** the mediation implemented by depressive problems from the cortical area on sleep duration was significant ($\beta = 0.015$, $p = 2.5 \times 10^{-10}$). The indirect path (A, AB and B) shows that the depressive problems score mediates part of the effect of cortical area on sleep duration. Path A: Effect of the independent variable, the mean cortical area of the brain regions shown in Fig. 2E which are associated with both sleep duration and the depressive score, on the mediator, the depressive problems score; Path B: the effect of the mediator (depressive problems score) on the outcome (sleep duration); Path C shows that the regression coefficient (beta value) of the cortical area on the sleep duration was high when the sleep duration was not taken into account. The beta values show the regression coefficient of the effect of the independent variable (cortical area) on the dependent variable (sleep duration). Path C' indicates the direct effect of the cortical area on the outcome (sleep duration) controlling for the mediator (the depressive problems score). Path C' shows some reduction in the regression coefficient when the effect of the depressive problems score was taken into account. Path AB indicates the extent to which taking the depressive problems score into account can explain the 25.9% effect of the cortical area on sleep duration, which is significant as noted above at $p = 2.5 \times 10^{-10}$. **C) Mediation analysis:** the mediation implemented by sleep duration from the cortical area on cognition was significant ($\beta = 0.032$, $p = 1.5 \times 10^{-4}$). SE, standard error.



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