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Decoupling Sleep and Brain Size in Childhood: An Investigation of Genetic Covariation in the Adolescent Brain Cognitive Development Study

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ABSTRACT

BACKGROUND: Childhood sleep problems are common and among the most frequent and impairing comorbidities of childhood psychiatric disorders. In adults, sleep disturbances are heritable and show strong genetic associations with brain morphology; however, little is known about the genetic architecture of childhood sleep and potential etiological links between sleep, brain development, and pediatric-onset psychiatric symptoms.

METHODS: Using data from the Adolescent Brain Cognitive Development Study ($n_{Phenotype}$ = 4428 for discovery/replication, $n_{Genetics}$ = 4728; age 9–10 years), we assessed phenotypic relationships, heritability, and genetic correlations between childhood sleep disturbances (insomnia, arousal, breathing, somnolence, hyperhidrosis, sleep-wake transitions), brain size (surface area, cortical thickness, volume), and dimensional psychopathology.

RESULTS: Sleep disturbances showed widespread positive associations with multiple domains of childhood psychopathology; however, only insomnia showed replicable associations with smaller brain surface area. Among the sleep disturbances assessed, only insomnia showed significant heritability (h^2_{SNP} = 0.15, $p < .05$) and showed substantial genetic correlations with externalizing and attention-deficit/hyperactivity disorder symptomatology (r_Gs > 0.80, ps $< .05$). We found no evidence of genetic correlation between childhood insomnia and brain size. Furthermore, polygenic risk scores calculated from genome-wide association studies of adult insomnia and adult brain size did not predict childhood insomnia; instead, polygenic risk scores trained using attention-deficit/hyperactivity disorder genome-wide association studies predicted decreased surface area at baseline as well as insomnia and externalizing symptoms longitudinally.

CONCLUSIONS: Findings demonstrate a distinct genetic architecture underlying childhood insomnia and brain size and suggest genetic overlap between childhood insomnia and attention-deficit/hyperactivity disorder symptomatology. Additional research is needed to examine how genetic risk manifests in altered developmental trajectories and comorbid sleep/psychiatric symptoms across adolescence.

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Sleep disturbances are nearly universally observed in childhood and adult psychiatric disorders and are often among the most impairing comorbidities (1). In adults, genome-wide association studies (GWASs) have shown that sleep-related behaviors are heritable and polygenic, with more than 200 associated genetic loci, and show significant genetic correlations with adult psychiatric disorders including depression and schizophrenia (2–5). Genetic variants associated with adult sleep disorders are enriched for genes expressed in the brain and have implicated pathways involved in locomotor behavior, neurodevelopment, and synaptic transmission, among others (2–5), suggesting a neurogenetic basis for individual differences in sleep behavior. Yet, while the heritable polygenic contributions to adult sleep disturbances have been established, much less is known about the origins of sleep-related traits in childhood, a developmental period during which sleep disruptions are extremely common, affecting an estimated 20% to 30% of the general pediatric population (6–8). Identifying a genetic basis for childhood sleep disturbances—and potential shared genetic etiology with neurodevelopmental, psychiatric disorders—would provide a critical foundation for understanding fundamental aspects of developmental biology and for fostering potential clinical interventions for the millions of children who experience sleep disturbances.

Adolescence is characterized by age-related decreases in gray matter volume (VOL), surface area (SA), and cortical thickness (CT) (9,10), coinciding with normative shifts in the timing of homeostatic and circadian rhythms (11) and the emergence of lifelong chronic psychiatric disorders (12). Childhood and adolescent sleep disturbances have been linked to widespread changes in brain morphology, including reduced white matter integrity and smaller brain SA and VOL, as well as to lower cognitive scores and higher psychiatric

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symptoms (13–15). In addition to sleep disturbance, atypical brain structure has also been observed across major psychiatric disorders (16,17), and recent work suggests that deviations from normative trajectories of structural brain development may be a predictor of psychiatric symptoms in children and adolescents (18). Thus, biological interactions between sleep, brain structure, and mental health may be particularly important during childhood, when dynamic changes occur in all three domains. Indeed, childhood symptoms of attention-deficit/hyperactivity disorder (ADHD) and depression have been shown to mediate the relationship between childhood sleep and brain size (14,15), and it has recently been hypothesized that the relationship between sleep, brain structure, and mental health is due to shared genetic and phenotypic effects on brain morphology (19). However, few large-scale genetic studies have been conducted to identify a heritable basis for sleep disturbances in childhood or to elucidate potential genetic relationships between sleep disturbances and childhood cognitive and psychiatric traits. By contrast, there has been robust and well-powered genomics research in adults indicating significant genetic pleiotropy between adult insomnia, sleep duration, neuropsychiatric disorders (2,3,5), and brain SA (20), indicating that the genetic risk for these traits in adulthood is in part shared. Parallel analyses of the shared genetic architecture between childhood sleep psychiatric symptoms and brain structure have not been performed and may provide novel insights into the developmental origins of comorbid psychiatric/brain traits.

To address these questions, we performed a comprehensive examination of the phenotypic and genetic relationship between sleep, cognition, mental health, and brain structure in youths who participated in baseline and follow-up assessments of the Adolescent Brain Cognitive Development (ABCD) Study (21). Using parent-report data, we determined the extent to which individual variability across six dimensions of sleep disturbances predicted individual variability in fluid, crystallized, and total cognition, 20 subscales of psychiatric symptomatology, and magnetic resonance imaging (MRI) measures of brain VOL, SA, and CT at 9 to 10 years of age. To estimate the contribution of common genetic factors, we calculated the heritability of—and genetic correlations between—childhood sleep, cognition, psychiatric symptoms, and global brain size. Finally, we examined the extent to which polygenic risk scores (PRSs) for sleep, brain, and psychiatric traits predict brain and behavioral phenotypes in children at 9 to 10 years of age and psychiatric symptoms 1 year later.

METHODS AND MATERIALS

Subjects

Participants were youths who completed the baseline and 1-year follow-up assessment of the ABCD Study (21), an ongoing multisite longitudinal investigation of brain development in the United States. De-identified structural neuroimaging, genetic, demographic, and behavioral data were obtained from the ABCD 2.0.1 National Data Archive data release (https://doi.org/10.15154/1504041). See Supplement 1 for additional information.

Sleep Disturbance Scale for Children

The Sleep Disturbance Scale for Children (SDSC) was used to generate dimensional indices of sleep problems. The SDSC is a parent-report questionnaire designed to identify the presence of sleep disturbances over the past 6 months in children with or without clinically significant sleep disorders (22). Individual item-level scores on the SDSC are grouped into 6 sleep disorder subscales: disorders of initiating and maintaining sleep (e.g., hours of nightly sleep, night waking), sleep breathing disorders (e.g., gasps, snores), disorders of arousal (e.g., sleepwalking, nightmares), sleep-wake transition disorders (e.g., twitching, jerking, sleep-talking), disorders of excessive somnolence (e.g., daytime tiredness), and sleep hyperhidrosis (e.g., excessive night sweating). The disorders of initiating and maintaining sleep subscale encompasses a single question relating to sleep duration as well as several questions indexing sleep quality (e.g., insomnia-related symptoms); we focused our analysis on disorders of initiating and maintaining sleep questions indexing insomnia-related symptoms (see Supplement 1). For all SDSC sleep measures, higher scores are indicative of more frequent sleep problems.

Child Behavior Checklist

The Child Behavior Checklist (CBCL) is a widely used parent-report questionnaire indexing child behavior across a number of psychiatric domains (23). CBCL scales have good construct validity and high discriminability (24,25); however, the CBCL is not a clinically validated diagnostic test. Here, we assess the relationship between sleep and T scores on 14 psychiatric syndrome scales and 6 DSM-oriented scales.

NIH Toolbox Cognition Battery

Cognitive function was assessed using the NIH Toolbox Cognition Battery (26), which was administered to children on an iPad. Summary scores indexing cognitive function composite score, fluid cognition composite score, and crystallized cognition composite scores were obtained for each child.

Structural MRI

Structural MRI (sMRI) data were collected by individual sites affiliated with the ABCD consortium on a Siemens Prisma, Philips, or GE 750 3T scanner (27). Morphometric measurements of CT, SA, and subcortical VOL were calculated in FreeSurfer (https://surfer.nmr.mgh.harvard.edu/) using the Desikan parcellation atlas (28). As recommended in the ABCD NDA 2.0.1 Release Notes for Imaging Instruments, exclusionary criteria included subjects with MRI findings that were considered for clinical referral (n = 402), subjects with poor-quality T1 images (as described above; n = 11), and subjects for whom the FreeSurfer parcellation performed poorly (n = 391). See Supplement 1 for additional information.

Phenotypic Associations

To demonstrate the robustness of the reported associations, the sample was split into discovery and replication cohorts. One child per twin/triplet was included to ensure the statistical independence of the data in each cohort; siblings were randomly assigned. The final sample for phenotypic

association analyses consisted of 8856 subjects, which were split into discovery (n = 4428) and replication (n = 4428) cohorts using the ISLR package in R version 4.0.2 (R Foundation for Statistical Computing).

Statistical analyses were performed in R. Linear mixed-effects models were run using the lme4 package to test the relationship between SDSC subscales and sMRI indices. Dependent variables included CT and SA (34 regions per hemisphere) as well as 39 measures of subcortical VOL. Independent variables were sleep-related phenotypes. Age, socioeconomic status (average of parental education and family income), sex, and parent-reported ethnicity were specified as fixed effects; family ID and MRI scanner were modeled as random effects. Analyses were performed with/without controlling for global sMRI measures. The relationship between CBCL and SDSC subscales was assessed using a series of log-linked gamma distribution general linear models and identical covariates. Results were deemed to be significant and to replicate if they survived false discovery rate correction ($q <$ .05) in the discovery cohort and demonstrated a $p <$ .05 in the replication cohort.

Single Nucleotide Polymorphism–Based Heritability and Genetic Correlations

Ancestry was determined by merging ABCD genotype data (see Supplement 1) with data from the 1000 Genomes Project (29) followed by principal component (PC) analysis and application of a k-nearest neighbors classification algorithm to the first four ancestry PCs. Subsequent analyses were restricted to subjects of European ancestry to control for population stratification. PLINK v1.90 (30) was used to prune single nucleotide polymorphisms (SNPs) for linkage disequilibrium, minor allele frequency <1%, missingness per individual >10%, missingness per marker >10%, and Hardy-Weinberg equilibrium ($p < 10^{-6}$). The genetic relationship matrix was computed from autosomal chromosomes using GCTA v1.93 (31). A relatedness cutoff of 0.05 was applied, leaving 4728 unrelated European subjects and 157,123 genotyped SNPs that passed quality control. Ancestry PCs for the European cohort were calculated in PLINK.

SNP-based heritability (i.e., the proportion of phenotypic variance that is accounted for by common genetic variation) was estimated using GCTA's restricted maximum likelihood. Owing to nonnormality, the SDSC subscales were binarized; subjects scoring in the top 25% of each subscale were defined as experiencing sleep problems (i.e., cases), and the remainder served as a control group. Rank-based inverse normal transformation was applied to continuous phenotypes to correct for deviations from normality. For heritability estimates, covariates included age, sex, socioeconomic status, 10 ancestry PCs, and genotyping batch, in addition to MRI scanner for neuroimaging phenotypes. Bivariate genetic correlations—indicating the extent to which two traits' shared phenotypic variance is due to shared genetic causes—were calculated in GCTA with identical covariates (32).

Polygenic Risk Score Profiling

Polygenic risk scores (PRSs) were computed for European subjects using PRS-CS (33) (see Supplement 1) with summary statistics from GWASs of insomnia (2), ADHD (34), and brain SA (20). Genotype data were imputed using the Michigan Imputation Server (35) using the TOPMed reference panel with Eagle v2.3 phased output and mixed ancestry for quality control. Individuals with >10% missing genotypes; SNPs with >10% missingness rate, minor allele frequency <5%, or out of Hardy-Weinberg equilibrium ($p < 10^{-6}$); and SNPs in the major histocompatibility complex were removed. A relatedness cutoff of 0.05 was applied, leaving 3386 subjects at baseline and 1669 at follow-up. The extent to which youths' PRSs predicted the binary insomnia phenotype was assessed using logistic regression controlling for age, socioeconomic status, sex, and 10 ancestry PCs. Predictions of baseline and follow-up CBCL subscales were assessed using log-linked gamma general linear models using identical covariates. Linear mixed-effects models were used to assess the relationship between PRS and brain structure, using an additional covariate of MRI scanner. All regressions using follow-up data were controlled for sleep or psychiatric symptoms at the first time point.

RESULTS

Sample Characteristics

The mean age of youths in the discovery and replication cohorts was 118.8 months (9.9 years), with a range of 108 to 131 months (9.0–10.9 years). Cohorts were matched on age, cognitive functioning, sex, ethnicity, handedness, and site (Table S2 in Supplement 2). The cohorts were ethnically diverse, with roughly 2% of participants self-identifying as Asian, 14% as Black, 20% as Hispanic, 54% as White, and 10% as Other. Males and females represented approximately 52% and 48% of the sample, respectively.

Widespread Associations Between Child Sleep Disturbance and Psychiatric Symptoms

Phenotypic associations between sleep and psychiatric symptoms were tested in discovery (n = 4428) and replication (n = 4428) cohorts. Regression analyses revealed replicable positive associations; greater frequency of any sleep disturbance predicted higher levels of psychiatric symptomatology across all 20 CBCL subscales (βs = 0.009–0.10) (Figure 1; Tables S3–8 in Supplement 2). In addition, a small but significant negative relationship was observed between insomnia and fluid cognition (β = −0.008) (Figure 1; Table S3 in Supplement 2).

Childhood Insomnia Is Uniquely Associated With Decreased Brain SA and VOL

We next examined the relationship between childhood sleep disturbances and global measures of brain structure (mean CT, mean SA, and whole-brain VOL) at baseline. More frequent insomnia showed replicable associations with lower SA and smaller VOL (Figure 2A; Table S9 in Supplement 2). No other sleep disturbance showed replicable associations with global brain structure, nor were any measures associated with CT. As such, childhood insomnia was uniquely associated with global measures of childhood brain structure.

At the regional level, greater frequency of insomnia symptoms was related to reduced SA in the frontal, temporal, and

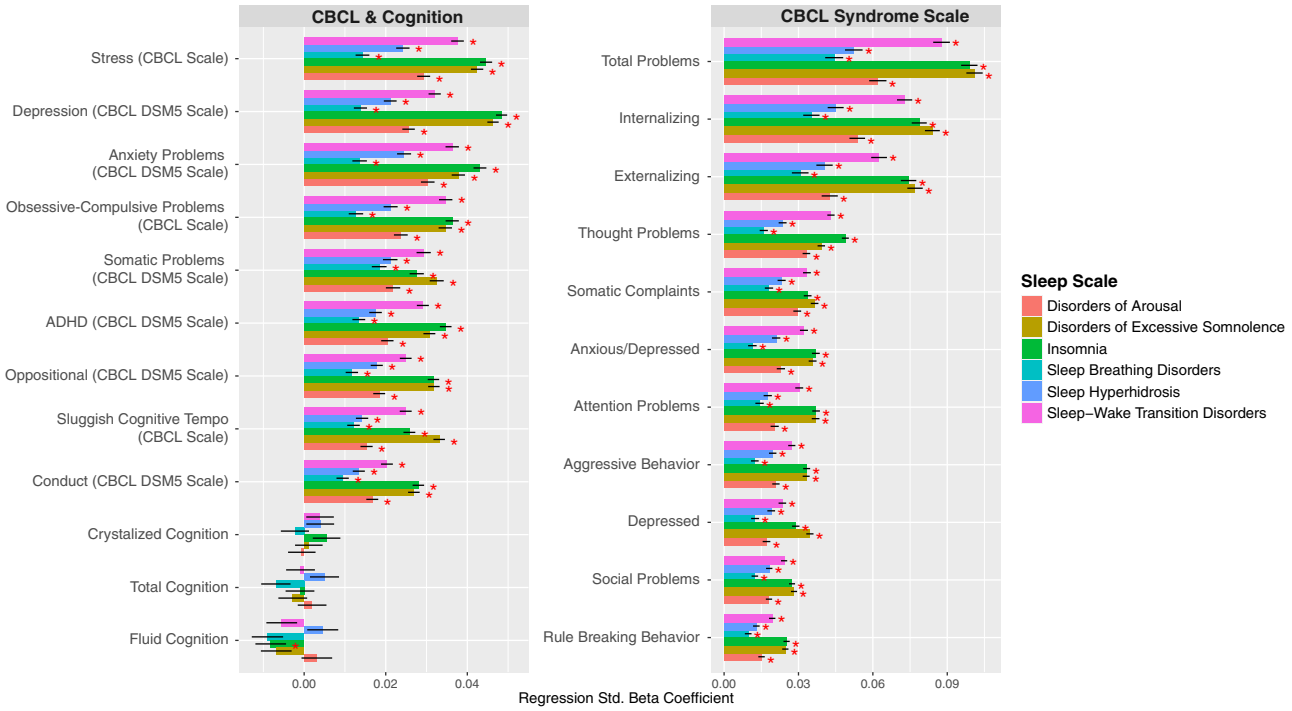

Figure 1. Broad phenotypic associations between childhood sleep and psychiatric symptoms. Sleep disturbances show replicable associations (discovery cohort: n = 4428; replication cohort: n = 4428) with CBCL subscales of behavioral/emotional problems and NIH Toolbox fluid cognition. Variables showing a significant association with sleep subscales in the discovery cohort after false discovery rate correction ($q < .05$) and demonstrating a nominally significant association in the replication cohort ($p < .05$) are denoted by an asterisk. Data shown reflect associations in the discovery cohort. For statistical associations in the replication cohort, see Supplement 1. ADHD, attention-deficit/hyperactivity disorder; CBCL, Child Behavior Checklist.

parietal regions, as well as to smaller VOL of cerebral white matter (Figure 2B; Tables S10 and S11 in Supplement 2). Regional findings were no longer significant when controlling for global measures, indicating that the association between insomnia and whole-brain SA and VOL is an important contributor to the observed region-level effects

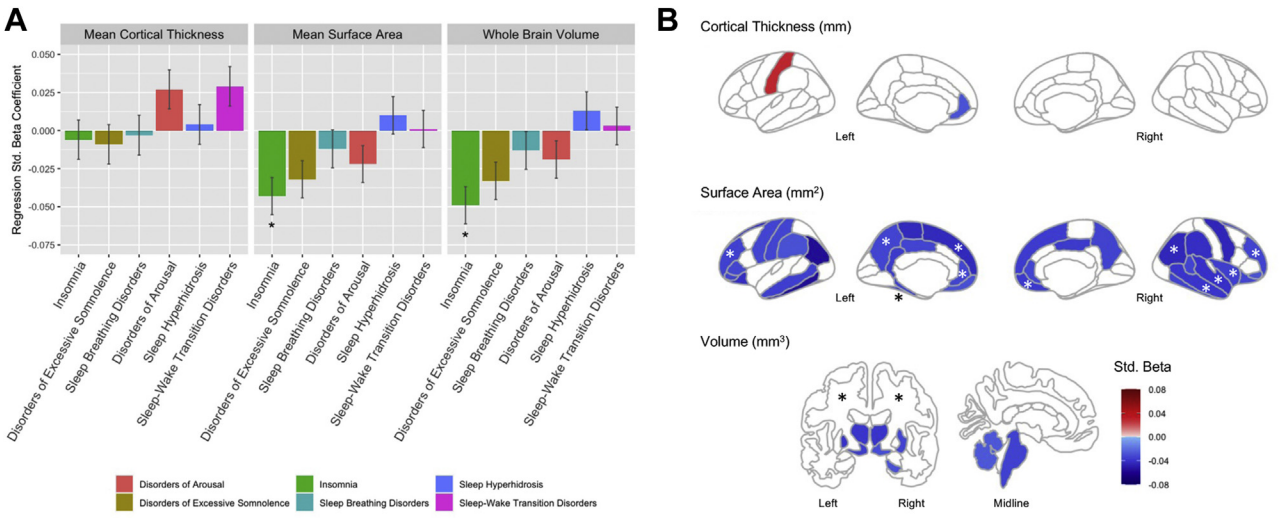

Figure 2. More frequent insomnia symptoms are associated with smaller brain size in 9- to 10-year-old youths. **(A)** Associations between sleep disturbances and global measures of mean cortical thickness, mean surface area, and whole-brain volume. Variables showing a significant association with sleep subscales in the discovery cohort (n = 4428) after false discovery rate correction ($q < .05$) and demonstrating a nominally significant association in the replication cohort (n = 4428) ($p < .05$) are denoted by an asterisk. **(B)** Brain regions demonstrating a significant association with insomnia in the discovery cohort ($q < .05$) are shown in color; regions also demonstrating a significant association in the replication cohort ($p < .05$) are denoted by an asterisk. In both panels, plotted data reflect associations in the discovery cohort. For statistical associations in the replication cohort, see Supplement 1.

(Tables S12 and S13 in Supplement 2). No other SDSC subscales demonstrated replicable effects (Tables S14–30 in Supplement 2).

Childhood Insomnia Exhibits Significant SNP-Based Heritability

We next sought to determine the contribution of common genetic variation to childhood sleep, psychiatric symptoms, and brain structure. Among childhood sleep-related phenotypes, significant SNP-based heritability was observed for insomnia only (h^2_{SNP} = 0.15, $p < .05$) (Figure 3A; Table S31 in Supplement 2). Significant SNP-based heritability was also observed for CBCL subscales indexing symptoms of ADHD, attention problems, somatic problems, externalizing, oppositional defiant disorder, and total problems (h^2_{SNP} = 0.15–0.22, $ps < .05$), NIH Toolbox measures of fluid, crystallized, and fluid cognition (h^2_{SNP} = 0.29–0.36, $ps < .001$) and neuroimaging measures of whole-brain VOL, mean SA, and mean CT (h^2_{SNP} = 0.27–0.37, $ps < .01$).

Genetic Overlap Between Childhood Insomnia, ADHD, and Externalizing Behaviors

Pairwise genetic correlations were performed between traits that demonstrated significant SNP heritability to investigate potential shared genetic influences on psychiatric symptoms and brain structure in childhood. Significant positive genetic correlations were observed between insomnia and CBCL total problems, externalizing symptoms, and ADHD symptoms (r_Gs > 0.84; $ps < .05$) (Figure 3B; Table S32 in Supplement 2). For neuroimaging traits, significant positive correlations were observed between whole-brain VOL and mean SA, between whole-brain VOL and crystallized cognition and total cognition, and between mean SA and crystallized cognition (r_Gs $>$ 0.53, $ps < .05$) (Table S32 in Supplement 2). Notably, however, we did not detect significant genetic correlations between childhood insomnia and brain CT, SA, or VOL. These results indicate a shared genetic basis among childhood insomnia, ADHD symptoms, and externalizing behaviors that does not contribute to decreased brain size.

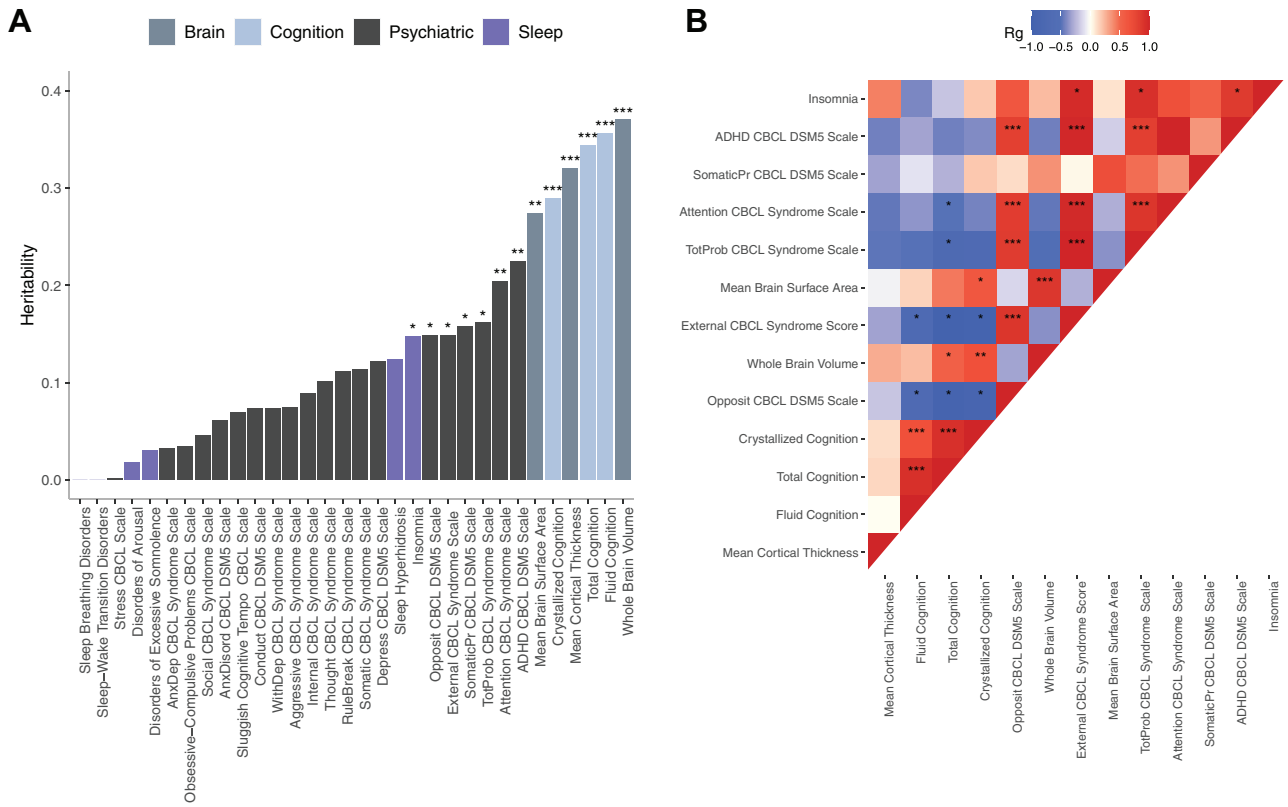

Figure 3. Genetic analyses indicate that childhood insomnia is heritable and demonstrates significant genetic correlation with ADHD and externalizing symptoms. **(A)** SNP-based heritability of childhood sleep-related behaviors, psychiatric symptoms, and brain size (n = 4728 [European ancestry]). Among sleep-related traits, only insomnia demonstrates significant SNP-based heritability (h^2_{SNP} = 0.15, $p < .05$). **(B)** Genetic correlations between pairs of traits that displayed significant SNP heritability. Childhood insomnia shows significant genetic pleiotropy with ADHD, externalizing, and total problems subscales of the Child Behavior Checklist (r_Gs > 0.84, $ps < .05$; n = 4728 [European ancestry]). *$p < .05$, **$p < .01$, ***$p < .001$. ADHD, attention-deficit/hyperactivity disorder; AnxDep, anxious/depressed; AnxDisord, anxiety disorder; CBCL, Child Behavior Checklist; Depress, depression; Opposit, oppositional defiant disorder; SNP, single nucleotide polymorphism; SomaticPr, somatic problems; TotProb, total problems; WithDep, withdrawn/depressed.

Distinct Genetic Contributions to Childhood Versus Adult Insomnia

The previous data identify a heritable basis for childhood insomnia, exhibiting genetic and phenotypic overlap with ADHD/externalizing symptoms. To replicate and extend these associations, we calculated PRSs using the largest available GWAS summary statistics of insomnia (in adults) and ADHD. Surprisingly, PRSs trained using weights derived from adult insomnia GWAS did not predict the frequency of childhood insomnia symptoms at 9 to 10 years of age, frequency of insomnia symptoms at follow-up 1 year later, or the binary insomnia phenotype at either time point (Figure 4A, B; Table S33 in Supplement 2). The insomnia PRS did, however, predict baseline ADHD symptoms ($\beta = 0.006$, $p < .01$) (Figure 4B), indicating that the GWAS was adequately powered to detect phenotypic associations. Mirroring our observed genetic correlations, higher ADHD PRS was associated with the binary insomnia phenotype at both the baseline and 1-year follow-up time points ($\beta_{Baseline} = 0.11$, $\beta_{Follow\text{-}up} = 0.15$, $ps < .05$) (Figure 4B). As a positive control, the ADHD PRS also significantly predicted baseline and follow-up externalizing ($\beta_{Baseline} = 0.02$, $\beta_{Follow\text{-}up} = 0.01$, $ps < .05$) and ADHD ($\beta_{Baseline} = 0.01$, $\beta_{Follow\text{-}up} = 0.01$, $ps < .01$) symptoms (Figure 4B). Together, these results demonstrate that the common genetic variants contributing to the heritability of insomnia symptoms in adults are largely distinct from those in children.

Insomnia-Brain Structure Associations Are Driven by ADHD PRS

Finally, we sought to better understand the observed, replicated phenotypic associations between insomnia and decreased brain SA. Here, we generated PRSs to predict the

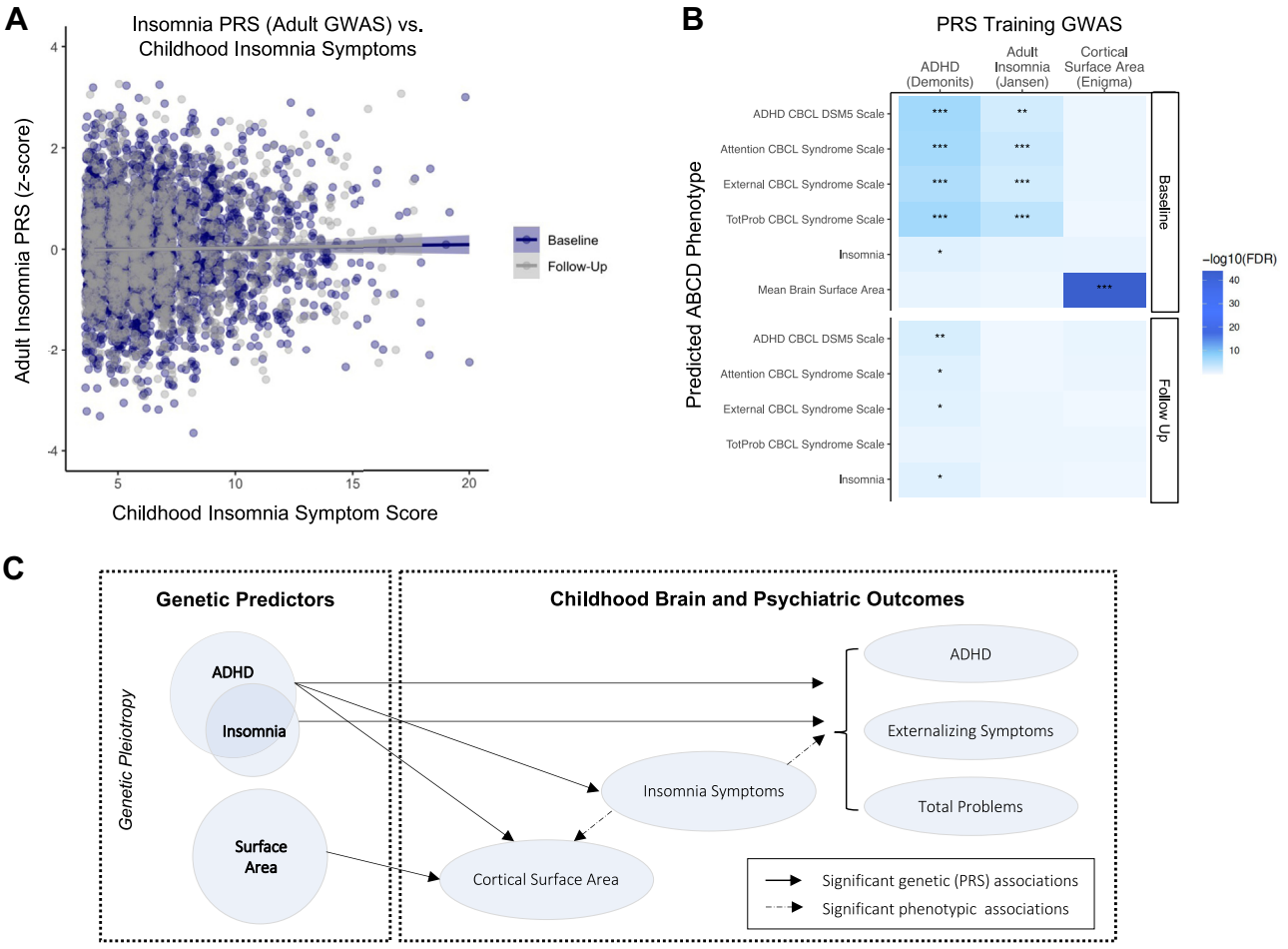

Figure 4. Polygenic risk for ADHD—but not insomnia—contributes to smaller brain size, insomnia, and externalizing behaviors in childhood. **(A)** PRSs trained using weights from GWAS of insomnia (2) in adulthood did not predict insomnia symptoms in 9- to 10-year-old children (baseline) or at follow-up 1 year later (*ps* = not significant). **(B)** PRSs trained using GWASs of ADHD (34) predicted not only externalizing-related behaviors at baseline and follow-up, but also insomnia at both time points. **(C)** Proposed model of associations between genetic risk, sleep, and mental health outcomes. The pleiotropic effects of shared genetic risk between ADHD and insomnia drive observations of smaller brain surface area, more frequent insomnia symptoms, and childhood externalizing symptoms. $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$. ABCD, Adolescent Brain Cognitive Development; ADHD, attention-deficit/hyperactivity disorder; FDR, false discovery rate; GWAS, genome-wide association study; PRS, polygenic risk score; TotProb, total problems.

genetic component of brain SA using the largest available GWAS from ENIGMA (20). As a positive control, the SA PRS very strongly predicted brain SA in the ABCD cohort ($\beta = 0.23$, $p < .001$) (Figure 4B; Table S33 in Supplement 2). In contrast, the SA PRS was not associated with childhood insomnia symptoms (p = not significant), affirming our null genetic correlation results. To determine whether genetic overlap with ADHD symptoms could account for the observed insomnia-brain structure associations, we performed a series of follow-up analyses in brain regions where we found replicable phenotypic associations (Figure 2B). Notably, the ADHD PRS significantly predicted lower SA in three regions—the left superior frontal gyrus, left rostral middle frontal gyrus, and right insula (βs = −0.04 to −0.03, ps < .05). Additionally, the association between insomnia and brain SA disappeared when conditioning on ADHD symptoms. Together, these findings support a dissociable pleiotropic model in which genetic risk for ADHD symptomatology contributes separately to both smaller brain SA and insomnia in childhood, such that insomnia symptoms are not predicted by brain structure (Figure 4C). In support of this model, we observed that the ADHD PRS continues to predict the binary insomnia phenotype at baseline and follow-up time points even when controlling for brain structure (i.e., mean cortical SA; $\beta_{Baseline} = 0.11$, $\beta_{Follow\text{-}up} = 0.15$, ps < .05) and its potential genetic drivers (i.e., SA PRS; $\beta_{Baseline} = 0.11$, $\beta_{Follow\text{-}up} = 0.15$, ps < .05). Altogether, these findings refine our understanding of the genetic architecture of childhood insomnia as well as its relationship to adult insomnia, childhood brain structure, and developmental psychopathology.

DISCUSSION

The current study examined phenotypic relationships, heritability, and genetic correlations between childhood sleep disturbances, brain size, and psychiatric symptoms. Among the six childhood sleep disturbances examined, only childhood insomnia showed replicable associations with brain size and significant heritability ($h^2_{SNP} = 0.15$). We demonstrate positive genetic correlations between insomnia and ADHD/externalizing symptoms, indicating shared genetic etiology (i.e., pleiotropy) across these complex childhood traits. At the phenotypic level, the frequency with which youths experienced insomnia symptoms was broadly associated with greater parent-reported psychiatric symptomatology and was negatively associated with structural neuroimaging measures of whole-brain VOL, mean cortical SA, and regional SA in the frontal, parietal, and temporal cortices. Despite these phenotypic associations, we did not observe genetic correlations between childhood insomnia and brain size, suggesting distinct genetic mechanisms. Further, PRSs trained using weights from adult GWASs of brain size did not predict childhood insomnia symptoms. Rather, insomnia could be predicted by the PRS for ADHD, even when controlling for brain structure. These findings highlight a model of shared polygenic mechanisms underlying sleep quality and externalizing traits in childhood and suggest that childhood insomnia is associated with genetic risk for ADHD.

One mechanism through which sleep may affect trajectories of brain development is through alterations of normative developmental processes, including synaptic pruning. In adult mice, chronic sleep deprivation has been associated with upregulation of astrocytic phagocytosis and microglial activation, resulting in enhanced synaptic degradation (36). Thus, long-term disturbances in sleep may promote prolonged microglial activation, making the brain more susceptible to other genetic and environmental insults. Indeed, we found that poorer sleep—across multiple dimensions of sleep behavior—is consistently associated with higher levels of parent-endorsed psychiatric symptoms. Notably, the relationship between more frequent sleep problems and higher levels of psychiatric symptoms was not specific to any one sleep domain, suggesting that disruptions to sleep cycles generally may increase liability for psychiatric symptoms. Alternatively, these findings may be due to correlated scores across the SDSC sleep subscales, as has been reported previously (37). Indeed, while the SDSC was designed for use in typically developing children and in those with sleep disturbances, the six-scale factor structure may not provide an optimal fit in youths with elevated psychiatric symptoms (38,39), potentially resulting in overlap in terms of the variance explained by each subscale. Overall, our multitrait sleep analysis extends the findings of recent population-representative pediatric sleep studies, which have narrowly focused on either sleep duration (15,40) or a limited number of psychiatric traits (14), and suggest that behavioral interventions aimed at improving the full range of sleep issues experienced by youths may improve mental health across the clinical spectrum.

The SNP-based heritability of childhood insomnia was moderate ($h^2_{SNP} = 0.15$), similar to estimates previously reported in adults ($h^2_{SNP} = 0.07$–0.17) (2,41). We also observed similar estimates of heritability for childhood cognition ($h^2_{SNP} = 0.29$–0.36) and brain size (thickness, SA, VOL; $h^2_{SNP} = 0.27$–0.37) as those documented in large-scale genomics studies of adult educational attainment ($h^2_{SNP} = 0.22$) (42) and brain structure ($h^2_{SNP} \sim 0.26$–0.34) (20,43). In adults, common genetic variants affecting sleep, brain size, and mental health show high genetic correlations, suggestive of substantial pleiotropy (2,20,41). To test whether the heritable polygenic contributions to childhood sleep quality also affect childhood brain size, we generated bivariate genetic correlations between sleep-brain-psychiatric traits in our 9- to 10-year-old sample. Surprisingly, and in contrast to the adult literature, genetic correlations between childhood insomnia and brain size did not support the existence of genetic pleiotropy.

To validate these results, we used SNP weights derived from large-scale GWASs of adult insomnia and cortical SA to generate individual-level PRSs in the ABCD sample. Mirroring our null genetic correlations, the PRS for brain SA did not predict childhood insomnia. Instead, the PRS for ADHD was a significant predictor of both insomnia and SA in the frontal cortex and insula, which is consistent with recent studies showing genetic associations between ADHD, narcolepsy (44), and sleep disturbances more broadly (37). Our findings of positive genetic correlations between childhood sleep disturbance and ADHD symptoms are also in agreement with previous research documenting behavioral comorbidity (45,46) and overlapping affected neural systems (14). We hypothesize that the genetic relationship between ADHD and childhood insomnia induces a phenotypic correlation between childhood

insomnia and brain size. Altogether, these data indicate that despite similar heritability estimates, childhood and adult insomnia show distinct genetic correlations with other brain and behavioral traits and suggest that different genetic mechanisms may underlie the relationship between childhood sleep/neurodevelopmental and adult sleep/adult-onset psychiatric disorders. Supporting this hypothesis, animal studies indicate that sleep deprivation has age-dependent effects on hippocampal microglial activation, resulting in reduced expression of microglia receptors, impaired synaptic pruning, and greater numbers of excitatory synapses in adolescent mice versus increased gene expression of proinflammatory cytokines in adult mice (47). Together, these findings suggest that poor sleep may induce age-related differences in gene expression, leading to heterogeneous brain and behavioral correlates in children and adults. Ultimately, however, multiple waves of longitudinal data will be required to fully elucidate the temporal relationship between sleep, brain size, and cognitive/psychiatric symptoms throughout the human lifespan.

This study has several limitations. First, genetics analyses were restricted to youths of European ancestry to control for population stratification. This resulted in a modest sample size for genetics analyses and may have limited power to detect heritability and genetic correlations for childhood brain and psychiatric traits. Second, analyses were limited to youths within a narrow age range, when behavioral manifestations of psychiatric illness may not yet be present. This may have reduced the observed heritability of psychiatric traits that typically emerge later in adolescence/adulthood (e.g., internalizing problems). Thus, it will be crucial for future studies to examine how heritability estimates and patterns of genetic pleiotropy change across time, which may inform our understanding of the biological mechanisms underlying emerging comorbidities during particular developmental windows. Third, to maintain consistency, we relied on parent-report measures of children's sleep and psychiatric symptoms. Previous research is mixed, finding both low-moderate agreement between parent- and youth-report internalizing and externalizing behaviors (48) and strong correlations between informants (49). As there is no consensus regarding the use of parent versus youth informants as an index of adolescent mental health, further work is needed to examine how the relationship between youths' self-reported sleep and mental health may account for additional variance not adequately captured in parent report measurements. Finally, the standardized effect sizes observed in the current study ranged from $\beta = -0.003$ to 0.04 ($r = -0.05$ to 0.09) for associations between insomnia and other behavioral traits and from $\beta = -0.008$ to 0.10 ($r = -0.058$ to 0.15) for insomnia-brain associations. Our findings are inline with recent reports from large-scale neuroimaging studies such as the UK Biobank, in which the largest brain-behavior associations account for roughly 1% to 5% of variance explained (50), and findings from the ABCD study, in which significant behavioral associations have a median effect size of $r = 0.05$, with an interquartile range of 0.03 to 0.09 (51). The smaller-than-anticipated effect sizes that have emerged from well-powered cohort studies have led some to suggest that our interpretation of effect size may need to be recalibrated (51), as decades of psychiatric research on small sample sizes may have led to inflated expectations of population effect sizes, which in reality may be small and act in an additive manner to influence brain and behavioral development (52,53).

In sum, using publicly available data from a sociodemographically diverse sample of youths, we sought to elucidate the phenotypic and genetic associations between sleep, mental health, and brain structure. Overall, these data indicate that childhood insomnia is associated with polygenic risk for ADHD and that the link between genetic risk for sleep disturbance, sleep behavior, and psychiatric symptoms may change across the lifespan, underscoring the importance of further elucidating the relationship between sleep-related genes, brain, and behavior in developmental populations. As sleep is crucial for optimal cognition and mental health, a better understanding of the genetic and neural underpinnings of sleep disturbances in children is essential to further our understanding the relationship between sleep and brain development, informing public policy surrounding guidelines for optimal sleep during childhood, and designing effective interventions aimed at improving cognitive and psychiatric outcomes in youths who experience sleep difficulties.

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