Longer screen time utilization is associated with the polygenic risk for Attention-deficit/hyperactivity disorder with mediation by brain white matter microstructure

Anyi Yang,a,1 Edmund T. Rolls,a,b,c,d,1 Guiying Dong,a,b Jingnan Du,a,b Yuzhu Li,a,b Jianfeng Feng,a,b,c,e,f,g Wei Cheng,a,b,e* and Xing-Ming Zhaoa,b,f,h*

aInstitute of Science and Technology for Brain-Inspired Intelligence, Fudan University, Shanghai 200433, China
bKey Laboratory of Computational Neuroscience and Brain-Inspired Intelligence, Ministry of Education, Shanghai, China
cDepartment of Computer Science, University of Warwick, Coventry, UK
dOxford Centre for Computational Neuroscience, Oxford, UK
eFudan ISTBI—ZJNU Algorithm Centre for Brain-inspired Intelligence, Zhejiang Normal University, Jinhua, China
fMOE Frontiers Center for Brain Science, Fudan University, Shanghai, China
gZhangjiang Fudan International Innovation Center, Shanghai, China
hResearch Institute of Intelligent Complex Systems, Fudan University, Shanghai, China

Summary

Background Attention-deficit/hyperactivity disorder (ADHD) has been reported to be associated with longer screen time utilization (STU) at the behavioral level. However, whether there are shared neural links between ADHD symptoms and prolonged STU is not clear and has not been explored in a single large-scale dataset.

Methods Leveraging the genetics, neuroimaging and behavioral data of 11,000+ children aged 9–11 from the Adolescent Brain Cognitive Development cohort, this study investigates the associations between the polygenic risk and trait for ADHD, STU, and white matter microstructure through cross-sectionally and longitudinal analyses.

Findings Children with higher polygenic risk scores for ADHD tend to have longer STU and more severe ADHD symptoms. Fractional anisotropy (FA) values in several white matter tracts are negatively correlated with both the ADHD polygenic risk score and STU, including the inferior frontal-striatal tract, inferior frontal-occipital fasciculus, superior longitudinal fasciculus and corpus callosum. Most of these tracts are linked to visual-related functions. Longitudinal analyses indicate a directional effect of white matter microstructure on the ADHD scale, and a bi-directional effect between the ADHD scale and STU. Furthermore, reduction of FA in several white matter tracts mediates the association between the ADHD polygenic risk score and STU.

Interpretation These findings shed new light on the shared neural overlaps between ADHD symptoms and prolonged STU, and provide evidence that the polygenic risk for ADHD is related, via white matter microstructure and the ADHD trait, to STU.

Funding This study was mainly supported by NSFC and National Key R&D Program of China.

Copyright © 2022 The Author(s). Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

Keywords: Attention-deficit/hyperactivity disorder; Screen time utilization; Polygenic risk for attention-deficit/hyperactivity disorder; Brain tractography; Longitudinal analysis

*Corresponding authors at: Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, Shanghai 200433, China.
E-mail addresses: wcheng.fdu@gmail.com (W. Cheng), xmzhao@fudan.edu.cn (X.-M. Zhao).
1 These authors contributed equally to the study.

eBioMedicine 2022;80: 104039
Published online 1 May 2022
https://doi.org/10.1016/j.ebiom.2022.104039
Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable and neurodevelopmental disorder usually starting in childhood. ADHD and its co-occurrent behaviors are frequently reported to be associated with the behavior of screen time utilization (STU), which includes spending time with TV, smart phones and gaming devices. At the genetic level, different types of dopamine receptor or transmission genotypes like DRD2, have been reported to be correlated with ADHD and excessive video game playing. At the neural level, either ADHD or excessive screen-based activities has been found to be related to brain regions like the frontal lobe in their separate imaging studies.

Previous studies have reported the co-occurrence of ADHD and screen time utilization, while how they are linked is not clear. Our study demonstrates a coherent biological pathway involving genetics, white matter microstructure, and the behaviors of ADHD and STU. As a consequence, this research has important implications for a better science-based understanding of the association between the behaviors of ADHD and STU, at multidimensional levels.

This study has uncovered the shared neural links between the ADHD trait and prolonged STU, and how the neural links are associated with the genetics of ADHD. The results demonstrate a biological pathway from the polygenic risk for ADHD, via white matter microstructure (mostly involved in visual-related functions) and the ADHD trait, to STU. This suggests that the reduced structural connectivity involving pathways especially related to visual functions results in less strong executive control of visual functions in individuals with ADHD symptoms, and this increased sensitivity to and distractibility by visual stimuli may lead to increased screen time use.

Evidence before this study
Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable and neurodevelopmental disorder usually starting in childhood. ADHD and its co-occurrent behaviors are frequently reported to be associated with the behavior of screen time utilization (STU), which includes spending time with TV, smart phones and gaming devices. At the genetic level, different types of dopamine receptor or transmission genotypes like DRD2, have been reported to be correlated with ADHD and excessive video game playing. At the neural level, either ADHD or excessive screen-based activities has been found to be related to brain regions like the frontal lobe in their separate imaging studies.

Evidence before this study
Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable and neurodevelopmental disorder usually starting in childhood. ADHD and its co-occurrent behaviors are frequently reported to be associated with the behavior of screen time utilization (STU), which includes spending time with TV, smart phones and gaming devices. At the genetic level, different types of dopamine receptor or transmission genotypes like DRD2, have been reported to be correlated with ADHD and excessive video game playing. At the neural level, either ADHD or excessive screen-based activities has been found to be related to brain regions like the frontal lobe in their separate imaging studies.

Evidence before this study
Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable and neurodevelopmental disorder usually starting in childhood. ADHD and its co-occurrent behaviors are frequently reported to be associated with the behavior of screen time utilization (STU), which includes spending time with TV, smart phones and gaming devices. At the genetic level, different types of dopamine receptor or transmission genotypes like DRD2, have been reported to be correlated with ADHD and excessive video game playing. At the neural level, either ADHD or excessive screen-based activities has been found to be related to brain regions like the frontal lobe in their separate imaging studies.

Evidence before this study
Attention-deficit/hyperactivity disorder (ADHD) is a highly heritable and neurodevelopmental disorder usually starting in childhood. ADHD and its co-occurrent behaviors are frequently reported to be associated with the behavior of screen time utilization (STU), which includes spending time with TV, smart phones and gaming devices. At the genetic level, different types of dopamine receptor or transmission genotypes like DRD2, have been reported to be correlated with ADHD and excessive video game playing. At the neural level, either ADHD or excessive screen-based activities has been found to be related to brain regions like the frontal lobe in their separate imaging studies.
between the ADHD trait and prolonged STU; 2) brain structural connectivity or psychopathology mediate the association between polygenic risk for ADHD and STU. To test these hypotheses, several analyses were performed: 1) assessment of the bivariate association between polygenic risks for ADHD, the ADHD trait, STU, and white matter anatomical microstructure in children; 2) examination of the longitudinal association between the ADHD trait and STU; and 3) quantification of the mediation effect between polygenic risks for ADHD and STU through anatomical microstructure and the ADHD trait.

Methods

Participants
The participants for this analysis were from the ABCD cohort, an ongoing study of 11,000+ children who completed the baseline and follow-up assessments throughout the United States. The participants (aged 9–11 at baseline) were recruited from sample schools around 21 nationally distributed sites to represent the sociodemographic diversity of the United States. The genetic, diffusion tensor imaging (DTI) and behavioral data as well as demographic background of this investigation were obtained from the NIMH Data Archive ABCD Data Release 3.0 (https://nda.nih.gov/study.html?id=901).

Ethics
All procedures of the ABCD study were approved by a central Institutional Review Board (cIRB) at the University of California, San Diego, and in some cases by local IRB in a few research sites (e.g., Washington University in St. Louis). Parents provided written informed consent after the procedures had been fully explained, and children provided assent before enrolment in the study.

Pre-processing of genotype data
Genotyping was acquired through saliva or whole blood samples and was centrally performed by the Rutgers University Cell and DNA Repository using the Affymetrix NDA SmokeScreen Array. The preliminary pre-processed genotype data provided by the ABCD team contains 11,099 unique individuals with 516,598 genetic variants (for more details, see https://nda.nih.gov/study.html?id=901).

The ABCD samples contain many siblings and diverse ethnicity, which might bias the statistical results due to the cryptic relatedness and population stratification. Therefore, careful pre-processing procedures were adopted on the genotype data to increase the credibility of PRS prediction and subsequent analysis. First, 5807 European samples were selected according to their genetic ancestry factors (genetic_af_european > 0.95). Second, the quality control was performed by PLINK v1.90 with the following steps: (1) removal of SNPs with minor allele frequency < 5%; (2) removal of SNPs with missing samples > 20%; (3) removal of samples with missing genotypes > 20%; (4) removal of SNPs deviating from Hardy–Weinberg equilibrium ($p < 10^{-9}$); (5) removal of samples deviating $\pm 3$ sd from the samples’ heterozygosity rate mean; (6) removal of cryptic relatedness by randomly excluding individuals in a pair of samples with proportion identity by descent $P_L_HAT > 0.4$. Third, missing data imputation was performed using the Michigan Imputation Server, with the 1000 Genomes Project EUR (Phase 3, hg19) reference panel and Eagle v2.4 phasing. Fourth, the post imputation QC was conducted to remove those imputed SNPs: 1) with no RS IDs; 2) with imputation quality scores ($rsq < 0.9$); 3) with minor allele frequency < 5%; 4) with missingness > 20%; 5) deviating from Hardy–Weinberg equilibrium ($p < 10^{-9}$). Finally, 2,805,958 genetic variants and 4,673 samples remained for further analysis. The first ten ancestry principles components were calculated by GCTA v1.92.

PRS calculation
The polygenic risk score is a weighted count of genetic risk alleles from a set of SNPs in a genotype dataset, with weights introduced from another independent and the same ancestry-based GWAS results. We downloaded GWAS summary statistics of the ADHD study from the Psychiatric Genomics Consortium (https://www.med.unc.edu/pgc/download-results/adhd/). Only the GWAS results of European ancestry were considered in this study to match the ABCD European samples described above, as the PRS prediction depends on the similarity between the original study population and the external target population. Then, we calculated the polygenic scores by PRSice-2, with an SNP clumping threshold $\rho' = 0.1$ and a clumping window of 250 kb to remove SNPs in linkage disequilibrium. The PRSs calculated using SNPs at 10 $p$-value thresholds for their GWAS significance were included: $5 \times 10^{-8}$, $5 \times 10^{-7}$, $0.0001$, $0.0005$, $0.001$, $0.005$, $0.01$, $0.05$, $0.1$, $0.5$. The PRS capturing the largest average phenotypic variance $R^2$ for the measurements focused in this study was used in the following analysis, as $R^2$ is a frequently used indicator to evaluate the performance of PRS models. In addition, normalization (mean = 0, sd = 1) was performed for all PRSs in order to fairly compare their effects on different phenotypes.

Diffusion tensor imaging
The DTI data were obtained by the ABCD Imaging Acquisition Workgroup on three 3-Tesla scanner platforms, including Phillips, General Electric 750, and Siemens Prisma. The high angular resolution diffusion acquisition workgroup on three 3-Tesla scanner platforms, including Phillips, General Electric 750, and Siemens Prisma. The high angular resolution diffusion...
images were scanned with the following parameters: matrix size $140 \times 140$, 81 slices, FOV $240 \times 240$, resolution $1.7 \times 1.7 \times 1.7$ mm, TR $4100$ms, flip angle $77\degree$. Diffusion directions 91, b-values $500/1000/2000/3000$. The microstructural measures of fractional anisotropy (FA), mean diffusivity, longitudinal diffusivity, and transverse diffusivity were calculated by conventional DTI methods. The white matter fiber tracts were segmented using Atlas Track, where visualization of each individual fiber tract is shown in Figure S1 and their corresponding connected brain regions are shown in Table S1. Only the measure of FA value in S1 and their corresponding connected brain regions are listed in Table S1.

The quality control procedure of the ABCD cohort and preprocessed by the ABCD team, with 11,736 samples available for baseline, and 5665 samples for 2-year follow-up.

The quality control procedure of the ABCD-preprocessed imaging data was performed by following the recommended image inclusion criteria of the ABCD 3.0. Specifically, we excluded samples with the following criteria: (1) with problematic MR findings (mrif_score = 3 or mrif_score = 4); (2) with dMRI series not passing rawQC (iqc_dmri_ok_ser = 0); (3) with dMRI total number of repetitions for all OK scans less than 103 (iqc_dmri_ok_nreps < 103); (4) with dMRI B0 Unwarp unavailable (apqc_dmri_bounwarp_flag ~ 1); (5) dMRI Manual Post-Processing QC failed (dmri_postqc_qc = 0) (6) with dMRI registration to T1w larger than 17 (apqc_dmri_regti_rigid > 17); (7) dMRI Maximum dorsal cutoff score larger than 47 (apqc_dmri_fov_cutoff_dorsal > 47); (8) dMRI Maximum ventral cutoff score larger than 54 (apqc_dmri_fov_cutoff_ventral > 54). Finally, 9459 samples remained at baseline, and 4499 samples were available at 2-year follow-up.

**Screen time utilization and ADHD assessments**

Screen time utilization was assessed by the total amount of self-reported time using various electronic devices on both typical weekdays and weekend days (abcd_ssmty01), such as spending time on Facebook or watching movies. We calculated a weighted sum score to represent a daily STU as: $5/7 \times$ hours of STU in a typical weekday + $2/7 \times$ hours of STU in a typical weekend day. The data were available for baseline (11067 samples) and 1-year follow-up (11236 samples).

To evaluate the children’s level of ADHD symptoms, the ADHD CBCL DSM5 Scale from the Parent Report Child behavior checklist (CBCL, abcd_cbclso1) was used. The data were available for baseline (11067 samples), 1-year follow-up (11235 samples), and 2-year follow-up (6571 samples).

**Statistical analysis**

We fitted a linear regression model to investigate the relationship between the polygenic risk score for ADHD (PRS$_{ADHD}$), neural measures and behavioral assessments using R software (v3.6.3). For behavioral assessments, we mainly focused on STU and the ADHD scale in this study. For multiple comparison purposes, false discovery rate (FDR) was adopted across all association analyses: (1) correction of p-values was performed to evaluate the association between PRS$_{ADHD}$ and neural measures, where children’s age (month/12), sex, batch, total intracranial volume, the first 10 principal components, household income, parental education, site, body mass index and puberty were regressed out as covariates to reduce model error. These are potential influential factors regarding anthropometry, instrumental measurement or environment and are always regressed out; (2) correction of p-values was performed to investigate the association between behavioral assessments and neural measures. As no genetic factors were considered here, there was no need to limit to samples of European ancestry. We retained only one child per family according to the family ID, and considered children’s age (month/12), sex, batch, total intracranial volume, genetic ancestry proportion factors (genetic_af_african, genetic_af_european, genetic_af_east_asian, and genetic_af_american), household income, parental education, site, body mass index and puberty as covariates. Such a procedure enabled the utilization of all otherwise rejected samples, thereby leading to more robust results. The association analyses were performed on the ABCD baseline data.

A standard three-variable mediation analysis can be performed with the R package *Mediation* (version 4.5.0) to explore whether a potential mediator $M$ of interest can explain the association between an independent variable $X$ and outcome variable $Y$. To investigate the extent to which the relationship between PRS$_{ADHD}$ ($X$) and STU ($Y$) is mediated by the brain or the ADHD scale, two mediation models were established to explore the indirect effect between $X$ and $Y$: (1) a brain morphometry measure ($M$); (2) the ADHD scale ($M$). A bootstrap strategy with 10,000 resampling iterations was used to estimate the bias-corrected significance of the mediation. The mediation analyses were performed on the ABCD baseline data.

According to the longitudinal panel data in the ABCD cohort, it was possible to explore the longitudinal relationships in the following aspects: (1) the ADHD scale and STU whose data are both accessible at baseline and 1-year follow-up; (2) the ADHD scale and DTI measures whose data are both accessible at baseline and 2-year follow-up. We conducted a traditional cross-lagged panel model (CLPM) with the R package *lavaan* (version 0.6-7), where maximum likelihood estimation was carried out to fit the structural equation model. Specifically, the CLPM model can be described as

$$X_{t+1} = aX_t + \beta_1Y_t + \gamma_1Z_1 + \delta,$$
Y_{t+1} = \alpha_2 X_t + \beta_2 Y_t + \gamma_2 Z_t + \delta_2 \tag{2}

where $X_t$ and $X_{t-1}$ are the first phenotype at time $t$ and $t+1$, $Y_t$ and $Y_{t-1}$ are the second phenotype at time $t$ and $t+1$, $Z_t$ is the covariate, $\alpha_1$, $\alpha_2$, $\beta_1$, $\beta_2$, $\gamma_1$, $\gamma_2$ are the coefficients, and $\delta_1$ and $\delta_2$ are the error terms of the model.

Lastly, a serial mediation analysis was performed by using model 6 in processR (https://github.com/carbonmoon/processR, version 0.2.6), an R package implementation of the PRSCESS Macro, through which we assessed the indirect effect of PRSADHD on STU through both the ADHD scale and brain measures. The model investigated the path of PRSADHD ($X$) — a brain morphometry measure ($M$) — the ADHD scale ($M$) — STU ($Y$), and was performed on the ABCD baseline data. Specifically, the serial mediation model can be described as

\[ Y = b_1 M_t + b_2 M_{t-1} + c_1 X_t + e_1 Z_t + e_t \]

\[ M_t = a_1 X_t + e_2 Z_t + e_2 \]

\[ M_{t-1} = a_2 X_t + d_1 M_t + e_3 Z_t + e_3 \]

where $Z$ is the covariate, $a_1$, $a_2$, $b_1$, $b_2$, $c_1$, $c_2$, $d_1$, $e_1$, $e_2$ and $e_3$ are the coefficients, and $e_1$, $e_2$ and $e_3$ are the error terms of the model. The serial mediation effect is then assessed the indirect effect of PRS ADHD on STU ($Y$), and was performed on the ABCD baseline data. Specifically, the serial mediation model can be described as

\[ Y = b_1 M_t + b_2 M_{t-1} + c_1 X_t + e_1 Z_t + e_t \]

\[ M_t = a_1 X_t + e_2 Z_t + e_2 \]

\[ M_{t-1} = a_2 X_t + d_1 M_t + e_3 Z_t + e_3 \]

where $Z$ is the covariate, $a_1$, $a_2$, $b_1$, $b_2$, $c_1$, $c_2$, $d_1$, $e_1$, $e_2$ and $e_3$ are the coefficients, and $e_1$, $e_2$ and $e_3$ are the error terms of the model. The serial mediation effect is then assessed the indirect effect of PRS ADHD on STU ($Y$), and was performed on the ABCD baseline data. Specifically, the serial mediation model can be described as

\[ Y = b_1 M_t + b_2 M_{t-1} + c_1 X_t + e_1 Z_t + e_t \]

\[ M_t = a_1 X_t + e_2 Z_t + e_2 \]

\[ M_{t-1} = a_2 X_t + d_1 M_t + e_3 Z_t + e_3 \]

where $Z$ is the covariate, $a_1$, $a_2$, $b_1$, $b_2$, $c_1$, $c_2$, $d_1$, $e_1$, $e_2$ and $e_3$ are the coefficients, and $e_1$, $e_2$ and $e_3$ are the error terms of the model. The serial mediation effect is then assessed the indirect effect of PRS ADHD on STU ($Y$), and was performed on the ABCD baseline data. Specifically, the serial mediation model can be described as

\[ Y = b_1 M_t + b_2 M_{t-1} + c_1 X_t + e_1 Z_t + e_t \]

\[ M_t = a_1 X_t + e_2 Z_t + e_2 \]

\[ M_{t-1} = a_2 X_t + d_1 M_t + e_3 Z_t + e_3 \]

where $Z$ is the covariate, $a_1$, $a_2$, $b_1$, $b_2$, $c_1$, $c_2$, $d_1$, $e_1$, $e_2$ and $e_3$ are the coefficients, and $e_1$, $e_2$ and $e_3$ are the error terms of the model. The serial mediation effect is then assessed the indirect effect of PRS ADHD on STU ($Y$), and was performed on the ABCD baseline data. Specifically, the serial mediation model can be described as

\[ Y = b_1 M_t + b_2 M_{t-1} + c_1 X_t + e_1 Z_t + e_t \]

\[ M_t = a_1 X_t + e_2 Z_t + e_2 \]

\[ M_{t-1} = a_2 X_t + d_1 M_t + e_3 Z_t + e_3 \]

where $Z$ is the covariate, $a_1$, $a_2$, $b_1$, $b_2$, $c_1$, $c_2$, $d_1$, $e_1$, $e_2$ and $e_3$ are the coefficients, and $e_1$, $e_2$ and $e_3$ are the error terms of the model. The serial mediation effect is then assessed the indirect effect of PRS ADHD on STU ($Y$), and was performed on the ABCD baseline data. Specifically, the serial mediation model can be described as

\[ Y = b_1 M_t + b_2 M_{t-1} + c_1 X_t + e_1 Z_t + e_t \]

\[ M_t = a_1 X_t + e_2 Z_t + e_2 \]

\[ M_{t-1} = a_2 X_t + d_1 M_t + e_3 Z_t + e_3 \]

where $Z$ is the covariate, $a_1$, $a_2$, $b_1$, $b_2$, $c_1$, $c_2$, $d_1$, $e_1$, $e_2$ and $e_3$ are the coefficients, and $e_1$, $e_2$ and $e_3$ are the error terms of the model. The serial mediation effect is then assessed the indirect effect of PRS ADHD on STU ($Y$), and was performed on the ABCD baseline data. Specifically, the serial mediation model can be described as

\[ Y = b_1 M_t + b_2 M_{t-1} + c_1 X_t + e_1 Z_t + e_t \]

\[ M_t = a_1 X_t + e_2 Z_t + e_2 \]

\[ M_{t-1} = a_2 X_t + d_1 M_t + e_3 Z_t + e_3 \]

where $Z$ is the covariate, $a_1$, $a_2$, $b_1$, $b_2$, $c_1$, $c_2$, $d_1$, $e_1$, $e_2$ and $e_3$ are the coefficients, and $e_1$, $e_2$ and $e_3$ are the error terms of the model. The serial mediation effect is then assessed the indirect effect of PRS ADHD on STU ($Y$), and was performed on the ABCD baseline data. Specifically, the serial mediation model can be described as

\[ Y = b_1 M_t + b_2 M_{t-1} + c_1 X_t + e_1 Z_t + e_t \]

\[ M_t = a_1 X_t + e_2 Z_t + e_2 \]

\[ M_{t-1} = a_2 X_t + d_1 M_t + e_3 Z_t + e_3 \]
We collected data from the Psychiatric Genomics Consortium (PGC) and Adolescent Brain Cognitive Development (ABCD) database. The DTI template for white matter fiber tracts we used was from Atlas Track. The polygenic risk scores for ADHD (PRSADHD) of 4673 children with European ancestry from the ABCD cohort were obtained based on the summary statistics of an independent ADHD GWAS study. Cross-sectionally bivariate associations were performed between PRSADHD, white matter microstructure, and behavioral assessments. The behaviors we mainly focused on in this study are the ADHD scale and screen time utilization (STU). Longitudinal and mediation analyses were performed to explore integrative relationships between PRSADHD, white matter microstructure, the ADHD trait and STU. Potential confounding factors were regressed out in all the analyses (see Methods).
<table>
<thead>
<tr>
<th>Basic information</th>
<th>Age (month)</th>
<th>Gender (Male/Female)</th>
<th>BMI</th>
<th>Parents income</th>
<th>Parents education</th>
</tr>
</thead>
<tbody>
<tr>
<td>118.96 ± 7.46</td>
<td>5847/5216</td>
<td>19.07 ± 4.23</td>
<td>7.26 ± 2.29</td>
<td>16.66 ± 2.68</td>
<td></td>
</tr>
<tr>
<td>Puberty</td>
<td>5914/1694/2118/155/1180</td>
<td>5.87 ± 2.68</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Screen time utilization measurement</th>
<th>Screen Time Youth Weekday Sum</th>
<th>Screen Time Youth Weekend Sum</th>
<th>Screen Time Youth daily average</th>
</tr>
</thead>
<tbody>
<tr>
<td>(stq_y_ss_weekday)</td>
<td>(stq_y_ss_weekday)</td>
<td>(stq_y_ss_ave_daily)</td>
<td></td>
</tr>
<tr>
<td>3.47 ± 3.1</td>
<td>4.64 ± 3.61</td>
<td>3.8 ± 3.07</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>cbcl_scr_syn_anxdep</td>
<td>cbcl_scr_syn_withdep</td>
<td>cbcl_scr_syn_somatic</td>
<td>cbcl_scr_syn_social</td>
<td>cbcl_scr_syn_thought</td>
<td>cbcl_scr_syn_thought</td>
</tr>
<tr>
<td>2.52 ± 3.07</td>
<td>1.0 ± 1.7</td>
<td>1.5 ± 1.95</td>
<td>1.62 ± 2.28</td>
<td>1.64 ± 2.20</td>
<td></td>
</tr>
</tbody>
</table>

| Attention Problems CBCL Syndrome Scale         | Rule-Breaking Behavior CBCL Syndrome Scale | Aggressive Behavior CBCL Syndrome Scale | Internalizing Problems CBCL Syndrome Scale | Externalizing Problems CBCL Syndrome Scale |
| cbcl_scr_syn_attention                          | cbcl_scr_syn_rulebreak               | cbcl_scr_syn_aggressive               | cbcl_scr_syn_internal                  | cbcl_scr_syn_external             |
| 3 ± 3.51                                       | 1.2 ± 1.87                          | 3.28 ± 4.36                          | 5.06 ± 5.53                           | 4.48 ± 5.87                      |

| Total Problems CBCL Syndrome Scale            | Depressive Problems CBCL DSM5 Scale | Anxiety Disorder CBCL DSM5 Scale | Somatic Problems CBCL DSM5 Scale | ADHD CBCL DSM5 Scale |
| cbcl_scr_syn_totprob                           | cbcl_scr_dsm5_depress               | cbcl_scr_dsm5_anxdisord            | cbcl_scr_dsm5_somatic              | cbcl_scr_dsm5_adhd             |
| 18.26 ± 17.96                                 | 1.27 ± 2.01                         | 2.06 ± 2.44                        | 1.08 ± 1.5                           | 2.64 ± 2.98                    |

| cbcl_scr_dsm5_opposit                         | cbcl_scr_dsm5_conduct               | cbcl_scr_dsm5_conduct               | cbcl_scr_dsm5_conduct               | cbcl_scr_dsm5_conduct             |
| 1.77 ± 2.04                                   | 1.3 ± 2.37                          | 0.53 ± 1.01                        | 1.35 ± 1.82                           | 2.91 ± 3.35                    |

Table 1: The demographic characteristics of participants from the ABCD analyzed here.
Note: The detail information of the measurement can be found on https://nda.nih.gov/data_dictionary.html.
Figure 2. Associations between PRSADHD and behavioral assessments. (a) The Manhattan plot of the association between PRSADHD and all the behavioral assessments shown in Table S4. A point above the grey dotted line denotes that this assessment is significantly correlated with PRSADHD (FDR < 0.05). (b) The scatter plots colored by density show the top four non-redundant assessments which are significantly correlated with PRSADHD as shown in (a), including the ADHD scale, daily average screen time utilization, Attention Problems scale and Externalizing Problems scale. ‘n_neighbours’ means ‘number of dots’ around each dot. All p-values were calculated by t test from linear regression analyses.
Lower FA of white matter tracts is associated with higher PRS for ADHD, and longer STU

In this section, we described the associations between brain microstructure and PRSADHD as well as behavioral assessments. For global measures, the mean FA value of all fibers tracts was found to be significantly correlated with PRSADHD (standardized β = −3.46, \( p = 5.48 \times 10^{-4}, \) t test, \( R^2 = 0.33\% \), FDR < 0.05), which also holds for both left and right tracts (\( p < 1 \times 10^{-3}, \) FDR < 0.05; Table S6). STU was significantly negatively correlated with the mean FA value of all tracts (standardized β = −3.23, \( p = 1.25 \times 10^{-3}, \) t test, \( R^2 = 0.78\% \), FDR < 0.05), and the same for both the left and right hemisphere tracts (\( p < 5 \times 10^{-3}, \) FDR < 0.05; Table S7).

For regional measures, higher PRS was related to lower FA values of the uncinate fasciculus, corticospinal tract, inferior frontal-opercular fasciculus (IFO), (temporal/parietal) superior longitudinal fasciculus (SLF), corpus callosum (CC), inferior frontal superior frontal tract, anterior thalamic radiations, and inferior fronto-striatal tract (IFS) (all with FDR < 0.05; Figure 3a and Table S6). At the same time, longer STU was found correlated with lower FA values in (parietal/temporal) SLF, fornix, CC, uncinate fasciculus, IFO, corticospinal tract, forceps minor, IFS, and superior corticostriate (all with FDR < 0.05; Figure 3b and Table S7).

Table 2 and Figure 3c show the brain areas correlated with both PRSADHD and STU, and Table S8 and Figure S3 show the brain areas correlated with the ADHD scale. Moderate spatial correlation of β maps was observed between the ADHD scale and STU (\( r = 0.57, \) \( p = 1.66 \times 10^{-4}, \) Pearson correlation). The association analysis between the ADHD scale and white matter tracts was repeated while including head motion (\( \text{iqc}_\text{dmri}_1, \text{mean}_\text{motion} \)) as a covariate (Table S9).

The pattern of spatial β maps for the ADHD scale was consistent with and without correcting for head motion (\( r = 0.936, \) \( p < 5 \times 10^{-15}, \) Pearson correlation), and lower FA values of the uncinate fasciculus, IFO, parietal SLF and superior corticostriate, can still be found associated with higher ADHD scale (FDR < 0.05). These results support the first hypothesis that prolonged STU and the ADHD trait share a positive neural overlap.

The mean FA of white matter tracts and the ADHD scale mediate the relationship between PRS for ADHD and STU

With the longitudinal analyses, which showed a direct effect of brain white matter microstructure on the ADHD scale, as well as a bi-directional effect of the ADHD scale on STU, we performed mediation analyses to test the second hypothesis that brain structural connectivity or the ADHD trait can mediate the association between PRSADHD and STU. It was found that the FA value of white matter tracts shown in Figure 3c and Table 2 significantly mediated the relationship between PRSADHD and STU (path AB: accounting for 3.17% of the total effect, \( \beta = 0.006, 95\% \text{ CI}: [5.62 \times 10^{-4}, 0.012], \) \( p = 0.025, \) bootstrap test; Figure 4d). The ADHD scale was also a significant mediator between PRSADHD and STU (path AB: accounting for 14.78% of the total effect, \( \beta = 0.027, 95\% \text{ CI}: [0.016, 0.041], \) \( p < 1 \times 10^{-4}, \) bootstrap test; Figure 4d).

Based on the associations outlined above, we hypothesized that there was also an indirect path between PRSADHD and STU through both white matter tracts and the ADHD scale (sequentially). As predicted, there was a significant indirect path between PRSADHD and STU through mean FA of white matter tracts and the ADHD scale (path ADB: accounting for 0.53% of the total effect, \( \beta = 0.001, 95\% \text{ CI}: [2.36 \times 10^{-4}, 1.93 \times 10^{-7}], \) \( p = 0.03, \) bootstrap test; Figure 4e). The second hypothesis was thus supported by these mediation analyses. Similar results were also found across neighboring PRS thresholds (Figure S4a–f), except that the indirect path between PRSADHD at threshold 0.05 and STU through both white matter tracts and the ADHD scale did not quite reach but was very close to the significant threshold of \( p < 0.05 \) (\( p = 0.056, \) Figure S5f).

Discussion

Leveraging cross-sectional and longitudinal data from a large-scale dataset, it was found that individuals with a higher polygenic risk for ADHD tend to prolong their screen activities and have more severe ADHD symptoms (Figure 2). Longitudinal analyses indicate a directional effect of white matter microstructure on the
Figure 3. The brain regions correlated with PRS\textsuperscript{ADHD} or STU. The brain tracts analyzed with DTI significantly (FDR < 0.05) correlated with (a) PRS\textsuperscript{ADHD}, (b) STU; (c) both PRS\textsuperscript{ADHD} and STU. The number above each brain anatomical section is the MNI coordinate for the selected plane. All $p$-values were calculated by t test from linear regression analyses.
ADHD scale, and a bi-directional effect between the ADHD scale and STU (Figure 4a, b). Furthermore, the mediation analysis demonstrated that some white matter tracts (shown in Figure 3c and Table 2), and the ADHD scale, substantially mediate the association between PRSADHD and STU (Figure 4c–e). Our study has several strengths: (1) the use of longitudinal data with a large number of participants leads to robust findings; (2) the utilization of PRS serves as a good representation of the ADHD polygenic architecture; (3) the feasibility to uncover relationships between genetic risk for ADHD and the ADHD trait with STU. Collectively, this investigation lends a multidimensional perspective to the association between the behaviors of ADHD and STU through multimodal data.

The relationships between ADHD and STU illuminated here can be described at several levels. At the behavioral level, STU had a significant bi-directional correlation with the ADHD scale. The finding is reasonable given that children with ADHD tend to explain why children with ADHD find it difficult to tear themselves away from prominent visual sensory stimulation to perform instead more planned activity. With changes in the axonal bundles of frontal-striatal circuitry, problems may arise. The IFO is considered as a key contributor to visual information processing, such as the

demonstrated to be linked to ADHD in children.72,73 The IFS links the inferior frontal cortex to the striatum, and changes of structural connectivity in frontal-striatal circuitry have often been demonstrated to be linked to ADHD in children.74-75 The frontal-striatal circuitry may involve linking inhibitory control and executive function.74-75 In this context, the abnormalities of frontal-striatal circuitry may help explain why children with ADHD find it difficult to tear themselves away from prominent visual sensory stimulation to perform instead more planned activity. With changes in the axonal bundles of frontal-striatal circuitry, problems may arise. The IFO is considered as a key contributor to visual information processing, such as the
Figure 4. The longitudinal and mediation analyses. (a) Longitudinal analysis between the ADHD scale and the mean FA of the significant fiber tracts shown in Fig. S3 at baseline and 2-year follow-up. (b) Longitudinal analysis between the STU and the ADHD scale at baseline and 1-year follow-up. The p-values of longitudinal analyses were calculated by z-test from the CLPM model. (c, d) Mediation analysis between PRSADHD and STU through (c) mean FA value of regional findings shown in Fig. 3c; (d) the ADHD scale. The p-values of mediation effect were calculated by bootstrap test with 10000 resampling iterations. (e) Serial mediation analysis between PRSADHD and STU through mean FA value of white matter tracts shown in Fig. 3c and the ADHD scale (sequentially). The p-values of the serial mediation effect were calculated by bootstrap test with 10000 resampling iterations. Path C shows the association between PRSADHD and STU when mediators are not taken into account. Path C* shows the association between PRSADHD and STU when mediators are taken into account. The mediation relationship is labelled with a red dotted line in (c–e).
visual guidance for movement. The role of the IFO is mainly supported by its anatomic terminations in the occipital lobe, which contains early visual cortical areas. Reduced FA in IFO is a notable finding in previous adolescent and adult ADHD studies. The SLF is widely known for its connections involving the frontal, temporal, parietal, and occipital cortices, and is involved in visually mediated processes and the maintenance of attention. Alteration of the SLF has been frequently reported in people with ADHD, and we also provided evidence for its involvement in STU. Additionally, the CC area indicated in our findings plays a role in integrating visuomotor and cognitive processes between the two hemispheres. Clearly, most of these tracts with significant negative correlations with PRS are crucial for visual-related function, except for the IFS which is involved in inhibitory and executive function. It has been shown that in ADHD, there is increased functional connectivity of visual cortical areas, and this was related to the dominant effects of visual stimuli in ADHD. Putting these findings together, it is hypothesized that the reduced tractography reported here to be associated with PRS may reduce top-down executive control from prefrontal cortex and related areas on early visual cortical areas.

Few previous studies have examined the linkage between ADHD, white matter microstructure and STU simultaneously. It shows that widespread reductions of FA in white matter tracts at baseline are significantly correlated with more severe ADHD symptoms at two-year follow-up; and the reverse was not found. This provides evidence that early abnormal white matter might be a biomarker for a later diagnosis of ADHD. Concurrently, the longitudinal analysis showed a bi-directional effect between STU and the ADHD scale. Subsequent mediation analysis indicates that PRS is linked to STU through both white matter tracts and the ADHD trait. It is hypothesized that children with high polygenic risk for ADHD tend to have alterations in white matter tracts that are linked to visual-related functions, making individuals with ADHD symptoms sensitive to external visual stimulation with reduced attentional and executive control, and so are easily distracted by screen-related activities. The findings extend a previous study on correlations between PRS and white matter structure and ADHD symptomatology, and is informative for future research on biological processes involving ADHD and STU.

However, there are still some issues that need to be addressed in the future. Firstly, we focused on the white matter microstructure in this study because anatomical measures are reported to be more closely related to genetic factors than functional connectivity. At the time of the writing of this paper, there is no clear meta-analytic evidence of common functional alterations across individuals with ADHD. In the future, other types of imaging data like functional MRI may be considered. Secondly, the present analysis does not provide mechanistic insights into how genes may drive brain dysfunction and influence behaviors. Other gene-based methods like transcriptome-wide association studies might replace the PRS used in this study to help understand the molecular mechanisms by which genes affect phenotypes. Thirdly, the STU assessment we used is self-reported, which may skew towards underestimation since the adolescents may pay little attention to the starting or ending time when they use electronic devices. Even if the STU assessment is parent-reported, it may also lead to biased results as parents cannot stay beside their children all the time, and thus the parental reported result may be based on subjective estimation. Fourthly, the head motion is a noteworthy issue. A previous study reported that the differences in head motion between ADHD and control samples might bias the results of between-group comparison of FA. Although the ADHD trait considered here is not a categorical disorder but a continuous scale of ADHD symptoms from samples with healthy backgrounds, and consistent patterns of brain spatial β maps for the ADHD scale was observed with and without head motion as a covariate, it is still an open issue that should be considered in future ADHD imaging studies. Finally, due to the lack of some longitudinal measures, we could not test the long-term relation between brain development and STU. However, this could be addressed in the future as the ABCD project is an on-going study.

In summary, leveraging the large-scale data of the ABCD, we found significant associations between the polygenic risk for ADHD, and STU, with white matter microstructure involved in visual function and the ADHD trait as factors involved in the association. These findings may be helpful when designing treatment strategies in future.

**Contributors**

W.C. and X.M.Z. conceived and designed research; A.Y. performed research; A.Y., and G.D. analyzed data; J.F., J.D., and Y.L. has directly accessed and verified the underlying data reported in the manuscript; E.T.R. supervised the whole project; A.Y. wrote the original draft of the paper; and X.M.Z., W.C., and E.T.R. reviewed and polished the paper. All authors read and approved the final version of the manuscript.

**Declaration of interests**

The authors declare that they have no conflicts of interest.

**Data sharing statement**

Genotype, neuroimaging and behavioral data from ABCD dataset can be obtained from https://nda.nih.gov/abcd with the approval of the ABCD consortium.
GWAS summary statistics of the ADHD study can be directly downloaded from https://www.med.unc.edu/pgc/download-results/adhd/.

Acknowledgments
X.M.Z. was supported by the National Key R&D Program of China (No. 2020YFC1712403), National Natural Science Foundation of China (NSFC) (No. 61932008, No. 61723168), Shanghai Municipal Science and Technology Major Project (No. 2018SHZDZX01), J.F.F. was supported by National Key R&D Program of China (No. 2018YFC1712400 and No. 2019YFA0709502), Shanghai Municipal Science and Technology Major Project (No. 2018SHZDZX01), Shanghai Center for Brain Science and Brain-Inspired Technology, and the III Project (No. B18015). W.C. was supported by grants from the National Natural Science Foundation of China (No. 82071997) and Shanghai Rising Star Program (No. 20QA1408700).

We deeply appreciate the contributors of the Adolescent Brain Cognitive Development (ABCD) Study (https://abcdstudy.org). Data of the ABCD Study is held in the NIIMH Data Archive (NDA). The ABCD Study is a multisite, longitudinal study designed to recruit more than 10,000 children age 9–10 years and follow them over 10 years into early adulthood. It is supported by the National Institutes of Health and additional federal partners under award numbers U01DA041048, U01DA050989, U01DA051016, U01DA041022, U01DA051018, U01DA051037, U01DA050987, U01DA041174, U01DA041106, U01DA041179, U01DA041028, U01DA041144, U01DA050988, U01DA051039, U01DA041156, U01DA041025, U01DA041120, U01DA051018, U01DA041148, U01DA041093, U01DA041089, U24DA041123, U24DA041147. A full list of supporters is available at https://abcdstudy.org/federal-partners.html. A listing of participating sites and a complete list of funders of the PGC database is available at https://pgc.org/.

Supplementary materials
Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ebiom.2022.104039.

References